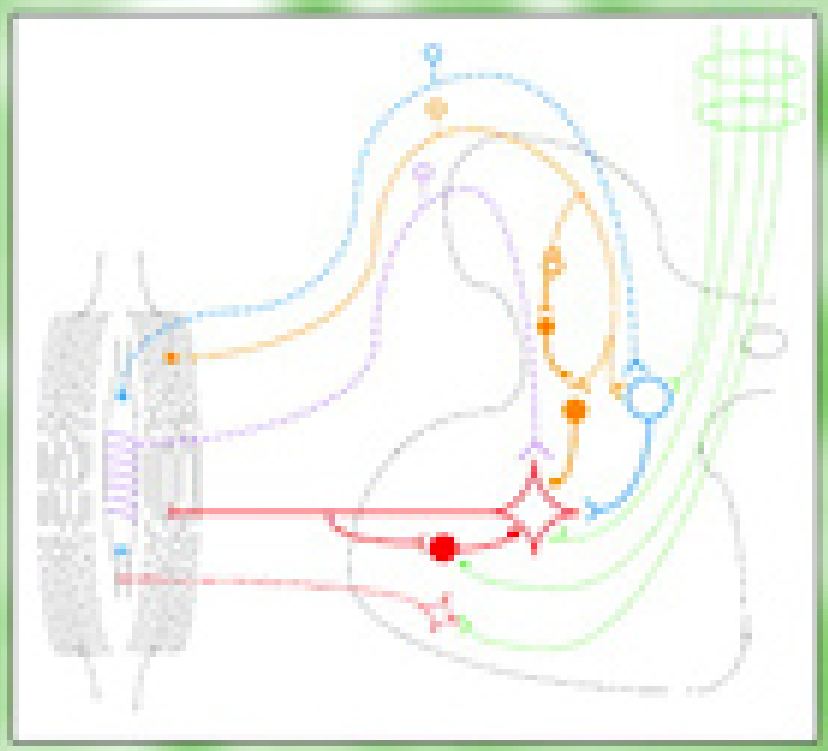
The Circuitry of the Human Spinal Cord

Its Role in Motor Control and Movement Disorders



Emmanuel Pierrot-Deseilligny
and David Burke

CAMBRIDGE

CAMBRIDGE www.cambridge.org/9780521825818

This page intentionally left blank

THE CIRCUITRY OF THE HUMAN SPINAL CORD

Studies of human movement have proliferated in recent years, and there have been many studies of spinal pathways in humans, their role in movement, and their dysfunction in neurological disorders. This comprehensive reference surveys the literature related to the control of spinal cord circuits in human subjects, showing how they can be studied, their role in normal movement, and how they malfunction in disease states. The distinguished authors each bring to the book a lifetime's research and practice in neuroscience, motor control neurobiology, clinical neurology and rehabilitation. Chapters are highly illustrated and consistently organised, reviewing, for each pathway, the experimental background, methodology, organisation and control, role during motor tasks, and changes in patients with CNS lesions. Each chapter concludes with a helpful résumé that can be used independently of the main text to provide practical guidance for clinical studies. This is therefore the last word on the role of the spinal cord in human motor control. It will be essential reading for research workers and clinicians involved in the study, treatment and rehabilitation of movement disorders.

Emmanuel Pierrot-Deseilligny is Professor of Rehabilitation and Clinical Neurophysiology at the Hôpital de la Salpêtrière, University of Paris.

David Burke is Professor and Dean of Research and Development at the College of Health Sciences, University of Sydney.

THE CIRCUITRY OF THE HUMAN SPINAL CORD

Its Role in Motor Control and Movement Disorders

Emmanuel Pierrot-Deseilligny
Hôpital de la Salpêtrière

and

David Burke
University of Sydney

CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo

Cambridge University Press
The Edinburgh Building, Cambridge CB2 2RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521825818

First published in print format 2005

ISBN-13 978-0-511-12544-7 eBook (EBL)
ISBN-10 0-511-12544-5 eBook (EBL)

ISBN-13 978-0-521-82581-8 hardback
ISBN-10 0-521-82581-4 hardback

Contents

Preface

Spinal mechanisms in the control of movement. In the 1910–1920s Paul Hoffmann demonstrated that percutaneous electrical stimulation of the posterior tibial nerve in human subjects produced a synchronised response in the soleus muscle with the same central delay as the Achilles tendon jerk. This landmark study long preceded Lloyd's identification of the corresponding pathway in the cat (1943). Subsequently, much of the primary knowledge about the spinal circuitry has come from animal experiments, but human studies have retained a unique role: the ability to shed direct light on how spinal mechanisms are used in the control of voluntary movement. In the 1940–1950s, many spinal pathways were analysed in 'reduced' animal preparations with regard to their synaptic input and to their projections to other neurones.

Modern views about spinal pathways began to emerge when Anders Lundberg and colleagues showed in the 1960s and 1970s that, in the cat, each set of spinal interneurones receives extensive convergence from different primary afferents and descending tracts, and that the integrative function of spinal interneurones allows the motoneurones to receive a final command that has been updated at a premotoneuronal level. Methods have now been developed to enable indirect but nevertheless valid measurements of spinal interneuronal activity in human subjects, and these techniques have demonstrated reliability, particularly when congruent results are obtained with independent methods. Their use has allowed elucidation of how the brain modulates the activity of specific spinal

interneurones to control movement. This, together with the abnormalities of motor control resulting from lesions in the central nervous system (CNS) and the underlying pathophysiology of movement disorders, is the subject of this book.

Over recent years, reappraisal of the role of direct cortico-motoneuronal projections in higher primates including humans has led to the view that the control of movement resides in the motor cortical centres that drive spinal motoneurone pools to produce the supraspinally crafted movement. This view belies the complex interneuronal machinery that resides in the spinal cord. It is a thesis of this book that the final movement is only that part of the supraspinally derived programme that the spinal cord circuitry deems appropriate. While the capacity of the spinal cord to generate or sustain even simple movements, particularly in human subjects, is limited, the influence that it plays in shaping the final motor output should not be underestimated. The recent recording by Eberhard Fetz and colleagues from spinal interneurones during, and before, voluntary movement in the awake monkey well illustrates this role of the spinal cord. A goal of rehabilitation of patients with upper motor neurone lesions should be to harness the residual motor capacities of the spinal cord and, for this to occur, the information in this book is critical. The techniques described in this book will also allow assessment in patients of whether any regeneration is 'appropriate'.

Studying motor control in human subjects. There has been an explosion of studies on human movement and of the dysfunction that accompanies different neurological disorders, and the prime rationale for this book is to summarise the literature related to the control of spinal cord circuitry in human subjects. Of necessity, only some interneuronal circuits can be studied reliably in human subjects, and no one book can provide a complete overview of the role of spinal circuitry in normal and pathological movement: there are no data for the many circuits that cannot yet be studied in human subjects, let alone the cat. This book is intended to provide a comprehensive account of (i) how some well-recognised and defined circuits can be studied, (ii) how they are used in normal movement, and (iii) how they malfunction in disease states.

It is as well to retain some reservations about conclusions of studies in human subjects: (i) All studies on human subjects are indirect and cannot be controlled as rigorously as in the cat. (ii) Some pathways cannot be explored quantitatively, because their effects are contaminated by effects due to other afferents (e.g. effects due to group II afferents are always contaminated by group I effects whatever testing method is used). (iii) For methodological reasons (stability of the stimulating and recording conditions), isometric voluntary contractions have been the main motor tasks during which changes in transmission in spinal pathways have been investigated. However, recent technological advances now allow the investigation of spinal pathways during natural movements, including reaching and walking. (iv) With transcranial magnetic stimulation of the motor cortex, it is possible to investigate the corticospinal control of spinal interneurones, but there are little data for other descending controls from basal ganglia and the brainstem, other than vestibular projections. (v) In patients, spinal circuitry has usually been explored under resting conditions, but the functionally important deficits may appear only during attempted movements (reinforcement of spasticity during movement, dystonia).

Methodological advances. The H reflex has served motor control well but, over the last 30 years, other techniques have been developed to allow more accurate probing of spinal pathways in human subjects, providing data that can validate and extend the findings from H reflex studies. As a result, knowledge of the role of spinal pathways in normal and pathological motor control has increased greatly, and this provides a further motivation for this book. For example, the use of *post-stimulus time histograms* has allowed the investigation of single motoneurones in human subjects, the technique of *spatial facilitation* allows the exploration of the convergence of different volleys on spinal interneurones, and *transcortical stimulation* of the motor cortex allows the corticospinal control of spinal pathways to be investigated. This book details this newer knowledge for the use of

those who have an interest in the subject but who have not had time to read the rapidly accumulating original literature. Inevitably, there will be inconsistencies in conclusions from studies on intact human subjects who can respond to a stimulus. Greater validity comes from using a number of independent techniques to demonstrate the same finding, as is emphasised in the following chapters. Inconsistent or irreproducible findings can lead to controversy about the nature and the functional role of a specific pathway in normal subjects and in patients, and such inconsistencies are presented, and the validity of the method(s) used to explore that pathway is addressed. Possible future directions for the research are discussed.

Organisation of individual chapters. The different spinal pathways for which there are reliable and non-invasive methods of investigation are considered with, for each pathway:

(i) *A brief background from animal experiments*. Human investigations are indirect and it is crucial to know the essential characteristics of each pathway described in animal experiments with recordings from motoneurones and/or interneurones. Caution should always be taken in extrapolating from data obtained in 'reduced preparations' (anaesthetised, decerebrate or spinalised animals) to awake intact human subjects, but the validation of a technique for exploring a given pathway may require controls only possible in animal experiments and is more credible when there is a close analogy with animal experiments.

(ii) *A critical description of the available method(s)* that have been used to explore the relevant pathways selectively. Methodological details allowing the reader to use reliable methods are described.

(iii) *The organisation and descending control (in particular corticospinal) of these pathways in human subjects*. The basic organisation of each pathway may well be the same in humans and cats, but the strength of the projections of individual spinal pathways on different motoneurone pools and their descending control have been the subject of phylogenetic adaptations to different motor repertoires. For the human lower limb, more elaborate reflex assistance is required for bipedal stance and gait. That there has been this phylogenetic adaptation argues that spinal pathways have a functional role in human subjects and are not evolutionary relics.

(iv) *The changes in transmission in these pathways during various motor tasks*. How spinal reflex pathways are used in motor control cannot be deduced from experiments on 'reduced' animal preparations. It requires experiments performed during natural movements, as can be done in humans. This has been one major contribution of human studies to the understanding of motor control physiology. Thus, even though many of the conclusions are speculative, this book gives a large place to the probable functional implications of the described changes in transmission in spinal pathways during movement.

(v) *Changes in transmission in these pathways in patients with various lesions of the CNS*. This has provided new insights about the pathophysiology of the movement disorder in these patients.

Overall organisation of the book. The general methodologies that are used for investigating pathways are considered in a first chapter with, for each method, its advantages and its disadvantages. There is a risk that starting with a technical chapter would dissuade the non-specialist reader from delving further into the book. This *initial chapter* is useful to understand fully the particular techniques used for the investigation of the different pathways, *but it is not essential for comprehension of the following chapters*.

For those who wish to know how methods and concepts have evolved over the years and why some interpretations were erroneous even if, at the time, influential, the methods are described in detail, with their limits and caveats, and the results obtained and their interpretation(s) are critically evaluated in each chapter. Because human studies are fraught with

technical difficulties, much space has been alloted to methods and potential pitfalls.

For those who want to get to the gist of the matter reasonably quickly each chapter terminates with a résumé of its salient points. The résumés can be used on their own without reference to the detailed text. They give a practical 'recipe' on the choice of the appropriate technique and its proper use in routine clinical studies, together with data on the possible functional role of the particular pathway in motor control and in the pathophysiology of movement disorders.

The final two chapters summarise and synthesise the changes in transmission in spinal pathways during movement and how these changes contribute to motor control, and spinal mechanisms underlying spasticity and motor impairment in patients with Parkinson's disease. In these chapters, the physiological (Chapter 11) and pathophysiological (Chapter 12) roles of different spinal pathways, considered in the previous chapters, are presented with another approach: (i) how different motor tasks are controlled by spinal pathways (Chapter 11); (ii) how these pathways contribute to motor disorders (Chapter 12).

Acknowledgements

This book is dedicated to Evelyne and Katre. It would not have been possible if our wives had not appreciated the importance for us of bringing together in a single volume the accumulated knowledge on spinal mechanisms in the control of movement. They have encouraged, supported and tolerated us, understanding even when we were unreasonable, putting life on hold so that we could work.

We are greatly indebted to Paolo Cavallari, Jean-Michel Gracies, Hans Hultborn, Léna Jami, Stacey Jankelowitz, Elzbieta Jankowska, Dominique Mazevet, Leonor Mazières, Jens Nielsen, Uwe Proske and Marco Schieppati who have given generously of their time to read and comment on drafts of various chapters. Above all, particularly special thanks go to Paolo, Léna and Leonor who read the entire text.

Geneviève Bard and Mary Sweet have laboured long and hard in getting the text into presentable order, and we are grateful for their friendship, loyalty and meticulous attention to detail over our many years of association.

Finally, the studies summarised in the book represent the intellectual activity of collaborators, colleagues, students and staff. We are grateful to everyone who contributed to these studies, and to our colleagues and their publishers who have allowed us to reproduce Figures from their papers. Finally, the authors would like to thank INSERM and NH&MRC for support of their work.

Abbreviations

5-HT	5-hydroxytryptophan
ACh	acetylcholine
Aff.	affected
AHP	afterhyperpolarisation
APB	abductor pollicis brevis
Bi	biceps
CFS	critical firing stimulus
Co FRA	contralateral FRA
CPN	common peroneal nerve
CS or (Cort. sp.)	corticospinal
CUSUM	cumulative sum
Cut	cutaneous
Desc.	descending
DPN	deep peroneal nerve
ECR	extensor carpi radialis
ED	extensor digitorum
EDB	extensor digitorum brevis
EDL	extensor digitorum longus
EHB	extensor hallucis brevis
EHL	extensor hallucis longus
EMG	electromyogram
EPSP	excitatory post-synaptic potential
Erect sp	erector spinae
Exc	excitatory
FCR	flexor carpi radialis
FCU	flexor carpi ulnaris
FDB	flexor digitorum brevis
FDI	first dorsal interosseus
FDS	flexor digitorum superficialis
FHB	flexor hallucis brevis
FN	femoral nerve
FPL	flexor pollicis longus

FRA	flexion reflex afferent
Glut Max (or Glut)	gluteus maximus
GM	gastrocnemius medialis
GS	gastrocnemius-soleus
GTO	Golgi tendon organ
H	hamstrings
IN	interneurone
Inhib.	inhibitory
IPSP	inhibitory post-synaptic potential
ISI	inter-stimulus interval
L-Ac	L-acetylcarnitine
LC (or Loc. coer).	locus coeruleus
MC	musculo-cutaneous
MEP	motor evoked potential
MLR	medium-latency response
MN	motoneurone
MRI	magnetic resonance imaging
MT	motor threshold
MVC	maximal voluntary contraction
NA	noradrenaline
NRM	nucleus raphe magnus
PAD	primary afferent depolarisation
Per Brev	peroneus brevis
PL	peroneus longus
PN	propriospinal neurone
Ps	psoas
PSP	post-synaptic potential
PT	perception threshold
PTN	posterior tibial nerve
Q	quadriceps
RC	Renshaw cell
Rect Abd	rectus abdominis
RS or (Ret. Sp).	reticulo-spinal
Rubr. sp.	rubro-spinal
SLR	short-latency response
Sol	soleus
SPN	superficial peroneal nerve
SSEP	somatosensory evoked potential
Stim.	stimulus
TA	tibialis anterior
TFL	tensor fasciae latae
TMS	trans cranial magnetic stimulation
TN	tibial nerve
Tri	triceps brachii
Unaff.	unaffected
VI	vastus intermedius
VL	vastus lateralis
VS	vestibulo-spinal

1

General methodology

The following chapters discuss methods that allow the selective investigation of different spinal pathways. Whatever the pathway investigated, its activation produces changes in the excitability of spinal motoneurones, 'the final common path' in the motor system. A prerequisite for any investigation of changes in the spinal circuitry in human subjects is therefore to be able to assess changes in motoneurone excitability quantitatively, using valid reproducible methods. Several non-invasive methods have been developed, and these are considered in this chapter with their advantages and disadvantages. All are, of course, indirect, and valid conclusions can only be obtained if congruent results are obtained with different methods relying on different principles. All may be, and many have been, used in studies on patients, but here the methodology should be simple and rapid.

This initial chapter is technical and non-specialist readers could bypass it, referring back if they need to clarify how results were obtained or understand the advantages and limitations of a particular technique. However, the chapter is required reading for those who want to understand fully the particular techniques used for the different pathways and how to use those techniques.

The monosynaptic reflex: H reflex and tendon jerk

The 'monosynaptic reflex' forms the basis of the first technique available to investigate spinal pathways in animals and humans. The principle is based on the apparent simplicity of the monosynaptic projection of Ia afferents to homonymous motoneurones. Subsequent studies have shown that the so-called monosynaptic reflex is not as simple as was initially thought. We will consider successively: (i) the initial findings; (ii) the principles underlying the monosynaptic reflex testing method; (iii) the basic methodology of the H reflex; (iv) limitations related to mechanisms which can change the size of the reflex by altering its afferent volley; (v) 'pool problems' related to the input–output relationship within the motoneurone pool.

Initial studies

Animal studies

The monosynaptic reflex depends on the projection of muscle spindle Ia afferents to homonymous motoneurones and was used in the early 1940s as a tool for investigating changes in excitability of the motoneurone pool (Renshaw, 1940; Lloyd, 1941). When used as a test reflex, the monosynaptic reflex allows one to assess the effect on the motoneurone pool of conditioning volleys in peripheral afferents or descending tracts. During the 1940s and early 1950s this method was used to reveal important features of the input to spinal motoneurones. Intracellular recordings later allowed more detailed analysis of the synaptic input to motoneurones in animals (see Baldissera, Hultborn & Illert, 1981), but

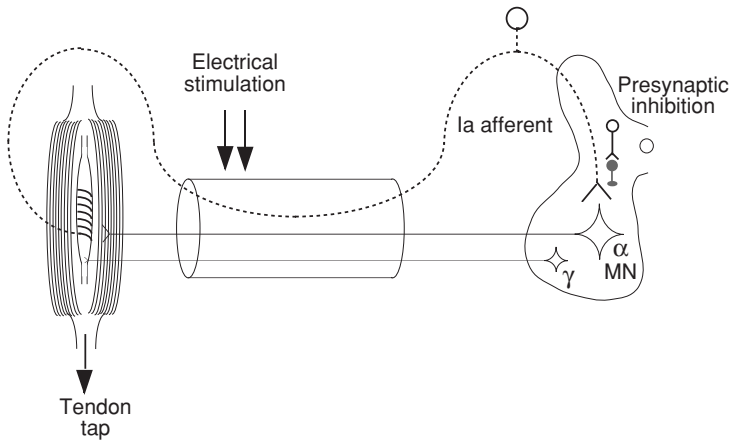


Fig. 1.1. Sketch of the pathway of the monosynaptic reflex. Ia afferents from muscle spindle primary endings (dotted line) have monosynaptic projections to α motoneurones (MNs) innervating the corresponding muscle (homonymous MNs). The H reflex is produced by electrical stimulation of Ia afferents, and bypasses muscle spindles. The tendon jerk is elicited by a tap that stretches muscle spindles and therefore also depends on the sensitivity to stretch of primary endings, a property that may be altered by the activity of γ efferents (however, see Chapter 3, pp. 117–18). The pathway of presynaptic inhibition of Ia terminals (see Chapter 8) is represented.

interestingly this greater precision did not change the main conclusions that had emerged from the experiments employing the monosynaptic reflex. This suggests that the monosynaptic reflex method produces reliable results.

Human studies

Percutaneous electrical stimulation of the posterior tibial nerve produces a synchronised response in the soleus muscle (Hoffmann, 1918, 1922). This became known as the Hoffmann reflex or H reflex (Magladery & McDougal, 1950). Magladery *et al.* (1951a) showed that the first motoneurones discharging in the H reflex do so at a latency consistent with a monosynaptic pathway (see Chapter 2). After the pioneer investigations of Paillard (1955), the H reflex, which is the equivalent of the monosynaptic reflex in animal studies, became the main tool in many motor control investigations and diagnostic studies performed on human subjects (for reviews, see Schieppati, 1987; Burke *et al.*, 1999; Pierrot-Deseilligny & Mazevet, 2000).

Underlying principles

The monosynaptic reflex arc

Pathway

Ia fibres from muscle spindle primary endings have monosynaptic excitatory projections to motoneurones innervating the muscle from which the afferents emanate (homonymous projections, Fig. 1.1). This pathway is responsible for the tendon jerk (see Chapter 2). The H reflex is produced by electrical stimulation of Ia afferents, which have a lower electrical threshold than α motor axons, particularly for stimuli of relatively long duration (see p. 6).

The H reflex, tendon jerk and short-latency spinal stretch reflex

These are all dependent on monosynaptic excitation from homonymous Ia afferents. However, the afferent volleys for these reflexes differ in many respects (cf. Chapter 3): (i) the electrically induced afferent

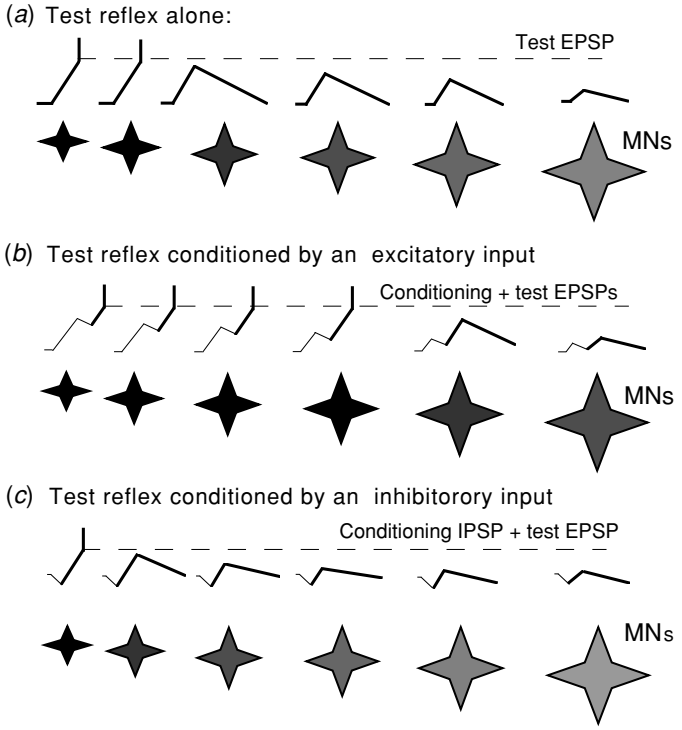


Fig. 1.2. Principles of the monosynaptic reflex. (*a*) Orderly recruitment of motoneurones (MNs) by a given Ia input: the size of the monosynaptic Ia EPSP (upper row) decreases as MN size increases (lower row). The dotted horizontal line represents the threshold for discharge of the MNs. Only the smallest MNs (black) are fired by the test Ia volley, and the excitability of subliminally excited MNs decreases from the smallest to the largest (as indicated by the decreasing tone of grey). (*b*) Facilitation by an excitatory input. There is summation of the conditioning (thin lines) and test (thick lines) EPSPs. As a result, MNs which had just failed to discharge in the control reflex are raised to firing threshold and the size of the reflex is increased. (*c*) Inhibition by an inhibitory input. There is summation of the conditioning IPSP (thin line) and of the test EPSP (the test EPSP is also reduced by changes in the membrane conductance, see p. 27). As a result, MNs which had just been recruited in the control reflex cannot be discharged, and the size of the reflex is reduced. Note that the excitability of the MNs in the subliminal fringe of excitation is also modified by the conditioning input. Modified from Pierrot-Deseilligny & Mazevet (2000), with permission.

volley for the H reflex bypasses muscle spindles and produces a single synchronous volley in group Ia and Ib afferents; (ii) the tendon tap produces a highly dynamic stretch, which activates mainly muscle spindle primary endings and elicits a prolonged discharge in Ia afferents; (iii) the short-latency Ia spinal stretch reflex is overlapped by a medium-latency response due to a group II volley from muscle spindle secondary endings (see Chapter 7).

The orderly recruitment of motoneurones in the monosynaptic reflex

Figure 1.2(*a*) shows that, in the cat, the size of the test Ia excitatory post-synaptic potential (EPSP) evoked in individual motoneurones by a given afferent volley is larger in small motoneurones supplying slow motor units than in large motoneurones supplying fast units. As a result, motoneurones are recruited in an orderly sequence by the Ia input, from the smallest

to the largest, according to Henneman's size principle (see Henneman & Mendell, 1981). Motoneurones contributing to the human H reflex are recruited in a similar orderly sequence from slow to fast motor units (Buchthal & Schmalbruch, 1970). This orderly recruitment of motoneurones is preserved when they receive a variety of excitatory and inhibitory inputs (though not all, see pp. 18–20), such that facilitation will initially affect those motoneurones that just failed to discharge in the control reflex (dark grey motoneurones in Fig. 1.2(*b*)) and inhibition will affect those that had just been recruited into the control reflex (largest black motoneurones in Fig. 1.2(*a*)).

Principles of the monosynaptic reflex method

In the control situation, the test Ia volley elicited by stimulation of constant intensity causes some motoneurones to discharge producing the control test reflex (black motoneurones in Fig. 1.2(*a*)) and creates EPSPs in other motoneurones which thereby become subliminally excited (grey motoneurones in Fig. 1.2(*a*)). If motoneurones are now facilitated by a subthreshold conditioning volley, motoneurones that had just failed to fire in the control reflex will discharge when the conditioning and test EPSPs summate (Fig. 1.2(*b*)). The size of the test reflex will increase. By contrast, if motoneurones receive conditioning inhibitory post-synaptic potentials (IPSPs), the test Ia volley will not be able to discharge the motoneurones that had been recruited last into the control reflex, and the size of the test reflex will be decreased (Fig. 1.2(*c*)). The method allows one to distinguish between: (i) conditioning stimuli without effect on the excitability of motoneurones; (ii) those which evoke only subliminal excitation of the motoneurones when applied alone; and (iii) those which inhibit motoneurones. A variant of the method is to compare the amplitude of the reflex in two situations (e.g. 'natural reciprocal inhibition' of the reflex with respect to rest during voluntary contraction of the antagonistic muscle, cf. Chapter 5).

Basic methodology

H reflexes cannot be recorded with equal ease in different motor nuclei (cf. Chapter 2). In most healthy subjects *at rest*, H reflexes can usually be recorded only from soleus (Hoffmann, 1918), quadriceps (Gassel, 1963), hamstrings (Magladery *et al.*, 1951a) and flexor carpi radialis (FCR) (Deschuytere, Rosselle & DeKeyser, 1976). However, when a weak voluntary contraction is used to potentiate the reflex by raising motoneurone excitability close to firing threshold, H reflexes can be recorded from virtually all limb muscles, if the parent nerve is accessible to electrical stimulation (cf. Burke, Adams & Skuse, 1989; Chapter 2).

General experimental arrangement

Subject's posture

The subject should be comfortably seated in an armchair with the examined limb loosely fixed in a position avoiding stretch of the test muscle (see Hugon, 1973; Burke *et al.*, 1999). Thus, the lower limb is commonly explored with the hip semi-flexed (120°), the knee slightly flexed (160°) and the ankle at 110° plantar flexion. The upper limb is explored with the shoulder in slight abduction (60°), the elbow semi-flexed (110°), and the forearm pronated and supported by the arm of the chair. In patients, recordings can be performed supine, again avoiding stretch on the test muscle.

Awareness

The state of awareness of the subject may modify the amplitude of the H reflex, often in an unpredictable way. The H reflex increases during alertness, at least when the level of attention is high (Bathien & Morin, 1972). Task demands can induce variations in the

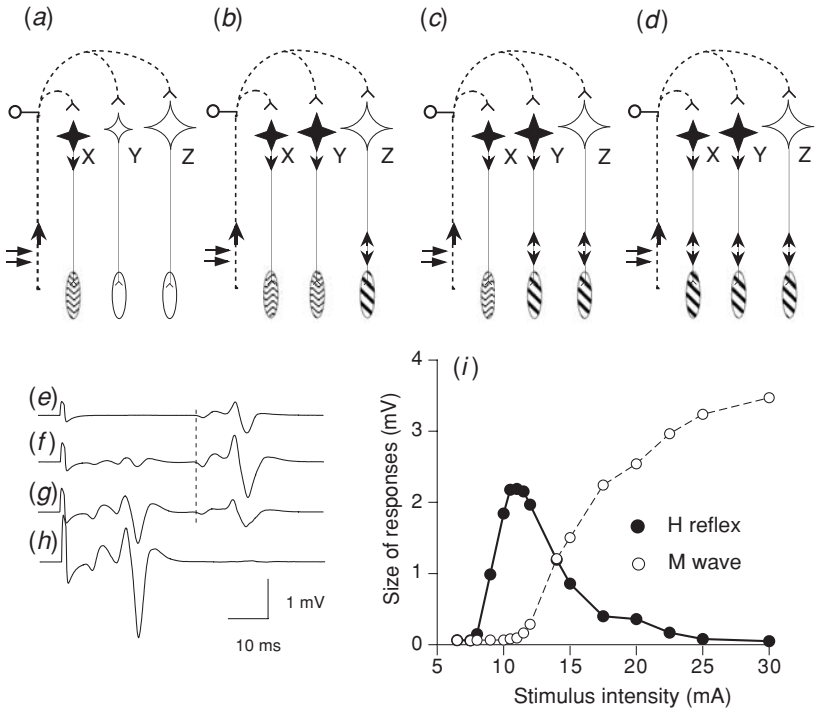


Fig. 1.3. Recruitment curve of the H and M waves in the soleus. (*a*)–(*h*) Sample EMG responses ((*e*)–(*h*)) and sketches of the corresponding volleys in Ia afferents and motor axons ((*a*)–(*d*)) when the stimulus intensity is progressively increased. MNs discharged by the Ia volley are black, muscle fibres activated by the H reflex are speckled and those activated by the M wave are hatched. (*a*) and (*e*), stimulation (9 mA) activates Ia afferents only and causes MN 'X' to fire in the H reflex. (*b*) and (*f*), stronger stimulation (12 mA) activates more Ia afferents and this causes MNs 'X' and 'Y' to fire in the H reflex, which increases in size. It also elicits a motor volley in the axon of MN 'Z' and an M wave appears in the EMG. The antidromic motor volley in MN 'Z' does not collide with the reflex response, because this MN does not contribute to the reflex. (*c*) and (*g*), even stronger stimulation (15 mA) causes MNs 'X' and 'Y' to fire in the H reflex and elicits a motor volley in the axon of MNs 'Z' and 'Y': as a result, an M wave appears in the muscle fibres innervated by MN 'Y'. The antidromic motor volley collides with and eliminates the reflex volley in the axon of MN 'Y', and the H reflex decreases. (*d*) and (*h*), yet stronger stimulation (30 mA) produces M_{max}, and the H reflex is eliminated by collision with the antidromic motor volley. The vertical dashed line in (*e*)–(*g*) indicates the latency of the H reflex. (*i*), the amplitudes of the H reflex (●) and of the M wave (○) are plotted against stimulus intensity. Modified from Pierrot-Deseilligny & Mazevet (2000), with permission.

H reflex related to the particular characteristics of the mental effort required by the task itself (Brunia, 1971). In practice, H reflexes should be recorded in a quiet room, and the influence of the mental effort involved in a difficult motor task should be taken into account. Conversely, the H reflex decreases during the early stages of sleep and is abolished during REM sleep (Hodes & Dement, 1964).

Recording the H reflex

Recording

Reflexes generally appear in the EMG as triphasic waveforms, particularly with soleus where the electrodes are not over the motor point (cf. Fig. 1.3(*e*)–(*g*)).

(i) Bipolar surface electrodes are commonly placed 1.5–2 cm apart over the corresponding muscle belly

for recording H and tendon reflexes. For the quadriceps the best place is on the anterior aspect of the thigh, 5–10 cm above the patella over the vastus intermedius. In the forearm, a selective voluntary contraction can be used as a first step to focus the reflex response on the desired motoneurone pool, because during the contraction the reflex discharge can be obtained at lower threshold in the contracting muscle.

(ii) Monopolar recordings, with an 'active' electrode over the mid-belly of the muscle and a 'remote' electrode over its tendon, have been recommended to minimise the effects of changes in geometry of the muscle during voluntary contraction (Gerilovsky, Ysvetinov & Trenkova, 1989). However, these changes are adequately taken into account if the reflex is expressed as a percentage of the maximal M wave (see p. 8) measured under the same conditions. In addition, the more distant the 'remote' electrode, the less likely is the recorded activity to come from only the muscle underlying the 'active' electrode.

Measurement

(i) Reflex latency is measured to the first deflection of the H wave from baseline, not to the first positive peak of the commonly triphasic waveform (see the vertical dashed line in Fig. 1.3(*e*)–(*g*)).

(ii) In practice it makes little difference whether the amplitude or the surface area of the reflex is assessed or whether amplitude is measured for the negative phase only or from negative peak to the following positive peak. Whichever way the H reflex is measured, the same method should be used for the maximal M wave, 'M_{max}' (see p. 8), and the amplitude of the H reflex must be expressed as a percentage of M_{max}.

Cross-talk

Pick up of the EMG potentials from an adjacent muscle can occur if there is spread of the test stimulus – electrical to another nerve (H reflex), or mechanical to another muscle (tendon jerk) (see Hutton, Roy & Edgerton, 1988). Even if this does not occur, it can still be difficult to be certain that a surface-recorded EMG potential comes exclusively from the underlying muscle rather than a synergist (e.g. responses elicited in the FCR and finger flexors after median nerve stimulation). In addition, responses evoked by a conditioning stimulus may also contaminate the test reflex, e.g. the H reflex in the antagonist FCR when studying reciprocal inhibition from wrist flexors to wrist extensors. Muscle palpation may help recognise inadvertent activation of inappropriate muscles. Another simple way of ensuring that the reflex response originates from the muscle over which it is recorded is to check that it increases during a selective voluntary contraction of that muscle.

Stimulation to elicit the H reflex

H reflexes are produced by percutaneous electrical stimulation of Ia afferents in the parent nerve. The technique is now well codified (see Hugon, 1973; Burke *et al.*, 1999).

Duration of the stimulus

The diameter of Ia afferents is slightly larger than that of α motor axons and their rheobasic threshold is lower, such that it is generally possible, particularly in soleus, to evoke an H reflex with stimuli below motor threshold (1 × MT). The strength–duration curves for motor axons and Ia afferents differ and, as a result, the optimal stimulus duration for eliciting the H reflex is long (1 ms; see Paillard, 1955; Panizza, Nilsson & Hallett, 1989). The stimulus intensity for the threshold H reflex then approaches rheobase for low-threshold Ia afferents, approximately 50% of rheobase for motor axons (Lin *et al.*, 2002).

Unipolar and bipolar stimulation

The best method for ensuring that Ia afferents are excited at lower threshold than motor axons involves placing the cathode over the nerve and the anode on the opposite side of the limb, so that current passes transversely through the nerve. The soleus and quadriceps H reflexes are commonly evoked by monopolar stimulation of the posterior tibial nerve

(cathode in the popliteal fossa, anode on the anterior aspect of the knee) and the femoral nerve (cathode in the femoral triangle, anode on the posterior aspect of the thigh), respectively. However, in areas where there are many nerves, bipolar stimulation may avoid stimulus encroachment upon other nerves: the median nerve (FCR) is so stimulated at the elbow. The same applies to the stimulation of the deep peroneal branch of the common peroneal nerve (tibialis anterior) at the fibular neck and of the sciatic nerve (hamstrings) at the posterior aspect of the thigh. It is generally stated that the cathode should then be placed over the nerve with anode distal (or lateral) to avoid the possibility of anodal block. However, there is little evidence that this is really a problem in practice.

Frequency of stimulation

Because of post-activation depression (see Chapter 2), there is reflex attenuation as stimulus rate is increased above 0.1 Hz. This attenuation requires at least 10 s to subside completely, but its effects are sufficiently small after 3–4 s to allow testing at 0.2–0.3 Hz. Use of these frequencies constitutes a compromise between reflex depression and the necessity to collect a large number of responses because of reflex variability. During a background contraction of the tested muscle, the attenuation with increasing stimulus repetition rate is reduced or even abolished (cf. Chapter 2).

Magnetic stimulation

The H reflex may also be evoked by magnetic stimulation of the parent nerve (or nerve root) and appears with the same latency as with electrical stimulation (Zhu *et al.*, 1992). One advantage of magnetic stimulation is the ease with which an H reflex can be elicited from deep nerves, such as the sciatic nerve in the thigh or the sacral nerve roots, which are difficult to access with percutaneous electrical stimulation unless needle electrodes are inserted (Abbruzzese *et al.*, 1985). However, with magnetic stimulation, the threshold for the H reflex is usually higher than that for the M wave. This difference is probably due to the extreme brevity (~0.05 ms) of the effective stimulus produced by magnetic stimulation, a stimulus duration that favours motor axons with respect to Ia afferents (Panizza *et al.*, 1992).

H and M recruitment curve

The recruitment curve

As the intensity of the electrical stimulus to the posterior tibial nerve is increased, there is initially a progressive increase in amplitude of the soleus reflex due to the stronger Ia afferent volley (Fig. 1.3(*a*), (*b*), (*e*), (*f*)). When motor threshold is reached, the short-latency direct motor response (M wave) appears in the EMG due to stimulation of motor axons ((*b*) and (*f*)). Further increases in the intensity of the test stimulus cause the M wave to increase and the H reflex to decrease ((*c*) and (*g*)). Finally, when the direct motor response is maximal, the reflex response is completely suppressed ((*d*) and (*h*)). This is because the antidromic motor volley set up in motor axons collides with and eliminates the H reflex response (Hoffmann, 1922, Fig. 1.3(*d*)). Note that, when it first appears in the EMG, the M response involves axons of the largest motoneurones (e.g. MN 'Z' in Fig. 1.3(*b*) and (*f*)), which have a high threshold for recruitment into the H reflex. Because they are not activated in the reflex, stimulation of these motor axons does not interfere with the reflex response. The variations of the H and M responses with the test stimulus intensity can be plotted as the recruitment curve of Fig. 1.3(*i*). Because of the orderly recruitment of motoneurones (see pp. 3–4), the sensitivity of the reflex to facilitation and inhibition depends on the last motoneurones recruited by the test volley (as long as the reflex is not on the descending limb of the recruitment curve, see below).

Maximal M wave (M_{max})

M_{max} is evoked by the stimulation of all motor axons and provides an estimate of the response of the entire motoneurone pool. This estimate is actually an

overestimate, because the necessarily strong stimulus will produce EMG activity in synergists in addition to the test muscle. Accordingly, the M_{max} following median nerve stimulation at the elbow comes from the FCR, finger flexors and pronator teres. Ignoring this issue, M_{max} should always be measured in the same experiment with the same recording electrode placement because: (i) comparing it with the reflex response provides an estimate of the proportion of the motoneurone pool discharging in the reflex; (ii) expressing the reflex as a percentage of M_{max} enables one to control for changes in muscle geometry due to changes in muscle length or contraction; (iii) expressing the test reflex as a percentage of M_{max} allows the investigator to be sure that the test reflex remains within the 'linear' range of the input/output relationship for the motoneurone pool (i.e. between ~10 and 60% of M_{max} for the soleus H reflex, see pp. 16–18).

The test reflex should not be on the descending limb of the recruitment curve

This is because the component of the H reflex seen in the EMG is generated by low-threshold motoneurones, which are insensitive to excitation or inhibition. Small motoneurones innervating slow motor units are first recruited in the H reflex (see pp. 3–4), whereas electrical stimulation will first activate motor axons of large diameter from high-threshold motoneurones. As a result, on the descending limb of the recruitment curve, the reflex response seen in the EMG will be produced by small motoneurones, in which the collision in motor axons has not taken place. The reflex response in the fastest motor units of the H reflex, i.e. those that were last recruited into the reflex and are thus sensitive to excitation and inhibition, will be eliminated by collision with the antidromic motor volley (Fig. 1.3(*c*) and (*g*)) (see Pierrot-Deseilligny & Mazevet, 2000).

Monitoring the stability of the stimulation conditions

If the H reflex is performed during a manoeuvre that can alter the stimulating conditions (e.g. muscle contraction, stance or gait), it is necessary to ensure that changes in the test H reflex are not due to a change in the position of the stimulating electrode. The reproducibility of a M wave can then be used to monitor the stability of the stimulation. To that end, stimulation should be adjusted to produce a small M wave in addition to the H reflex. If there is need for a test response without a M wave, the stability of stimulation can be monitored by alternating the test stimulus with a stimulus evoking a M wave through the same electrode. This procedure raises questions about the acceptable range of variability of the M wave in such studies. Some authors have used a range of $\pm 10\%$ of M_{max}, but this is a large range when compared to the changes expected in the H reflex, and changes not exceeding $\pm 10\%$ of the recorded M wave, not $\pm 10\%$ of M_{max}, are recommended. It should be realised that, during experiments involving a voluntary or postural contraction of the tested muscle, there will be changes in axonal excitability unrelated to stability of the stimulating conditions (Vagg *et al.*, 1998), and there will inevitably be some variability in the M wave from trial to trial.

Recruitment curves in other muscles

The recruitment curves for the quadriceps and FCR H reflexes are similar. However, the threshold of the M and H responses of FCR and quadriceps are generally closer than in soleus.

Tendon jerk

In proximal muscles (e.g. biceps and triceps brachii), the H reflex is difficult to record at rest without the M wave, and it then appears merged into the end of the M wave. For routine testing, it may be more convenient to test the excitability of these motoneurone pools using tendon reflexes. An electromagnetic hammer (such as a Brüel and Kjaer shaker, Copenhagen, Denmark) will produce reproducible transient tendon percussion. In healthy subjects at rest, a tendon jerk reflex can be elicited in the soleus, quadriceps, biceps femoris, semitendinosus, biceps and triceps brachii, FCR, extensor carpi radialis (ECR) and the masseter. Use of the tendon jerk introduces two complications.

Delay due to the tendon tap

The tendon tap introduces a delay, and in the soleus, the afferent volley for the tendon jerk will reach motoneurones ~5 ms later than the electrically induced volley producing the H reflex (cf. Chapter 2). An estimate of the *central* delay of the effect of a conditioning volley on a test tendon jerk may be obtained by comparing the first interstimulus interval (ISI) at which this effect occurs to the first ISI at which a heteronymous monosynaptic Ia volley delivered to the same nerve facilitates the tested motoneurones (see Mazevet & Pierrot-Deseilligny, 1994). An example would be the group Ia projection from median-innervated forearm muscles to biceps and triceps motoneurones.

Fusimotor drive

The amplitude of the reflex response produced by tendon percussion may depend on the level of γ drive directed to muscle spindle primary endings of the tested muscle (see Fig. 1.1). Accordingly, it has been argued that differences in the behaviour of H and tendon jerk reflexes reflect the involvement of γ drive in the tendon jerk (e.g. see Paillard, 1955). This belief has been called into question because H and tendon jerk reflexes differ in a number of other respects, as discussed in detail in Chapter 3. Of greater importance could well be the effects on the spindle response to percussion of the thixotropic properties of intrafusal fibres (see Chapter 3).

Random alternation of control and conditioned reflexes

In most investigations, the monosynaptic reflex is used as a test reflex to assess the effect of conditioning volleys on the motoneurone pool. The size of the reflex is compared in the absence (control reflex) and in the presence (conditioned reflex) of the conditioning volley. Control and conditioned reflexes should be randomly alternated, because: (i) this avoids the possibility of the subject voluntarily or involuntarily predicting the reflex sequence; and (ii) regular alternation produces erroneously large results (Fournier, Katz & Pierrot-Deseilligny, 1984), possibly due to post-activation depression (see Pierrot-Deseilligny & Mazevet, 2000).

Estimate of the central delay of a conditioning effect. Time resolution of the method

It is essential to estimate the central delay of an effect in order to characterise the neural pathway activated by a conditioning stimulus as mono-, di-, or polysynaptic. This can be done by comparing the earliest conditioning-test interval at which the test reflex is modified with the interval estimated for the simultaneous arrival of the conditioning and test volleys at spinal level. The greater the difference between these two values the longer the intraspinal circuit, and this could be because more synapses are involved. It should be noted that the H reflex method underestimates the true central delay. For example, despite the extra 0.8 ms due to the interneurone interposed in the pathway of disynaptic reciprocal Ia inhibition, the earliest conditioning-test interval with inhibition corresponds to the simultaneous arrival of the two volleys at spinal level (Chapter 5). This is due to two reasons (Fig. 1.4).

PSPs in individual motoneurones

The rise time of the EPSP is sufficiently long that the discharge of the last recruited motoneurones evoked by the monosynaptic input will not occur before the arrival of a disynaptic IPSP. This is so even though the synaptic delay at the interneurone delays the onset of the IPSP by 0.5–1.0 ms relative to the beginning of the monosynaptic EPSP (see Matthews, 1972, and Fig. 1.4(*a*)). In addition, an EPSP elicited by a conditioning volley entering the spinal cord after the test volley may summate with the decay phase of the test Ia EPSP and cause the motoneurone to discharge at a 'too early' ISI.

Motoneurones do not discharge at the same time in the test reflex

Even in the cat there is 0.5 ms between the firing of the first and last recruited motoneurones contributing to

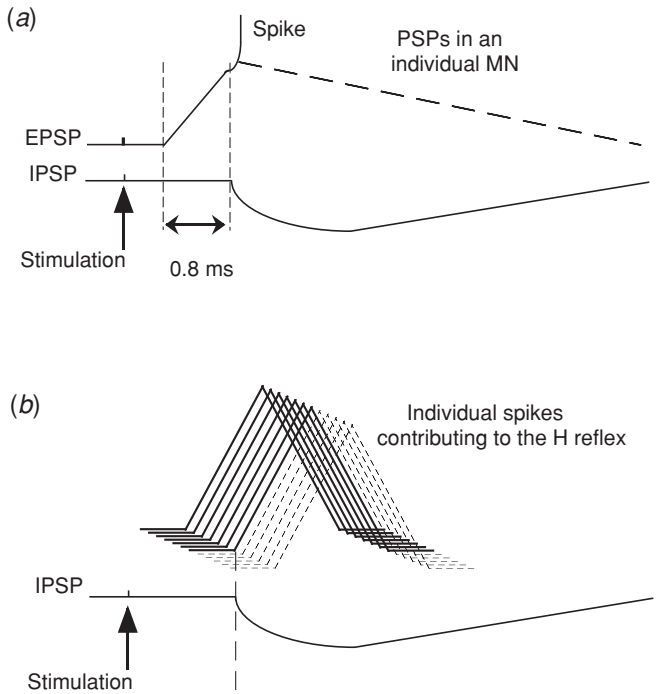


Fig. 1.4. A disynaptic IPSP can inhibit the monosynaptic reflex. (*a*) Post-synaptic (PSP) potentials in an individual motoneurone (MN): when volleys eliciting a monosynaptic Ia EPSP and a disynaptic IPSP enter the spinal cord simultaneously, the rise time of the EPSP in individual MNs allows the spike in the last recruited MNs to be inhibited by the IPSP, even though the latter does not begin until 0.5–1.0 ms after the beginning of the EPSP. (*b*) MNs contributing to the H reflex do not discharge simultaneously in the test reflex. Thus, a disynaptic IPSP elicited by a conditioning volley entering the spinal cord at the same time as the test monosynaptic Ia volley may inhibit the last spikes (thin interrupted lines) contributing to the monosynaptic reflex discharge, while the first spikes (thick continuous lines) are not modified. Adapted from Matthews (1972) (*a*), and Araki, Eccles & Ito (1960) (*b*), with permission.

the monosynaptic reflex (Araki, Eccles & Ito, 1960). In human subjects, where the afferent pathway is longer and the conduction velocity of Ia afferents slower, this interval has been estimated at 1.5 ms for the quadriceps H reflex (Fournier *et al.*, 1986) and ~2 ms for the soleus H reflex (Burke, Gandevia & McKeon, 1984). There are differences in the rise-times of mechanically and electrically evoked EPSPs (~10 ms for tendon percussion; ~2 ms for the electrically evoked volley), but this is not obvious in the reflex EMG potentials because the axons of the last recruited motoneurones have a more rapid conduction velocity than those first recruited. Figure 1.4(*b*) shows that, because of the desynchronisation at spinal level, the last individual spikes contributing to the monosynaptic test reflex discharge can be inhibited by a disynaptic IPSP elicited by a conditioning volley entering the spinal cord at the same time as the monosynaptic test volley.

The recovery cycle of the H reflex

The recovery cycle of the H reflex investigates the time course of the changes in the H reflex after a conditioning reflex for conditioning-test intervals up to 1–2 s. Such studies were in vogue in the 1950–1960s (Magladery *et al.*, 1951b, 1952; Paillard, 1955). However, the recovery cycle is no longer employed,

because it results from too many phenomena to be of practical use. Factors that could alter the test reflex include changes in excitability of Ia afferents (see below), post-activation depression (cf. pp. 13–14), presynaptic inhibition of Ia terminals activated by the conditioning volley (cf. Chapter 8), afterhyperpolarisation and recurrent inhibition of motoneurones (cf. Chapter 4), muscle spindle receptor unloading by the conditioning twitch (cf. Chapter 3), Golgi tendon organ activation by the conditioning twitch (cf. Chapter 6), and effects mediated by long loops (Táboríková & Sax, 1969).

When the conditioning and test volleys involve the same population of afferents, the conditioning discharge will change the excitability of the stimulated afferents for ~100 ms, and this is an additional complicating factor. Figure 1.5 shows the recovery cycle of the H reflex after a conditioning volley that was subthreshold for the H reflex even during contraction, comparing the results obtained with 'threshold tracking' ((*a*), see below) with those of conventional 'amplitude tracking' (*b*). There is an initial period of decreased excitability, corresponding to 'refractoriness', followed by a period peaking at 7–8 ms corresponding to 'supernormality' and a final phase corresponding to 'late subnormality'. These changes in excitability are those of the stimulated peripheral nerve axons (Chan *et al.*, 2002), and this finding indicates that two identical stimuli delivered to a nerve will not excite the same population of afferent axons when the interval between them is <100 ms.

Amplitude and threshold tracking of the compound H reflex

With threshold tracking, test stimuli are varied automatically by computer, much as in conventional threshold tracking (Bostock, Cikurel & Burke, 1998), to maintain a constant compound H reflex, the current being then referred to as the threshold for the H reflex. Reflex facilitation will produce a decrease in the required current, and reflex inhibition will produce an increase (cf. Chan *et al.*, 2002). This is illustrated in Fig. 1.5 where the curves obtained with threshold (*a*) and amplitude (*b*) tracking show reciprocal changes. A similar principle has been exploited by Shindo *et al.* (1994) in studies on the unitary H reflex (see pp. 37–9).

Advantages with threshold tracking

There are advantages with threshold tracking over amplitude tracking for H reflex studies.

(i) The results are less variable (cf. Fig. 1.5, ●).

(ii) The recorded response involves a constant population of motoneurones, and clamping the reflex response to a fixed size avoids the problem of size-related changes in test reflex sensitivity (see pp. 16–18).

(iii) The dynamic range of threshold tracking is wide, enabling threshold changes of 200% or more to be tracked. In contrast, amplitude tracking suffers from 'floor' and 'ceiling' effects: there is a limited range within which the size of test response can reflect changes in excitability and, once the response reaches maximum or is reduced to zero, further increases or decreases in excitability can no longer be reflected in the size of the test response.

Disadvantages with threshold tracking

(i) In order to maintain a constant reflex response, the intensity of the afferent volley must be altered, and this could introduce inaccuracies, because the reflex size also depends on mechanisms acting on the afferent volley (cf. pp. 12–16).

(ii) When excitability changes, there is a delay with threshold tracking before the new threshold is reached as the computer tracks to it. By contrast, with amplitude tracking, changes in reflex excitability produce instantaneous changes in the reflex response.

Limitations related to mechanisms acting on the afferent volley of the reflex

The pathway of the monosynaptic reflex is not as simple as it at first seems. Reflex size also depends on mechanisms acting on the afferent volley. As a result, many mechanisms other than changes in excitability of the motoneurone pool can alter the size of the reflex.

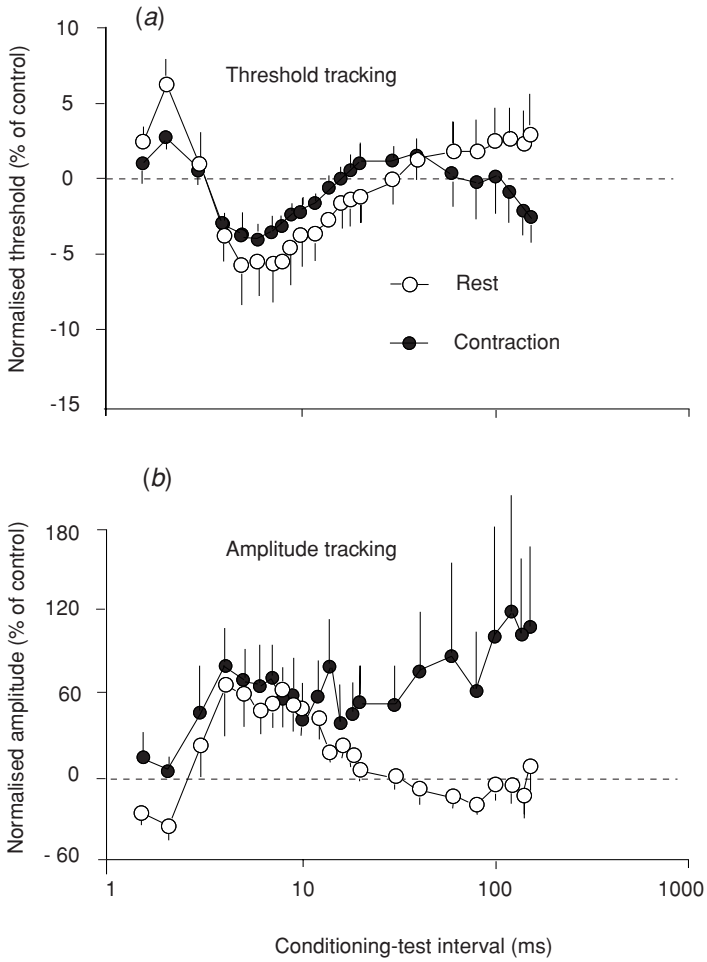


Fig. 1.5. The recovery cycle of the H reflex following a single subthreshold conditioning stimulus. The soleus H reflex was conditioned by a weak stimulus to the posterior tibial nerve (65% of the unconditioned test stimulus, subthreshold for the H reflex during contraction). Data representing the deviation from the unconditioned value (horizontal dashed line), using threshold tracking (*a*) and amplitude tracking (*b*) at rest (○) and during tonic soleus voluntary contractions (●) are plotted against the conditioning-test interval. In (*a*) the intensity of the test stimulus was altered to keep the test H reflex constant: an increase in excitability would therefore require less current. In (*b*), the test stimulus was constant: an increase in excitability would therefore increase the amplitude of the test H reflex. Note the logarithmic scale for the *x*-axis. Mean data ± SEM for six subjects. Adapted from Chan *et al.* (2002), with permission.

Alterations in the excitability of Ia afferents

Repetitive activation of cutaneous afferents (Kiernan *et al.*, 1997) and natural activity of motor axons (Vagg *et al.*, 1998) produce axonal hyperpolarization and thereby a significant reduction in the excitability of the active axons. The extent of hyperpolarization depends on the impulse load, but can be prominent. For example, with motor axons, contractions lasting only 15 s increase threshold by 10–20%, i.e. after the contraction, the stimulus had to be increased by 10–20% to activate the same number of axons

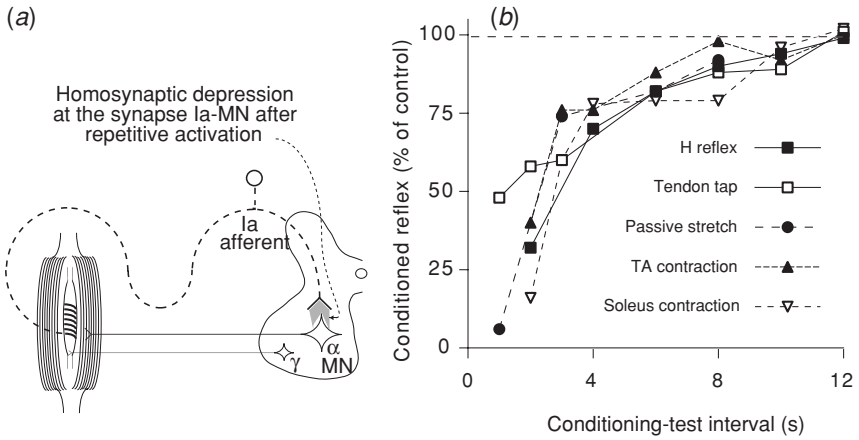


Fig. 1.6. Post-activation depression produced by different ways of activating the Ia afferent-MN synapse repetitively. (*A*) Sketch of the pathway (the grey area indicates the Ia afferent-motoneurone [MN] synapse). (*b*) The recovery of the soleus H reflex (expressed as a percentage of its control value) after various conditioning stimuli, plotted against the conditioning-test interval: preceding H reflex (■), subliminal tendon tap (□), passive dorsiflexion of the ankle (●), voluntary contraction of the tibialis anterior (▲) or of the soleus (▽). Modified from Crone & Nielsen (1989) and Hultborn *et al.* (1996), with permission.

(Vagg *et al.*, 1998). This issue is probably important for group Ia afferents and the H reflex, because the excitability of the afferents will decrease during a voluntary contraction if there is a fusimotor-driven increase in discharge from the active muscle (cf. Chapter 3). As a result, the reflex response to a fixed stimulus could change, independently of the other contraction-related changes (presynaptic inhibition of Ia afferents, post-activation depression, motoneurone excitability). Additionally, the contraction will activate Ib afferents and thereby reduce their excitability to electrical stimulation. This would reduce the number of Ib afferents in the afferent volley and the extent to which they limit the size of the H reflex (see pp. 14–16).

Presynaptic inhibition of Ia terminals

Ia terminals mediating the afferent volley of the monosynaptic reflex are subjected to presynaptic inhibition accompanied by primary afferent depolarisation (PAD). Changes in presynaptic inhibition of Ia terminals can cause major changes in the amplitude of the H reflex, and the possibility that a change in presynaptic inhibition accounts for a change in the amplitude of the H reflex must therefore always be considered. Several methods have been developed to assess presynaptic inhibition of Ia terminals in human subjects, as described in detail in Chapter 8.

Post-activation depression

A different presynaptic mechanism limiting monosynaptic reflexes is post-activation depression at the Ia fibre-motoneurone synapse, probably due to reduced transmitter release from active Ia afferents, a phenomenon which is described in detail in Chapter 2 (pp. 96–100). Post-activation depression occurs when (and only when) the conditioning stimulus or manoeuvre activates the very afferents responsible for the test response. H reflex depression has been reported to occur following a preceding H reflex (Magladery & McDougal, 1950), a subliminal tendon tap (Katz *et al.*, 1977), passive dorsiflexion of the ankle (Hultborn *et al.*, 1996), and voluntary contraction of soleus or stretch of soleus produced by contraction of tibialis anterior (Crone & Nielsen, 1989; see also Wood, Gregory & Proske, 1996). The effects of this phenomenon can be profound, as illustrated in Fig. 1.6, showing the time course

of the recovery of the soleus H reflex after these manoeuvres. In all cases, there was dramatic reflex depression at short intervals (1–2 s), with gradual recovery over 10 s. The depressive effects of the stimulus rate on reflex size are generally taken into consideration in reflex studies, but the same cannot be said for the post-activation depression occurring under other circumstances. It is likely that misinterpretations have arisen because this phenomenon was neglected in studies comparing changes in the test reflex during or after a voluntary contraction. In addition, when the effects of a conditioning volley are compared at rest and during contraction, *post-activation depression may also alter the transmission through the conditioning pathway* (e.g. see Chapter 5, p. 221), though not all afferent inputs are similarly affected (see Lamy *et al.*, 2005; Chapter 7, p. 310).

Contribution of oligosynaptic pathways to the H reflex

Limitation of the size of the H reflex

In soleus, when the intensity of the test stimulus is increased, the amplitude of the H reflex commonly reaches its peak before the antidromic volley set up in motor axons collides with and annihilates the reflex response (see p. 7). Thus, there is a limitation to the size of the H reflex independent of the collision with the antidromic volley in motor axons. Táboríková & Sax (1968) demonstrated that, in normal subjects, the percentage of soleus motoneurones activated in the H reflex by maximal stimulation of Ia afferents ranges from 24 to 100, usually ∼50%. In the homogeneous soleus, this implies the existence of factors limiting the size of the reflex.

Curtailment of the compound EPSP by an oligosynaptic IPSP

The first motoneurones discharging in the H reflex do so at a latency consistent with a monosynaptic pathway (Magladery *et al.*, 1951a). However, based on estimates from post-stimulus time histograms (PSTHs) of the discharge of single motor units, it has been argued that the duration of the compound group I EPSP underlying the H reflex is so short (some 1–2 ms) that the monosynaptic Ia component of the EPSP must be curtailed by oligosynaptic inhibition, and that this would help limit the size of the H reflex (Burke, Gandevia & McKeon, 1984). Transmission in two disynaptic inhibitory pathways could truncate the monosynaptic Ia excitation: (i) Ib inhibitory interneurones activated by the group I test volley produce autogenetic inhibition with an onset ∼0.7 ms after the onset of the facilitation due to the group Ia monosynaptic EPSP in motoneurones (Pierrot-Deseilligny *et al.*, 1981; Chapter 6, pp. 253–5); (ii) Renshaw cells are activated by the reflex discharge of low-threshold motoneurones (Chapter 4, p. 159) and could produce recurrent inhibition that would prevent the discharge of higher-threshold motoneurones.

Disynaptic limitation of the group Ia excitation

Recent experimental evidence for a disynaptic limitation of the group Ia excitation that is the basis of the H reflex has been provided for the quadriceps (Marchand-Pauvert *et al.*, 2002). The evidence is as follows. At rest and during weak contractions of quadriceps stimulation of the deep peroneal nerve produces a late facilitation of the quadriceps H reflex with a central delay of 6–12 ms (Fig. 1.12(*c*), Δ), but this is suppressed during a contraction of 10–20% maximum voluntary contraction (MVC) (Fig. 1.12(*c*), ●, and thick line in Fig. 1.7(*b*)). However, the corresponding facilitation of the on-going EMG is not suppressed (Fig. 1.12(*b*), ●). Such a discrepancy raises the possibility of an inhibitory mechanism gating the afferent volley of the test reflex, the nature of which was clarified in experiments involving PSTHs of single motor units in quadriceps (Fig. 1.7(*c*)–(*f*)). Panel (*c*) shows the peak of homonymous group I excitation evoked by femoral stimulation, panel (*d*) the weak facilitation at around 27 ms elicited by separate stimulation of the deep peroneal nerve, and (*e*) the significant reduction of the femoral excitation on combined stimulation. Suppression on combined stimulation when the stimuli by themselves produce

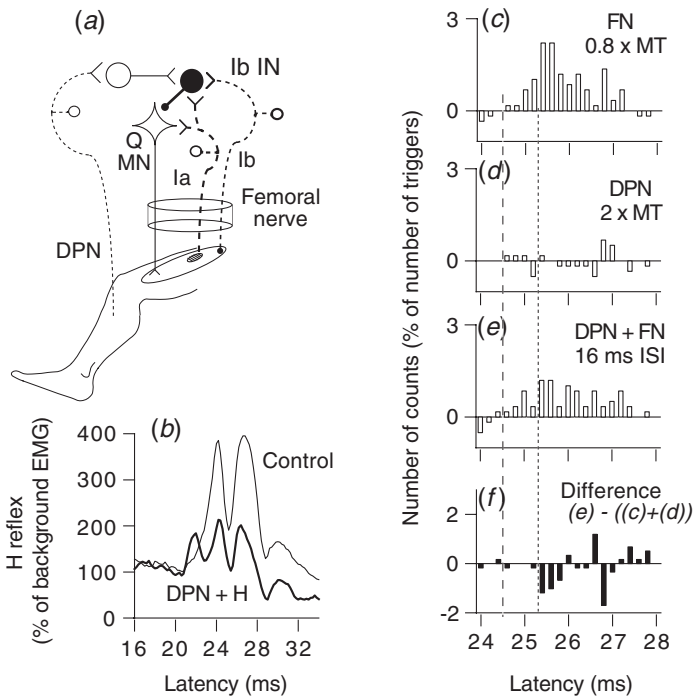


Fig. 1.7. Evidence for suppression of the H reflex by disynaptic autogenetic inhibition from afferents in the test volley. (*a*) Sketch of the presumed pathway: when facilitated by the deep peroneal nerve (DPN) volley, 'Ib' inhibitory interneurones (IN) co-activated by Ia and Ib afferents in the femoral nerve (FN) test volley truncate the monosynaptic EPSP in the last recruited quadriceps (Q) motoneurones (MN). (*b*) The rectified and averaged Q H reflex (20 sweeps, 5 kHz sampling rate) during a contraction (10% of MVC), showing control responses (thin line) and conditioned responses (thick line, stimulation of the DPN at 2 × MT, 13 ms ISI). (*c*)–(*e*) PSTHs of the discharge of a single unit in vastus lateralis (after subtraction of the background firing, 0.2 ms bin width, quadriceps contraction 20% MVC). (*c*) Stimulation of FN by itself (0.8 × MT); (*d*) the DPN by itself (2 × MT), and (*e*) both nerves, the DPN preceding the FN stimulus by 16 ms. (*f*) The suppression of the FN group I excitation, calculated as (*e*) – ((*c*) + (*d*)). The number of counts in each bin is plotted against the latency after FN stimulation (even in (*d*) where only DPN stimulation was given). Note the lack of suppression in the initial bins of the femoral group I excitation (the dashed and dotted vertical lines highlight the onset of the femoral peak at 24.6 ms and the suppression at 25.4 ms, respectively). Adapted from Marchand-Pauvert *et al.* (2002), with permission.

facilitation reflects convergence (see p. 47) of the two volleys onto common inhibitory interneurones (as in the wiring diagram in Fig. 1.7(*a*)). The suppression spared the first 0.8 ms of the femoral group I excitation. This is consistent with disynaptic inhibition elicited by the test group I volley. Because of the synaptic delay at the interneurone, the inhibitory input would reach the motoneurone after the direct monosynaptic Ia input, and there should be no change in the bins of the histogram appropriate for this interneuronal delay. Thus, post-synaptic inhibition due to afferents in the test volley should not affect the onset of the femoral excitation, and initial sparing should be demonstrable, as it was.

Can the results obtained for the quadriceps be generalised?

So far, evidence for a limitation of the H reflex by disynaptic inhibition elicited by the test group I volley

has only been demonstrated for the quadriceps. However, the limitation should be more pronounced for the soleus than for the quadriceps, because the degree of desynchronisation of the reflex discharge is more marked in the former (see p. 10). This presumably reflects the longer afferent pathway of the soleus H reflex, which would allow greater dispersion of the afferent volley and thereby a greater influence on the reflex discharge from Ib afferents activated by the test stimulus. It is therefore probable that soleus H reflexes are also truncated by disynaptic inhibitory activity. This limitation could contribute to the absence of H reflex at rest in muscles such as tibialis anterior and extensor carpi radialis (see Chapter 2, p. 81).

Recurrent inhibition

There is so far no experimental evidence for recurrent inhibition elicited by the discharge of low-threshold motoneurones preventing the discharge of higher-threshold motoneurones, and it is probable that the peak of recurrent inhibition occurs too late to curtail significantly the test H reflex (see Chapter 4).

Consequences for the use of the H reflex

The sensitivity of the H reflex to di- or oligosynaptic inhibition by afferents in the test volley limits the value of H reflex studies. Motoneurones recruited last into the reflex will be most dependent on pathways with interposed interneurones, and the changes in the reflex, e.g. during movement, are largely determined by the recruitment of these motoneurones. It is possible to test for an oligosynaptic limitation of the H reflex by the test volley by comparing systematically the effects of a given input on the H reflex and on the peak of monosynaptic group I excitation in the PSTH of single units of the same muscle. Only those changes affecting the entire excitatory peak and, in particular, the initial 0.5–1.0 ms can be considered to have affected the monosynaptic pathway. This is because the onset of the test excitation, whether in PSTHs or in the H reflex itself, should be free from contamination by non-monosynaptic inputs from afferents in the test volley (Marchand-Pauvert *et al.*, 2002).

'Pool problems' related to the input–output relationship in the motoneurone pool

Size-related sensitivity of the test reflex (non-linearity within the motoneurone pool)

The effects of a constant conditioning volley are different when the unconditioned test reflexes are of different size. This is due in part to the method of normalising the results but, in addition, there is a different sensitivity of reflexes of different size to facilitation and inhibition, reflecting a non-linear input–output relationship within the motoneurone pool. This property of the motoneurone pool has been implied by several authors (e.g. Hunt, 1955; Meinck, 1980). The question was extensively investigated in human subjects and in the cat by Crone *et al.* (1990), using conditioning stimuli that produce excitation or inhibition at pre- and post-synaptic levels.

The distorting effects of normalisation

These are illustrated in Fig. 1.8(*a*). The soleus H reflex was conditioned by a heteronymous monosynaptic Ia volley from the femoral nerve. When expressed as a percentage of the control reflex, as is the case in most studies using the H reflex, the degree of facilitation is enormous with the smallest test H reflexes, and decreases the larger the test reflex. However, this is essentially a numerical artefact produced by normalisation of a fixed degree of facilitation to an increasing control reflex.

Sensitivity of reflexes of different size to facilitation and inhibition

The 'absolute' increase, expressed as a percentage of M_{max}, is a more suitable expression of the change in reflex size. Fig. 1.8(*b*) shows the data from Fig. 1.8(*a*). The amount of facilitation initially increased as the amplitude of the control H reflex increased, reached a maximum when the control reflex was around 30% of M_{max}, and then decreased with further increases in the amplitude of the control H reflex. The finite size of the soleus motor pool must

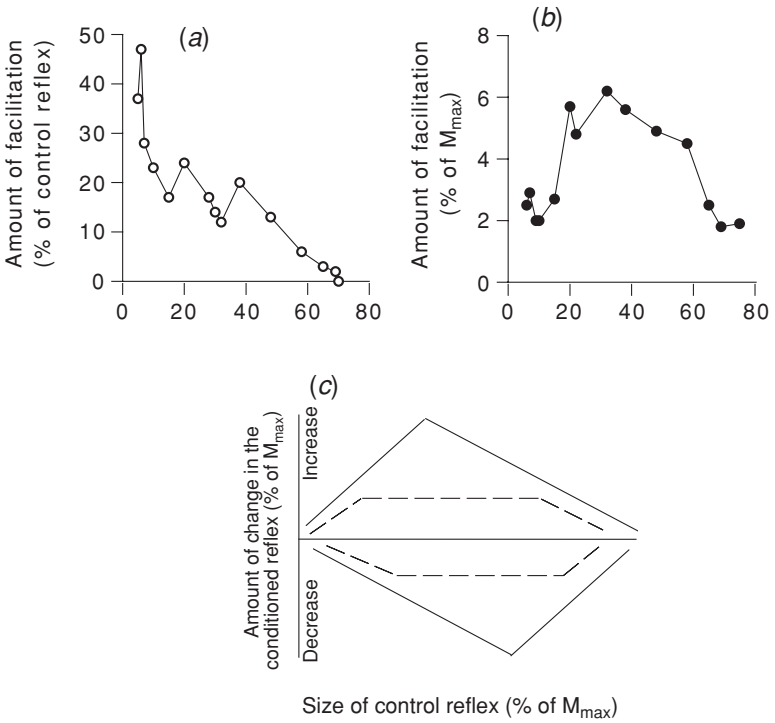


Fig. 1.8. Non-linearity within the MN pool. (*a*), (*b*) The amount of heteronymous monosynaptic Ia facilitation of the soleus H reflex (conditioned *minus* control reflex) elicited by a conditioning stimulus to the femoral nerve (1.1 × MT, 4.8 ms conditioning-test interval) expressed as a percentage of the control reflex size (*a*) or of M_{max} (*b*) and plotted against the control reflex size (in percentage of M_{max}). (*c*) Summarising diagram showing the sensitivity of monosynaptic reflexes to facilitation (upper part) or inhibition (lower part). Strong conditioning inputs, continuous lines; weak conditioning inputs, dashed lines. Modified from Crone *et al.* (1990), with permission.

put a limit to the amount of facilitation in the case of very large test H reflexes. It turned out, however, that the amount of facilitation caused by the conditioning stimulus decreased considerably before the facilitated H reflexes approached M_{max}. In human subjects and in the cat, monosynaptic reflexes of small and large size have a lower sensitivity than reflexes of intermediate size for various facilitatory and inhibitory inputs. This is summarised in the sketch in Fig. 1.8(*c*) where the amount of facilitation or of inhibition elicited by a constant conditioning input, facilitatory (upper part) or inhibitory (lower part), is plotted against the size of the control reflex. When the conditioning input is strong (continuous line), the number of additionally recruited (facilitation) or derecruited (inhibition) motoneurones first increases with increasing size of the control test reflex, and then decreases. When the effect of the conditioning input is modest (dashed lines), there is a 'plateau' region between the phases of increase and decrease.

Input–output relationship within the motoneurone pool

In the cat, the relationship between the Ia input and the reflex discharge is sigmoid (Hunt, 1955). The first part of the recruitment curve of the H reflex also conforms to a sigmoid relationship (see Fig. 1.3(*i*)). The mechanism behind this characteristic pattern

is probably a combination of the intrinsic properties of the individual motoneurones and the excitability profile of the motor pool (see Crone *et al.*, 1990), as well as the properties of the afferent volley. Whatever its mechanism, the relationship illustrating the changes in the amount of facilitation (or inhibition) with increasing control reflex size is the first derivative of the sigmoidal input–output relationship, and should be bell-shaped: 'however, if small conditioning stimuli are used the differential function will have a relatively flat peak, which could be interpreted as a plateau when dealing with inherently variable experimental data' (Capaday, 1997).

Consequences when using the monosynaptic reflex

The changes in sensitivity of the monosynaptic reflex can be large enough to lead to misinterpretations of results obtained using H reflexes. This factor must be taken into account: (i) when comparing the effects of a conditioning input under two situations (e.g. rest and contraction) which alter the size of the unconditioned H reflex; (ii) when using the spatial facilitation technique (see p. 48); (iii) when assessing the effects of conditioning stimulation on the H reflex in different subjects (a factor that has often been neglected when comparing normal and spastic subjects).

(a) When the conditioning effect is modest, the sensitivity of reflexes of medium size does not change significantly with the control reflex size as long as it remains in the 'plateau' region in Fig. 1.8(*c*). The intensity of the test stimulus should be chosen so that the control reflex remains within this range in the two situations which are compared. In practice, this implies using a control H reflex of at least 10% of M_{max} in soleus (Crone *et al.*, 1990) and quadriceps (Forget *et al.*, 1989), and 5% in FCR (Malmgren & Pierrot-Deseilligny, 1988). However, this does not guarantee a reliable comparison, because reflex responses of equal size may lie on input–output curves of different steepness (see pp. 18–20). A limitation of this strategy is that it is possible to study the behaviour of only a sample of motoneurones in the pool. This would represent no real limitation if all motoneurones in the pool behaved in a homogeneous way, but this is not the case (see pp. 18–20).

(b) When the sizes of the control reflexes evoked by the same test stimulus differ greatly in the two situations (e.g. the enormous facilitation of the H reflex at the onset of a contraction of the tested muscle), the above strategy is not feasible, and an alternative must be employed. 'Adjusting' the test stimulus intensity to keep the size of the unconditioned reflex constant may obviate the problem. However, changing the intensity of the test stimulus creates its own problem: it alters the afferent volley responsible for the reflex and, as seen above, this could introduce inaccuracies, because the reflex size also depends on mechanisms acting on the afferent volley (see pp. 12–16).

Conclusions

Because of the non-linearity of the input–output relationship of the motoneurone pool, and of the possible changes in the recruitment gain of the reflex (see below), there is no absolutely reliable way of comparing results obtained with the H reflex under all circumstances. The results of reflex studies should therefore be confirmed in single unit recordings (pp. 28–39).

Changes in the recruitment gain of the reflex

Definition

Changes in the size of the test reflex evoked by a conditioning input are commonly used to estimate the mean input to different motoneurones in the pool. However, problems can occur if the distribution of the conditioning input within the motoneurone pool differs from that of the monosynaptic Ia excitatory input, i.e. the input does not affect small motoneurones preferentially. Such a skewed distribution of conditioning inputs may produce a change in the

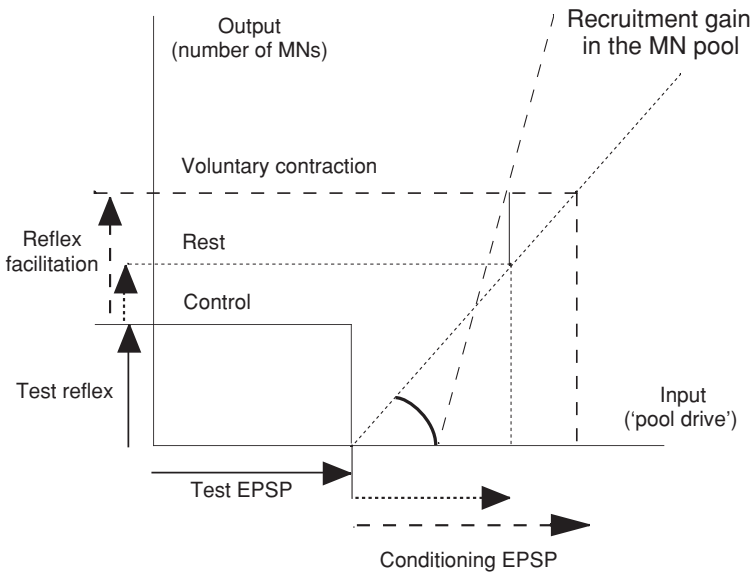


Fig. 1.9. Recruitment gain in the motoneurone pool. The input–output relationship for the soleus motoneurone pool is represented at rest (dotted oblique line) and during a possible change in the 'recruitment gain' occurring during contraction (dashed oblique line). Inputs: (i) the unconditioned test EPSP (continuous horizontal arrow), (ii) the conditioning femoral EPSP at rest (dotted horizontal arrow) and at the onset of soleus voluntary contraction (dashed horizontal arrow), and the 'recruitment gain' of the reflex (= the slope of the relationship). Output (i.e. the number of motoneurones recruited in the reflex) is represented by vertical arrows: unconditioned test reflex (continuous line; the intensity of stimulation having been 'adjusted' to produce control reflexes of the same size at rest and during contraction), and the amount of femoral-induced facilitation of the reflex at rest (dotted line) and at the onset of soleus voluntary contraction (dashed line). Modified from Pierrot-Deseilligny & Mazevet (2000), with permission.

'recruitment gain' of the reflex (Kernell & Hultborn, 1990).

Change in the slope of the input–output relationship

Figure 1.9 presents the input–output relationships for the soleus motoneurone pool under two situations, rest (dotted lines) and voluntary contraction (dashed lines), for a single example: the enhanced femoral-induced facilitation of the soleus H reflex observed at the onset of a soleus contraction. The femoral facilitation represents a heteronymous monosynaptic Ia projection, and its enhancement is due to decreased presynaptic inhibition of Ia terminals (see Chapter 8, p. 355). The input to the motoneurone pool (the 'pool drive') includes three factors: (a) the Ia EPSP evoked by the test volley; (b) the conditioning effect due to the femoral monosynaptic Ia projection; (c) the 'recruitment gain' of the reflex, i.e. the slope of the input–output relationship (which is assumed to be linear for this example). The vertical arrows on the left show the size of (i) the unconditioned test reflex, adjusted so that its size remains constant, (ii) the reflex facilitation produced by the conditioning femoral EPSP at rest, and (iii) the increased femoral facilitation of the reflex at the onset of contraction. If the slope of the input–output relationship were not modified during contraction, the increased femoral facilitation of the reflex at the onset of contraction would reflect a bigger conditioning EPSP (dashed horizontal arrow), presumably due to a decrease in presynaptic inhibition of Ia afferents. However, increased

reflex facilitation could occur if the various inputs associated with contraction had different effects on low- and high-threshold motoneurones, thus compressing the range of thresholds in the motoneurone pool (much as occurs when playing an accordion). This would increase the slope of the input–output relationship of the test reflex, as illustrated by the dashed oblique line in Fig. 1.9. As a result, a constant conditioning Ia EPSP would fire more motoneurones during contraction than at rest and produce greater facilitation of the reflex, without this being due to change in the specific pathway explored. Conversely, a decrease in the recruitment gain of the reflex could produce a decrease in the reflex facilitation evoked by a constant EPSP.

How to control for a change in 'recruitment gain'

A change in the 'recruitment gain' of the reflex has been observed in the tibialis anterior after stimulation of the sural nerve, where it resulted from a skewed distribution of cutaneous inputs within the motoneurone pool, with inhibition of early-recruited and facilitation of late-recruited motoneurones (Nielsen & Kagamihara, 1993; cf. Chapter 9, p. 425). The only way to discount this possibility with certitude is to record PSTHs of single units in order to detect whether the conditioning heteronymous Ia EPSP is changed in individual units (e.g. see Katz, Meunier & Pierrot-Deseilligny, 1988). However, it is somewhat reassuring that changes in the recruitment gain have so far been observed only in heterogeneous muscles with fast and slow units, like the tibialis anterior, and not in more homogeneous muscles, such as soleus.

Plateau potentials

In animal experiments it has been demonstrated that motoneurones and interneurones in the spinal cord can develop plateau potentials due to persistent inward currents that outlast the input and can thereby distort the relationship between input current and firing rate. In the extreme, plateau potentials can produce self-sustained firing (for review, see Hultborn, 1999). Plateau potentials would change the slope of the input–output relationship of the motoneurone pool (Hultborn *et al.*, 2003), and evidence for plateau-like behaviour has been demonstrated for human motoneurones (Gorassini, Bennett & Yang, 1998; Gorassini *et al.*, 2002). They may play a role in normal motor behaviour: plateau-like behaviour can be triggered by voluntary effort (Collins, Burke & Gandevia, 2001, 2002), particularly if it produces cramps (Baldissera, Cavallari & Dworzak, 1994). This newly discovered possibility would greatly distort the input–output relationship of the H reflex, and should be considered in situations where plateau-like behaviours can appear. It is uncertain whether phasic inputs such as those associated with the H reflex or tendon jerk are sufficient to trigger plateau potentials, even during voluntary effort. If so, there is a problem. If not, there is a concern that H reflex studies might provide insight into circuitry but not how that circuitry is normally used.

Normative data and clinical value

Normative data

Amplitude

The amplitude of the H reflex varies widely in normal subjects, and amplitude measurements in patients are therefore of little value except when pathology is asymmetrical. In human subjects there is no handedness-related side asymmetry in the H_{max}/M_{max} ratio for soleus and FCR (Aymard *et al.*, 2000).

Latency

Reflex latencies depend on the duration of the stimulus current, being longer the longer the stimulus (Mogyoros *et al.*, 1997). This means that the minimal latency for the reflex arc is not measured using a stimulus of 1 ms duration, an issue that is relevant if test and conditioning stimuli of different duration are used in an experiment. Reflex latencies have a strong correlation with the length of the reflex

pathway (measured as limb length or more simply as height) and a weak but significant correlation with age (Schimsheimer *et al.*, 1987). With older patients, it may be more accurate to use the height reported by the patient rather than that measured at the time of the test because the length of neural pathways does not change with age. Latency must be measured to the onset of the first deviation of the EMG potential from baseline. The following values are from the study of Schimsheimer *et al.* (1987) in which the stimulus duration was 1.0 ms:

Soleus H reflex: (94 control subjects)
mean latency: 30.0 ± 2.1 ms (mean ± SD)
right/left difference (i.e., symmetry): 0.09 ± 0.70 ms (mean ± SD)
H reflex = 3.00 + 0.1419 × height (in cm) + 0.0643 × age (in years) ± 1.47 (± SD)
FCR H reflex: (80 control subjects)
mean latency: 16.84 ± 1.33 ms (mean ± SD)
right/left difference: 0.002 ± 0.42 ms (mean ± SD)
H reflex = 0.44 + 0.0925 × height (in cm) + 0.0316 × age (in years) ± 0.83 (± SD)

Clinical value

H reflexes have a defined role in diagnostic testing, particularly when assessing polyneuropathies or when assessing proximal conduction. If testing is performed during a voluntary contraction, H reflexes can be recorded for all spinal segments innervating the upper and lower limbs, including those likely to be compromised by, e.g. disc prolapse (see Chapter 2, p. 95). Reflexes are attenuated in peripheral neuropathies (see p. 95) and the soleus H reflex is exaggerated in spastic patients (see Chapter 12, p. 562).

Critique: limitations, advantages and conclusions

The technique of the H reflex is simple, but strict methodology is required for valid interpretations of the results. The physiological mechanisms affecting the reflex discharge are not quite as simple as they first seem, and the complexity of the so-called monosynaptic reflex pathway imposes limitations on H reflex studies. Reflex size depends on the excitability of the motoneurones, but also: (i) on mechanisms acting on the afferent volley, and (ii) on 'pool problems' related to the input–output relationship in the motoneurone pool. However, they can usually be controlled by parallel investigations recording from single motor units (see pp. 28–39), and these should be performed systematically when studying motor control physiology in human subjects. Because it enables a comparison of the results obtained at rest and during movement, the H reflex remains the only available method with which it is possible to investigate how transmission in spinal pathways is changed when human subjects undertake motor tasks.

The F wave

Underlying principles and basic methodology

Antidromic re-excitation of motoneurones

A supramaximal electrical shock delivered to a nerve often elicits a late response, termed the F wave because it was initially recorded in muscles of the foot (Magladery & McDougal, 1950). The F wave occurs only when the stimulus excites motor axons directly, producing a M wave, and is produced by an antidromic motor volley (cf. Eisen & Fisher, 1999). Because the F response in single motor units is seen only when the axon of the unit has been activated (Trontelj, 1973), it is believed that the F response is evoked by antidromic reactivation ('backfiring') of motoneurones (for review see Eisen & Fisher, 1999; Espiritu, Lin & Burke, 2003). An antidromic volley in a single motor axon may produce an F wave, provided that the axon hillock and proximal axon are not refractory when the antidromic action potential discharges the soma. Biologically, the F wave is an artefact: F waves would occur under

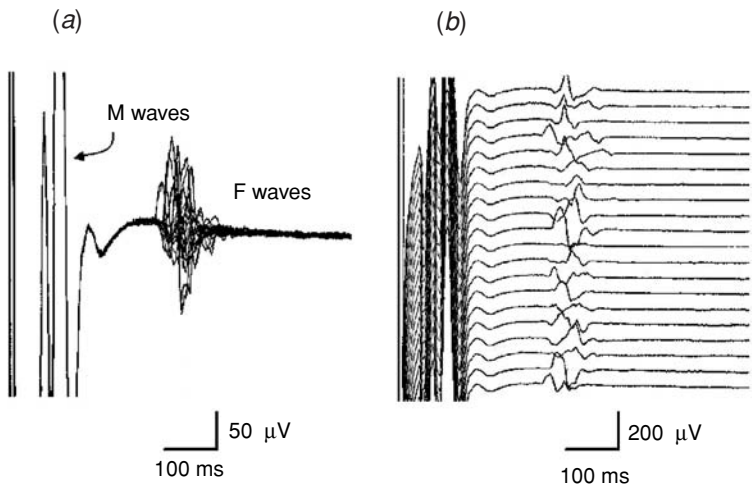


Fig. 1.10. F waves of the thenar muscles in response to supramaximal stimulation of the median nerve at the wrist at 1 Hz. (*a*) 20 consecutive responses superimposed at relatively high gain. (*b*) The same 20 responses shown in raster format, at lower gain. Note the variability of latency and morphology of consecutive responses. This occurs because different motoneurones produce F waves in each trial and the number of responding motoneurones per trial is very low, often only one.

natural conditions only if a motor axon had an ectopic focus that gave rise to an antidromic impulse. Studying F waves can provide little insight into how motoneurones behave normally because this manner of exciting the motoneurone differs from its excitation through a synaptic event.

Motoneurones involved in the F wave

It has been postulated that recurrent discharges only occur in a limited number of motoneurones, in part because the initial segment may not be excitable again after the antidromic impulse enters the somata of the motoneurones. If so, blockage at the initial segment may occur more commonly in the smaller, slower conducting motoneurones which are more rapidly depolarised, leading to preferential activation of the larger, faster conducting motoneurones. (Kimura *et al.*, 1984). Moreover, if some motoneurones in a muscle can produce H reflex discharges in response to the maximal afferent volley set up by the supramaximal stimulus for the F wave, F waves will not be recordable for these presumably low-threshold slowly conducting motor units (Esperitu, Lin & Burke, 2003). This is the case in panels *D* and *H* of Fig. 1.3: motoneurone 'Z' could produce an F wave because it was not activated in the H reflex but motoneurones 'X' and 'Y' could not.

Characteristics of the F wave

Occurrence in different muscles

F waves can occur when the nerve innervating any muscle is stimulated, but they may not be identifiable when their latency is so short that they merge with the end of the M wave. In contrast to the H reflex, the F response is most readily recorded in intrinsic hand and foot muscles, and it has attained special interest for the investigation of these muscles.

Variability and persistence

The F waves typically vary from trial to trial in amplitude, latency and shape (Fig. 1.10(*a*), (*b*)) because different motoneurones contribute to successive responses. The persistence is the percentage of

stimuli that produce F waves: it is usually >80% for the median, ulnar and tibial nerves, but can be as low as 5% for the peroneal nerve (Eisen & Fisher, 1999).

Latency

The F wave appears with a latency similar to the H reflex, slightly longer for soleus but slightly shorter for the thenar muscles (Burke, Adams & Skuse, 1989).

Amplitude

With stimuli delivered at a frequency of 1 Hz or less, the morphology of successive F waves varies considerably from trial to trial, reflecting the activity of different motor units in the muscle (Fig. 1.10(*b*)). The amplitude of individual F waves is normally that of a single motor unit, below 5% of M_{max} (Eisen & Odusote, 1979). This is because the axon hillock is reactivated in only a small number of motoneurones (usually 1–2) in response to the stimulus. The variability of latency and morphology results from different motoneurones 'backfiring' in different trials.

Chronodispersion

Clinical studies ordinarily assume that the minimal and maximal F wave latencies represent the fastest and slowest motor conduction times to and from the spinal cord, respectively. Thus, the degree of spread of latency of consecutive F waves (F chronodispersion) is often taken as a measure of the spread of conduction velocities of motor axons innervating the muscle (Yates & Brown, 1979). However, such measures apply only to those motoneurones that generate F waves. Reasons for the under-representation of slowly conducting motor units in F wave measurements are mentioned above. Comparison of F waves in tibialis anterior, abductor pollicis brevis and soleus has shown that there is an inverse relationship between F wave chronodispersion and F wave persistence at rest, and the shorter the chronodispersion the easier to elicit the H reflex in the motoneurone pool. During a steady contraction that allows the H reflex to appear in the tibialis anterior and the abductor pollicis brevis, overall F wave activity in these muscles increases in amplitude but decreases in duration. These findings are consistent with the view that reflex discharges prevent F waves in low-threshold motor units, and that chronodispersion is affected by the extent of reflex activity. In other words, chronodispersion and related F wave measures (such as mean F wave latency) do not assess motor properties exclusively (Espiritu, Lin & Burke, 2003).

F wave as a measure of excitability of motoneurones

Low sensitivity of the F response to changes in motoneuronal excitability

It has been suggested that the size of the F response depends on motoneurone excitability (Fisher, 1992). However, the sensitivity of the F response to changes in motoneurone excitability is much less than that of the H reflex. For example, the sensitivity of soleus motoneurones to the heteronymous monosynaptic Ia excitation from quadriceps is ten times less when assessed with the F wave than with the H reflex (Hultborn & Nielsen, 1995).

Comparison of the H and F responses

In contrast to the H reflex, the F response is not elicited by a group Ia volley, and it has therefore been argued that a comparison of the two responses could provide an indirect estimate of changes in presynaptic inhibition of Ia terminals. However, Hultborn & Nielsen (1995) have shown that the comparison of H and F responses may not be valid, for several reasons.

(i) Because re-excitation depends on a somatic spike elicited at a time when the axon is not refractory, a decreased F response may be seen when strong facilitation of motoneurones produces a very short initial segment-soma delay as well as with inhibition (which prevents the somatic spike). In addition, as seen above, because an H reflex discharge protects motoneurones from antidromic invasion, the increased H reflex occurring with

higher motoneuronal excitability would decrease the number of motoneurones that could produce an F response.

(ii) The two responses do not recruit preferentially the same motor units: small units with slow axons for the H reflex (p. 4), but large units with fast axons for the F response (p. 22).

(iii) The methods of activation of the motoneurones in the H reflex and the F response are so different that their sensitivity may be drastically different, even when the changes in motoneurone excitability are evenly distributed across the neuronal membrane. For all these reasons, the F wave provides a flawed measure of the excitability of the motoneurone pool.

Clinical applications

Peripheral neuropathies

F wave studies are sensitive in detecting acquired demyelinating polyneuropathies, where the latency of the F wave may be quite prolonged (see Eisen & Fisher, 1999). In acute demyelinating polyneuropathies, this may be the only conduction abnormality, apart from absence of H reflexes. In chronic demyelinating polyneuropathies, F waves may be absent.

Proximal lesions

F waves provide one of the few well-standardised tests of proximal conduction available for the assessment of motor conduction in nerve root and plexus lesions. A major limitation in the upper limb is that nerve root compression more commonly involves segments other than C8-T1 (innervating intrinsic hand muscles in which F waves can be easily recorded).

Spasticity

An increased mean F wave amplitude is a good reflection of spasticity: the mean F wave amplitude is then above 5% of M_{max} and often above 10% (see Eisen & Fisher, 1999; Chapter 12, pp. 562–3).

Conclusions

F waves are useful in routine clinical studies to assess motor conduction to and from the spinal cord but have a limited role in motor control investigations.

Modulation of the on-going EMG activity

Initial studies

Gassel & Ott (1969, 1970) showed that the time courses of the changes in the monosynaptic reflex and in the on-going averaged rectified EMG of triceps surae produced by a conditioning stimulus were similar.

Underlying principles and basic methodology

Basic methodology

The on-going EMG is full-wave rectified to sum both positive and negative deflections in the raw EMG and then averaged. The background EMG activity is measured, by assessing the EMG in the period preceding the conditioning stimulus (e.g. see Fig. 1.11(*c*)) or immediately following it or by randomly alternating conditioned and unconditioned trials, measuring the background EMG activity in the latter. Short sequences of 50–100 s are recommended to avoid muscle fatigue when using 'strong' contractions of >20% of MVC. The data recorded during 2–4 sequences may then be averaged to produce a single run containing 100–200 conditioned responses. The grand average is expressed as a percentage of the unconditioned baseline EMG. The baseline contraction level can be calibrated by comparing it to the averaged rectified EMG produced by a MVC for ~10 s. The rectified EMG is then plotted against the conditioning stimulus. An excitatory input to motoneurones will produce an increase in the on-going EMG activity (Fig. 1.12(*b*)), and an inhibitory input a suppression (Fig 1.11(*c*)). Note, however, that

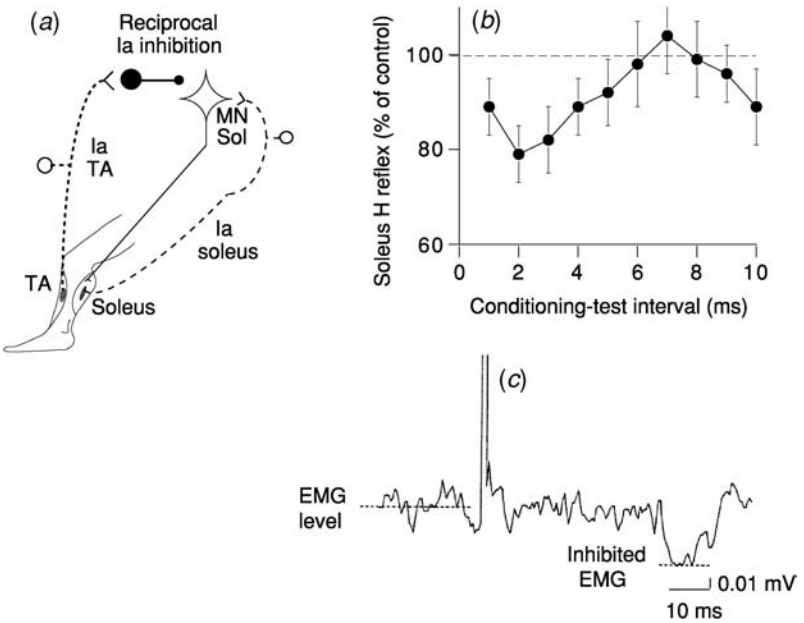


Fig. 1.11. Reciprocal Ia inhibition from ankle flexors to soleus measured by the H reflex technique and stimulus-triggered averaging of the on-going voluntary EMG activity. (*a*) Sketch representing the pathway of disynaptic reciprocal Ia inhibition from tibialis anterior (TA) to soleus (Sol) motoneurones (MN). The conditioning stimulus was applied to the deep peroneal nerve (1.2 × MT) and the subject performed a soleus voluntary contraction 5% of maximum voluntary contraction (MVC). (*b*) Time course of the inhibition of the soleus H reflex (conditioned reflex expressed as a percentage of its control value); the inhibition starts at the 1 ms ISI, is maximal (∼22%) at the 2 ms ISI and lasts only 4 ms. (*c*) Modulation of the rectified on-going soleus EMG. The EMG inhibition (difference between the two dashed horizontal lines) amounts to ∼60% of the background EMG level and lasts ∼15 ms. Adapted from Petersen, Morita & Nielsen (1998), with permission.

suppression may also result from a disfacilitation of motoneurones due to suppression of the excitatory input at a premotoneuronal level. Disfacilitation produces a smaller suppression of the EMG than inhibition of the motoneurones because it is not accompanied by changes in the membrane conductance of the motoneurones, which are the major factor suppressing motoneurone discharge with postsynaptic inhibition (see below).

Other methods

Other methods of treating the raw EMG, such as integrating the averaged unrectified EMG (advantageous when studying a relatively synchronous discharge of the motoneurones, e.g. see Fig. 2.3(*b*)) have been recommended (Poliakov & Miles, 1992).

Recruitment order of motoneurones

In isometric voluntary contractions motoneurones are recruited with increasing contraction force from slow to fast in a similar orderly sequence as in the H reflex (Milner-Brown, Stein & Yemm, 1973; Aimonetti *et al.*, 2000), in accordance with Henneman's 'size principle' (see p. 4).

Estimate of the central delay

The central delay can be deduced from the expected time of arrival of the conditioning volley at the segmental level of the motoneurone pool being tested. The calculations involve measuring the latency of the H reflex in the tested pool and correcting this value for the difference between the afferent conduction times of the conditioning and homonymous Ia

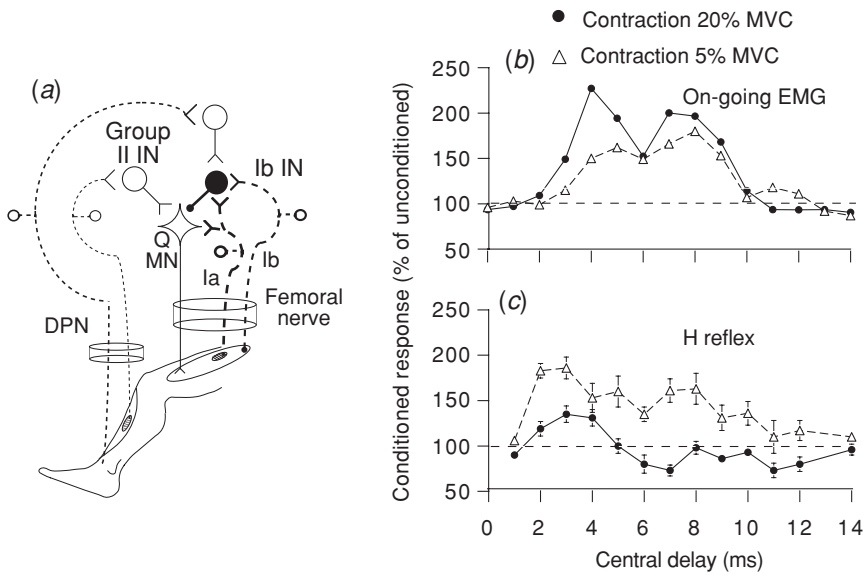


Fig. 1.12. Comparison of the changes in the on-going EMG and the H reflex of the quadriceps, and estimate of the central delay of the changes in the on-going EMG. (*a*) Sketch of the presumed pathways activated by a deep peroneal nerve (DPN) volley: the group II volley from pretibial flexors activates excitatory group II interneurones (IN) facilitating quadriceps (Q) motoneurones (MN), whereas other afferents (possibly joint afferents from the ankle) activate excitatory INs projecting onto Ib inhibitory INs co-activated by Ia and Ib afferents in the test volley. (*b*), (*c*) Results obtained in the same subject during the same experimental session. Effects of DPN stimulation on the on-going EMG activity (*b*) and the H reflex (*c*) of the Q during a weak tonic contraction involving only a few motor units (△) and a relatively strong tonic contraction of Q (20% MVC, ●). The difference in afferent conduction times between the fastest Ia afferents in the DPN and femoral volleys from stimulation sites to the segmental level for Q MNs was 6 ms (see Meunier *et al.*, 1990). (*b*) Changes in the rectified averaged EMG of Q (100 sweeps, 1 kHz sampling rate), normalised to the background level, plotted against the central delay: the latency of the H reflex being 21 ms, the 0 central delay (arrival of the DPN volley at the segmental level of Q MNs) was 27 (21 + 6) ms. Despite the normalisation to the enhanced level of the ongoing control EMG, early and late facilitations of the EMG are greater with the 20% contraction than with the 5% contraction. (*c*) The size of conditioned H reflex is expressed as a percentage of unconditioned reflex and is plotted against the central delay. Each symbol represents the mean of 20 measurements, vertical bars 1 ± SEM. The central delay of zero corresponds to a 6-ms ISI, i.e. when the femoral and DPN volleys would have arrived simultaneously at the Q MN pool. Modified from Marchand-Pauvert *et al.* (2002), with permission.

volleys from the stimulation sites to the spinal cord (see the legend of Fig. 1.12).

Changes in the on-going EMG and in the H reflex need not be identical

Inhibition of the motoneurone pool

The on-going EMG is more sensitive to inhibition than the monosynaptic reflex. For example, during a voluntary contraction of soleus, the peroneal-induced reciprocal Ia inhibition elicits only weak inhibition of the soleus H reflex, but more profound suppression of the on-going EMG of soleus (see Chapter 5, pp. 203–4). The duration of inhibition is also much longer when assessed as the modulation of on-going EMG (15 ms, Fig. 1.11(*c*)) than when using the H reflex (2–3 ms, Fig. 1.11(*b*)). These findings probably reflect a number of factors.

Artefact of normalisation

This is analogous to the apparently greater sensitivity of small H reflexes to inhibition or facilitation when expressed as a percentage of their control value (see p. 16). If only a *small* fraction of the pool is active (e.g. 5% MVC), inhibition (expressed as a percentage of control EMG value) will have a profound effect on the on-going EMG, whereas with the H reflex the same inhibition, which affects only the last-recruited motor units, will suppress a limited part of a test reflex of reasonable size (~15% of M_{max}).

Hyperpolarisation and changes in conductance

Secondly, the hyperpolarisation of motoneurones during the decay phase of the Ia IPSP could be sufficient to prevent the asynchronous firing of motoneurones in the EMG but not their synchronous response to the large monosynaptic Ia EPSP evoking the H reflex. This second explanation is consistent with animal experiments. The monosynaptic reflex is significantly depressed only during the initial phase of the underlying IPSP when the hyperpolarisation is accompanied by changes in the membrane conductance of the motoneurones, and is depressed little during the following decay phase (Araki, Eccles & Ito, 1960).

Further cause of discrepancy

A further factor that could cause a discrepancy between the changes in the H reflex and the on-going EMG is discussed below.

Mechanisms gating the afferent volley of the H reflex

A conditioning volley can affect the mechanisms acting on the afferent volley of the test H reflex (cf. pp. 12–16), and this is a further reason for a discrepancy between changes in the H reflex and the on-going EMG. An example of such a discrepancy is illustrated in Fig. 1.12, which compares the modulation by a peroneal volley of the on-going EMG activity (*b*) and of the H reflex (*c*) of the quadriceps. During weak tonic contraction of quadriceps, the H reflex and the on-going voluntary EMG underwent qualitatively similar biphasic facilitations, with early non-monosynaptic group I and subsequent group II excitations (see Chapter 7, pp. 293–7). In this instance, the effects obtained with the two methods were similar. In contrast, the changes in the H reflex and in the on-going voluntary EMG were different during stronger voluntary contractions of ~20% MVC. The reflex facilitation was replaced by inhibition at central delays of 6–12 ms, while the on-going EMG was facilitated more than with the weak contraction. The discrepancy between the EMG and H reflex modulations during the strong voluntary contractions suggests the existence of an inhibitory mechanism gating the afferent volley of the test reflex. As discussed on pp. 14–15, this is due to potentiation by the peroneal volley of oligosynaptic inhibition produced by group I afferents in the test volley for the H reflex. More generally, this illustrates that, while the results obtained with the two methods depend on motoneurone excitability, the H reflex also depends on factors that can alter the efficacy of the group I afferent volley in firing motoneurones. In this respect, changes in presynaptic inhibition of Ia terminals have been inferred from discrepancies between changes in the H reflex amplitude and in the on-going EMG recorded in the same muscle during various motor tasks (see Chapter 8, p. 340).

Critique: limitations, advantages and conclusions

Advantages

Ease and rapidity of the experiment

Gassel and Ott (1969, 1970) pointed out that the method allows one to obtain the full time course of the changes in motoneuronal excitability much more easily and rapidly than when using the monosynaptic reflex. This is a distinct advantage when investigating patients.

Absence of test stimulation

It is often difficult to ensure that the stimulus for the H reflex remains constant when overt movement occurs (such as in phasic contractions, cycling or gait). In addition, the gain of the input-output relationship on which the H reflex is operating (see pp. 18–20) may change as a function of the recruitment level during a motor task and at the same recruitment level in different tasks (see Capaday, 1997). Modulation of the on-going EMG has the merit of avoiding such limitations.

Comparison of the modulation of the on-going EMG obtained in different situations

It is possible with this method to compare easily the effects of conditioning stimuli on the on-going EMG recorded during various motor tasks, at an equivalent level of EMG activity. Thus, for example, it has been possible to compare: (i) cutaneomuscular responses in hand muscles during precision and grip tasks (Chapter 9, pp. 427–8), (ii) reciprocal Ia inhibition of ankle muscles during voluntary contraction and gait (Chapter 5, pp. 227–9), (iii) heteronymous recurrent inhibition of ankle muscles during voluntary contraction and postural adjustments (Chapter 4, pp. 183–4), and (iv) peroneal-induced group II excitation to quadriceps during voluntary contraction and gait (Chapter 7, pp. 318–19).

Limitations

Active motoneurone pool

The most obvious limitation of the method is that it can only be used in an active motoneurone pool. The method does not allow changes in transmission in neural pathways to be studied when moving from rest to activity.

Temporal resolution

The temporal resolution of the method is limited because of the different conduction velocities for individual motor units and the duration of their EMG potentials. It is therefore not possible with this method to estimate with precision the central delay of an effect evoked by conditioning stimulation. In addition, it is likely that the latency of onset of inhibition is overestimated when measured to the onset of the decrease in rectified EMG because the averaged rectified EMG trace cannot decrease until the end of the motor unit EMG potential.

Initial facilitation and subsequent suppression

Initial facilitation is obligatorily followed by a suppression, that results from the post-spike afterhyperpolarisation (AHP) and recurrent inhibition of the motoneurones. Accordingly, when there is an initial facilitation (due, e.g. to monosynaptic Ia excitation), differences in later events observed between two motor tasks may be difficult to interpret unless the initial facilitation is not modified.

Type of motoneurones involved

Surface EMG studies cannot reveal whether the different motoneurones in the pool respond uniformly to the stimulus, i.e. whether high-threshold motoneurones respond differently to low-threshold motoneurones.

Conclusions

Modulation of rectified on-going EMG activity recorded with surface electrodes has the great advantage of simplicity. This method gives a general overview of the response to a stimulus, but it is usually not a quantitative measure of motoneurone activity and its temporal resolution is weak.

Post-stimulus time histograms (PSTHs) of the discharge of single motor units

Changes evoked by a conditioning stimulus in a motoneurone pool depend on the distribution of

conditioning effects within the pool (see pp. 18–20). Such 'pool problems' are not an issue when studying the responses of single motor units. The ability to record post-stimulus histograms (PSTHs) of the discharge of single motor units represented a major breakthrough in motor control investigations in human subjects (for review, see Awiszus, 1997). Indeed, when a motoneurone is activated voluntarily, the effect of a particular input can be determined by constructing a histogram of the occurrence of motoneurone discharges following repeated presentation of a suitable stimulus. Pioneering studies were performed by Stephens, Usherwood & Garnett (1976), who pointed out that 'this procedure extracts from the naturally occurring spike train only those changes in firing time-locked to the stimulus'.

Underlying principles

Extraction of the changes in firing probability time-locked to the stimulus

The method does not assess the amplitude of a post-synaptic potential (PSP) in a motoneurone, but the resulting changes in its probability of discharge. The principles are presented in the sketch of Fig. 1.13, which shows the construction of the PSTH (bottom row) based on the time of occurrence of motor units potentials in a voluntarily activated motoneurone with the repeated presentation of a stimulus. When a motoneurone is activated voluntarily (first row), motor unit EMG potentials are recorded (second row) and converted into standard trigger pulses by a variable window discriminator (third row). Stimuli are delivered to produce an EPSP in the motoneurone, insufficient to cause the motoneurone to discharge in response to every stimulus, and a computer measures the latency of the trigger pulses following each stimulus. When the stimulus-induced EPSP does not reach discharge threshold for the motoneurone, the first spike to occur after the stimulus will be due to the motoneurone's background discharge, i.e. the 'spontaneous' spike in Fig. 1.13 (thin dashed lines in the first two rows of the figure). Its latency is unaffected by the stimulus. 'Spontaneous' spikes occur randomly with respect to the stimulus and, after many stimuli are delivered, the PSTH will be flat. However, if the EPSP produces a motoneurone discharge, a spike will occur after the stimulus at a latency determined by the latency of the EPSP (thick continuous lines of the first two rows of Fig. 1.13). With repetition, there will be an increased number of motoneurone discharges at that particular latency, creating a peak in the PSTH due to the increased probability of motoneurone discharge in response to the EPSP (bottom row). If the conditioning stimulus elicits an IPSP in the motoneurone, there will be a trough in the PSTH at the corresponding latency (Ashby & Labelle, 1977).

Different models

A number of different models have been proposed for estimating the size of PSPs underlying the changes in firing probability of a repetitively activated motor unit (for review, see Miles, 1997). Most of these models are theoretical and lack the synaptic noise which is particularly important in determining the discharge of spikes (Matthews, 1996). Kirkwood & Sears (1978, 1982) observed that the relationship between the shape of the primary peak in the PSTH and 'the common excitation potential' could be described as the sum of two linear terms, one being proportional to the EPSP and the second to its first derivative. Their conclusion was tested directly by Gustafsson & McCrea (1984). They confirmed that the shape of the PSTH for EPSPs and IPSPs is a combination of the PSP itself and of its first derivative, the influence of the derivative being less when the PSP is small with respect to the synaptic noise.

Basic methodology

Different authorities have adopted different methodologies for generating PSTHs, and the discussion below focuses on one of these (Fournier *et al.*, 1986), but with some reference to other techniques.

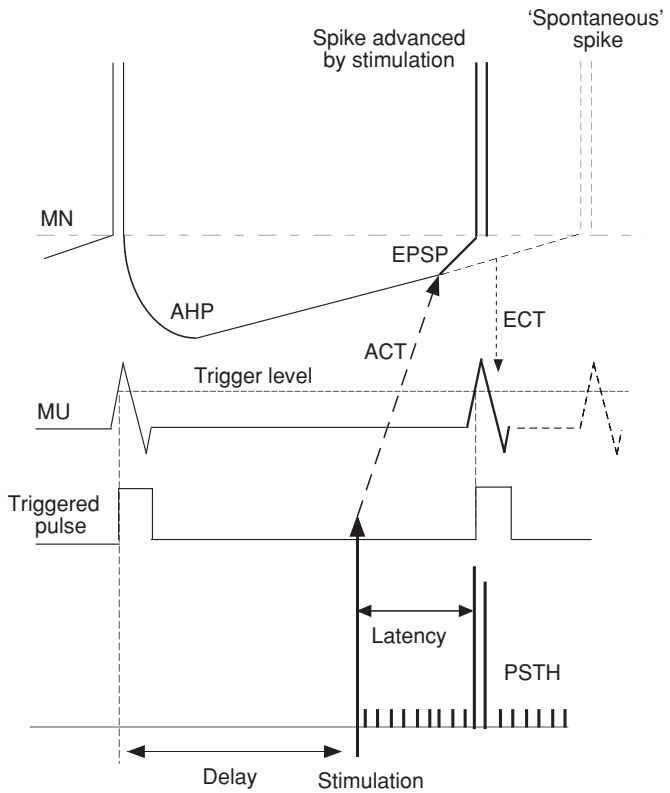


Fig. 1.13. The experimental design used in constructing PSTHs for single motor units. First row: consecutive spikes in the MN, with the post-spike afterhyperpolarisation (AHP) following the first spike and the firing level (dashed horizontal line). Second row: corresponding motor unit (MU) potentials. Third row: conversion of the MU potentials into trigger pulses by a discriminator with variable trigger level. The vertical thick arrow indicates the timing of stimulation, delivered with a fixed delay after the previous MU discharge. The latencies of MU potentials following stimulation are measured, and a histogram of these latencies is constructed (fourth row). The dashed spike and MU potential represent when the discharge due to the 'spontaneous firing' of the MN would have occurred. After an afferent conduction time (ACT, dashed oblique upward arrow) and a central delay, the stimulus produces an EPSP that advances the MN spike and the corresponding MU potential (thick continuous lines). The efferent conduction time (ECT) is represented by the dotted vertical downward arrow. Adapted from Fournier *et al.* (1986), with permission.

Recording

How to isolate one motor unit?

It is necessary to record reliably from a single motor unit that is voluntarily activated. To record from single motor units does not necessarily require needle electrodes. With the help of visual and auditory feedback, carefully placed surface electrodes and some training, most subjects can isolate a single unit by controlling a liminal contraction so that the motor unit action potential is the only one visible on the screen or is of greatest size. When there are several active units, it may be possible to isolate one of them with a window discriminator with variable upper and lower levels. Of necessity, the units so isolated are of low threshold, recruited at levels of force below 5% MVC, and presumably represent small motoneurones with slowly conducting axons.

A significant technical advance has been the use of differential surface electrodes (DE-2.3, Delsys Inc., Boston, USA), with which it is possible to isolate units during contractions as strong as 20% of MVC (Marchand-Pauvert *et al.*, 2002). However, recordings from high-threshold units still require the use of needle electrodes or intramuscular wires. Sophisticated template-matching paradigms now allow the automatic identification of a number of different motor units in the same recording sequence (e.g. see LeFever & De Luca, 1982; Miles, Le & Türker, 1989).

How to be sure that the results originate from the same unit?

The EMG potentials of different motor units may differ only slightly in shape and size. A simple procedure allows one to ensure that potentials recorded during the same session originate from the same unit (Fournier *et al.*, 1986). A conditioning stimulus is delivered, triggered by the motor unit potential but with a zero delay. The afferent volley will arrive at the motoneurone when it is still refractory due to the AHP, and this will prevent the conditioning EPSP from firing the motoneurone. If these stimuli cause a peak in the histogram, the data in the PSTH are from more than one motor unit or are contaminated by another unit.

Stability of the frequency of firing of the unit

Because the size of the peak (or trough) recorded in the PSTH to a constant conditioning stimulus varies with the motoneurone's discharge rate (see below), it is essential that the discharge remains as stable as possible, between 5 and 10 Hz in different muscles. It is important that there is stable background firing in the absence of stimulation, because irregularities in the background firing can produce the appearance of false peaks (or troughs) in the final PSTH (see p. 35).

Characterisation of the recorded units

The threshold and size of motor units may be inferred from the force at their recruitment, the macro-potential area of the EMG potential and the twitch contraction time (see Milner-Brown, Stein & Yemm, 1973; Aimonetti *et al.*, 2000).

Recordings from pairs of motor units

When comparing results obtained for low-threshold (slow) units and high-threshold (fast) units, it may be difficult to be certain whether different results are due to a difference in the inputs to these units or to the fact that high-threshold fast units require a stronger descending excitatory (and peripheral) drive. This can be tested by recording simultaneously with needle electrodes from pairs of units (one low-threshold, the other high-threshold), in which case there will be, of necessity, the same descending excitatory and peripheral drives (Aimonetti *et al.*, 2000).

Stimulation

Stimuli delivered randomly

Stimuli may be delivered randomly with respect to the motoneurone discharge (Stephens, Usherwood & Garnett, 1976; Ashby & Zilm, 1982b). The size of the peak elicited by a given EPSP then decreases when the frequency of firing increases (Ashby & Zilm, 1982a), because the higher the frequency, the higher the probability of the EPSP occurring during the AHP following a previous discharge. This simple method requires a longer recording because the EPSP will often reach the motoneurone during the AHP following a discharge and be unable to make the motoneurone discharge again. The more efficient alternative is to avoid the AHP by triggering the stimulator from the motor unit potential (see below). However, there is an advantage in delivering the stimuli randomly: if more than one motor unit can be discriminated reliably in the recording, it is possible to construct PSTHs off-line for each unit for the same recording sequence. This allows a more valid comparison of the responses of different units.

Stimulation may be triggered by the discharge of the single motor unit (Fournier et al., 1986; Fig. 1.13)

Each stimulus is then triggered at a fixed delay after the preceding motor unit action potential, but with the overall stimulus repetition rate limited to 2–3 Hz. This technique has advantages under two different conditions. (i) Stimuli can be delivered so that the peak of excitation occurs towards the end of the AHP following the previous motoneurone discharge, when the probability that the EPSP can make the motoneurone discharge is highest. (ii) Conversely the AHP can be used to attenuate the monosynaptic discharge of the motor unit. The monosynaptic discharge of a motoneurone is followed by a depression due to the AHP, and this will obscure later EPSPs or IPSPs. Preventing the monosynaptic discharge of the motoneurone could allow these late synaptic effects to become apparent. This can be done by delivering the stimulus at an appropriately short delay following the previous discharge. The delay is chosen so that the AHP reduces the probability of firing due to the monosynaptic EPSP, but not the effects of the late synaptic events which occur later on the recovery from the AHP. With this method of discharge-triggered stimulation, the size of the peak elicited by a given EPSP increases with the frequency of firing: the higher the frequency the lower the possibility of the EPSP occurring during the critical period of the AHP (see Katz, Meunier & Pierrot-Deseilligny, 1988). Note, however, that, while the technique may prevent discharge due to the monosynaptic input, the late events will be distorted in amplitude by the subliminal excitation produced by that input. When the stimulus is triggered by the preceding motor unit discharge, it is essential that there be counts in bins preceding the increased probability of discharge. Otherwise the AHP could be obscuring the onset of the peak. This is important because the initial 0.5–1.0 ms of the peak represents the only unequivocally monosynaptic component of the group I peak (cf. p. 34). A disadvantage of triggering the stimulus from the motor unit discharge is that, of necessity, only that one motoneurone can be studied in the recording sequence, even when more than one motor unit is active.

Intensity of the stimulation

The intensity of stimulation should be below threshold for a compound response (be it the H reflex, polysynaptic response or motor evoked potential) because, if not, small motor unit potentials might exceed the trigger level when superimposed on the compound response. This would cause a peak in the PSTH at the appropriate latency even when there was no effect on the discharge probability of the unit being studied.

Assessment of the timing of the changes in firing probability

Recording window

A computer cannot distinguish between counts due to the unit (i.e. those that must be analysed) and those due to stimulus artefact and/or the compound M wave. It is convenient to delay the beginning of the recording until such activity has subsided.

Estimation of the latency of a change in discharge probability

Within the recording, analysis is focused on the region of expected and/or visually identifiable peaks and troughs in the histogram. Consecutive bins with an increase (or a decrease) in firing probability are grouped together and tested with a χ^2 test to determine whether the firing probability after stimulation within the group differs from that in the control situation. A peak of excitation (or a trough of suppression) is accepted if there is a significant increase (or decrease) in firing probability in a group of adjacent bins. The latency of the first bin of the change in firing probability is taken to be the latency of the effect, but must be corrected for the trigger delay on the motor unit action potential. The trigger pulse that is fed into the computer is generated on the rapidly

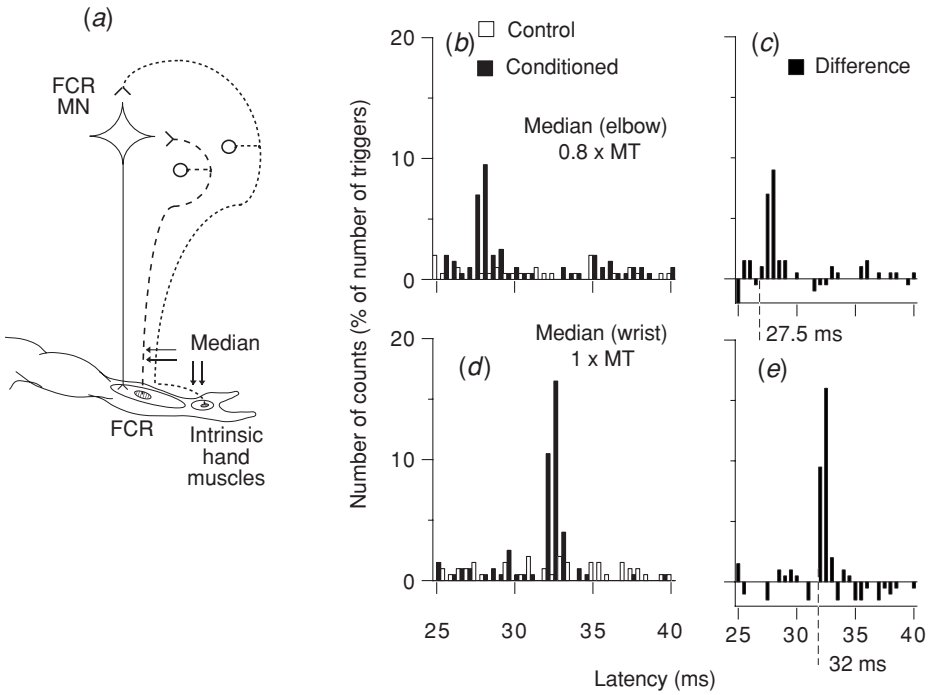


Fig. 1.14. Changes in firing probability of a FCR motor unit after stimulation of the homonymous and heteronymous group I afferents. (*a*) Sketch of the presumed pathways: a flexor carpi radialis (FCR) motoneurone (MN) receives monosynaptic excitation from homonymous (dashed line) and heteronymous (dotted line) Ia afferents, the latter from intrinsic hand muscles innervated by the median nerve. (*b*)–(*e*) PSTHs (0.5 ms bin width) after stimulation of homonymous Ia afferents in the median nerve at elbow level (0.8 × MT (*b*), (*c*)), and of the median nerve at wrist level just below 1 × MT ((*d*), (*e*)). The number of counts (expressed as a percentage of triggers) is plotted against the latency after stimulation. □ and ■ in (*b*) and (*d*) show the control and conditioned histograms, respectively, and columns in (*c*) and (*e*) the difference between them. Vertical dashed lines in (*c*) and (*e*) indicate the latency of the early homonymous (27.5 ms (*c*)) and heteronymous (32 ms (*e*)) peaks, respectively. Distance between wrist and elbow electrodes: 0.30 m. Conduction velocity in the fastest Ia afferents in the median nerve: 69 m s^{-1}. The difference in latencies of heteronymous and homonymous peaks (32–27.5 = 4.5 ms) is explicable by the difference in afferent conduction times (0.30/69 = 4.35 ms). Adapted from Marchand-Pauvert, Nicolas & Pierrot-Deseilligny (2000), with permission.

rising phase of the EMG potential, a few milliseconds after its onset, and this delay must be subtracted from the latency of the peak (or trough) in the PSTH (see Fig. 2.2(*c*), (*d*)). However, when comparing the effects of different conditioning stimuli, the trigger delay will be the same for all changes in firing probability of any one motor unit, provided that the recordings come from the same sequence. The trigger delay does not affect the difference in latencies in two PSTHs, and this is the critical measurement in such experiments (e.g. Fig. 1.14). The time resolution of the method depends only on the bin width. However, the narrower the bin width, the greater the number of stimuli necessary to produce a significant increase in each bin of the peak.

CUSUM

Ellaway (1978) devised a procedure (cumulative sum or CUSUM) to enhance the detection of small

changes in firing probability. The first step in constructing a CUSUM involves estimating the mean count in the bins of a control histogram (or the mean count in the pre-stimulus bins). The mean value is then subtracted from the counts in each bin of the entire PSTH. The residual counts in each bin are then summed sequentially (bin 1, then bins 1 + 2, then bins 1 + 2 + 3, etc. . . .) and plotted against time after the stimulus. The resulting function is an integral with respect to time. Normalisation of the counts in the PSTH as counts/stimulus/bin results in a measure with units of impulses/stimulus/s. Given that the CUSUM is the time integral of the PSTH, its units are then impulses/stimulus. The onset of a period of increased (or decreased) firing probability is indicated in the CUSUM by the onset of a positive (or negative) slope, and this allows a more confident estimate of latency than could reasonably be achieved using the raw histogram which inevitably contains irregular bin-to-bin fluctuations. In the CUSUM, the duration of an excitatory event is given by the duration of the increasing phase of the CUSUM. If the discharge then falls below control levels, the CUSUM begins to fall, but if it does not, the CUSUM remains at the higher level (as one would expect with a true integral).

Estimating the central delay of an effect

The latency of a peak (or trough) in the PSTH is the sum of the afferent and efferent conduction times plus the central delay of the pathway. To estimate the latter, it is convenient to record another PSTH for the same unit for homonymous monosynaptic Ia excitation, and to compare the latencies. Since it is the same unit, the trigger delay and the efferent conduction time are the same. The afferent conduction times for the homonymous Ia and the relevant afferent volleys may be estimated from the conduction velocities of the fibres (e.g. Fig 1.16) and the distance from stimulation sites to the spinal cord (cf. Chapter 2, pp. 70–3). From these calculations it is possible to compare the central delay of the tested effect to that of homonymous monosynaptic Ia excitation.

Changes in the mono- and non-monosynaptic components of the Ia peak

As discussed above (pp. 14–16), oligosynaptic pathways activated by the test volley can limit the extent of group I excitation. Only those changes affecting the entire excitatory peak and, in particular, the initial 0.5–1.0 ms have affected the monosynaptic pathway (cf. p. 16). This can only be ensured in experiments using PSTHs from single motor units because the temporal resolution of compound EMG responses is limited (see p. 28). To be certain that the first bins are capturing the true onset of monosynaptic excitation it is necessary that there are counts in earlier bins (see p. 32).

Assessment of the size and significance of the peaks and troughs in the PSTH

When stimulation is delivered randomly with respect to the firing of the unit

The background firing is then calculated during the period immediately preceding the stimulus. Using 1 ms bins, Mao *et al.* (1984) accepted a period of increased (or decreased) firing probability if the firing probability in 3 or more adjacent bins was above (or below) the mean background firing plus 2 SD.

When stimulation is triggered by the previous discharge

The probability of firing then depends on the AHP following the previous discharge. In the control situation, there is a progressive increase in the probability of discharge with increasing time intervals as the AHP subsides. To take such changes in firing probability into account, a control histogram of firing probability is constructed without stimulation. The control and conditioned situations (□ and ■, respectively, in Figs. 1.14(*b*), (*d*) and 1.15(*b*)) are randomly alternated in the same sequence and the control count is subtracted from the conditioned count for each bin in the PSTH (Figs. 1.14(*c*), (*e*) and 1.15(*c*)). A χ^2 test is used within different time-interval windows

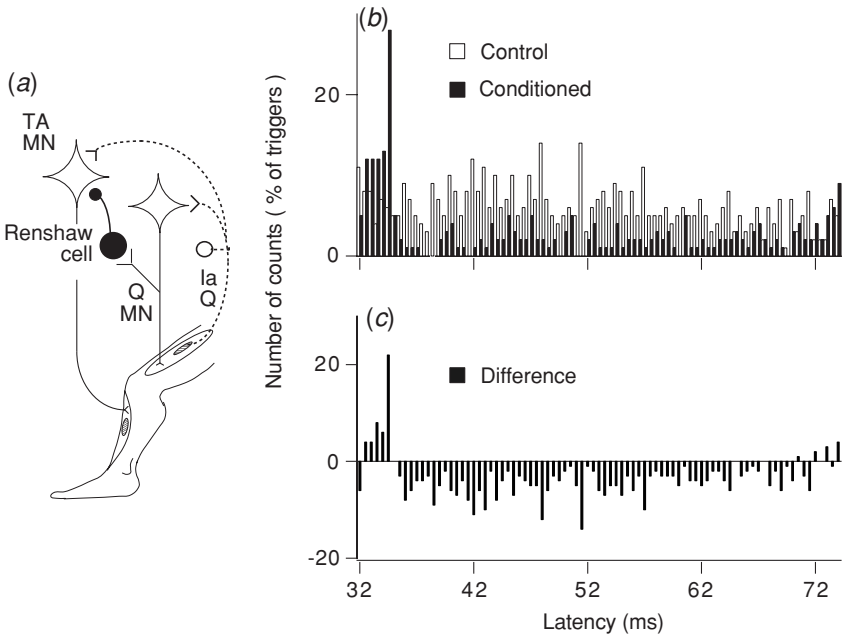


Fig. 1.15. Heteronymous Ia facilitation and recurrent inhibition from quadriceps to tibialis anterior. (*a*) Sketch of the presumed pathway: heteronymous Ia afferents from quadriceps (Q) produce monosynaptic excitation of a tibialis anterior (TA) motoneurone (MN), and recurrent collaterals from Q motor axons inhibit the TA MN through Renshaw cells. (*b*), (*c*) PSTHs (1 ms bin width, number of counts as a percentage of number of triggers) for a TA unit. (*b*) Control (□) and conditioned (■) histograms. (*c*) Difference between conditioned and control histograms. Femoral nerve stimulation that produced an H reflex in the quadriceps (20% of M_{max}) also produced an early peak of excitation in the TA motor unit, at a latency consistent with monosynaptic Ia excitation, followed by short-latency long-lasting recurrent inhibition. Adapted from Meunier *et al.* (1990), with permission.

to determine the extent to which the distribution of firing probability after stimulation differs from that in the control situation. A peak of excitation (or a trough of suppression) is accepted as genuine if there is a significant increase (or decrease) in firing probability in a group of adjacent bins. Sequences in which irregularities in the *control* sequence contribute significantly to the difference between the two situations are not retained for further analysis. As discussed earlier, bin-to-bin variability in the control PSTH is commonly due to failure to maintain a steady background discharge rate. Figure 1.14(*b*), (*c*) shows the large homonymous monosynaptic Ia peak evoked in a FCR unit by stimulation of the median nerve at the elbow. Stimulation of afferents in the median nerve at the wrist from intrinsic muscles of the hand elicited a peak at a longer latency ((*d*), (*e*)), and this difference in latency was explicable by the difference in the afferent conduction times for the homonymous and heteronymous Ia volleys (see the legend of Fig. 1.14). Figure 1.15 shows that the PSTH can also effectively demonstrate inhibition: in this case, recurrent inhibition from quadriceps to tibialis anterior.

Normalisation of the results

It is convenient to express the number of counts in each bin as a percentage of the number of triggers. Although the relationship between the amplitude of a peak (or a trough) in the PSTH and that of the underlying PSP is complex (see p. 29), the larger the

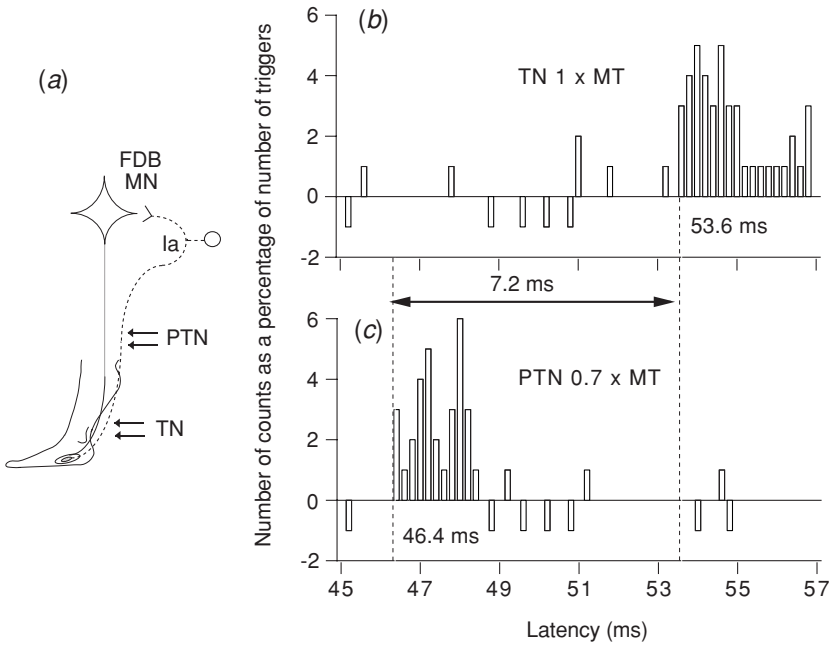


Fig. 1.16. Conduction velocity of tibial Ia afferents between the ankle and knee. (*a*) Sketch of the experimental paradigm: Ia afferents, with monosynaptic excitatory projections on homonymous motoneurones (MN), from intrinsic plantar muscles (flexor digitorum brevis, FDB) are stimulated at the ankle and knee. (*b*), (*c*) PSTHs (after subtraction of the background firing, 0.2 ms bin width) for a FDB unit are shown after stimulation of the tibial nerve (TN) at ankle level (1 × MT (*b*)) and of the posterior tibial nerve (PTN) at knee level (0.7 × MT (*c*)). The difference between the latencies was 7.2 (53.6–46.4) ms, and the distance between the electrodes 42 cm. This gives a conduction velocity (CV) of 58 m s^{-1} (0.42/0.0072). Modified from Marque *et al.* (2001), with permission.

PSP the higher the peak or the deeper the trough. Thus, the absolute size of the peak (or trough) can be estimated as the sum of the differences (conditioned *minus* control counts) in the different consecutive bins with increased (or decreased) firing probability contributing to a given peak or trough.

Assessment of the conduction velocity of Ia afferents

The PSTH method may also be used to calculate the conduction velocity of Ia afferents. The calculations involve measuring the latency of the monosynaptic Ia peaks measured in PSTHs for the same unit after stimulation of homonymous Ia fibres at two different sites (Chapter 2, p. 72), and dividing the distance between the two stimulation sites by the difference in the latencies (see Fig. 1.16).

Critique: limitations, advantages and conclusions

Limitations

Voluntary activation

The most obvious limitation of the method is that, like the modulation of the on-going EMG, PSTHs can be constructed only for an active motoneurone pool. Some subjects find it difficult to maintain the discharge of a specific motor unit in isolation, and when more activity develops there is a risk of spurious

counts not due to the original unit. Needle electrodes can allow better unit isolation but are inherently unstable, and less suited for the multiple recordings needed to characterise a response fully. Hook-wire electrodes allow selectivity and stability, but cannot be moved easily to record from different motor units in a different site in the muscle.

Afterhyperpolarisation

When Ia or corticospinal volleys produce a clear peak in the PSTH, the following AHP can suppress firing and obscure weaker effects of longer latency. Weak late effects may then be demonstrated (i) by decreasing the stimulus intensity (though this could reduce the size of the late effects), and (ii) by using the AHP to suppress the early peak. This would involve triggering the stimulus earlier after the previous spike so that the early peak falls within the AHP, but not so early that the late activity was also obscured (see p. 32).

Multiple peaks (or troughs)

The rising phase of the EPSP synchronises spikes at a fixed interval after the stimulus and generates secondary and tertiary peaks and troughs in the PSTH reflecting the auto-correlation function of the motoneurone discharge. These 'synchronisation-related errors' occur with time lags of the same order as the spontaneous mean inter-spike interval (Türker & Powers, 1999, 2003). Thus, the double peaks which occur in the PSTH at shorter intervals may be safely attributed to double EPSPs, e.g. the two peaks in Fig. 1.18(*f*) are probably due to corticospinal D and I waves evoked by transcranial electrical stimulation of the motor cortex (see p. 42).

Conclusions

The PSTH is a powerful technique that allows single motoneurones to be investigated in human subjects with good time resolution. It can be applied in virtually all muscles and, if needle or wire electrodes are used, high-threshold and low-threshold units can be studied. It is an indispensable complement to H reflex experiments to overcome various 'pool problems', to detect oligosynaptic limitation of the reflex by the test volley or to ensure a change in presynaptic inhibition of Ia terminals. The only important limitations are that it requires selective voluntary contraction involving only one detectable unit, and this unit may not be representative of the motoneurone pool. It is also impossible to document the changes in transmission produced by voluntary effort. For this reason the unitary H reflex described by Shindo *et al.* (1994) is important (see below).

Unitary H reflex

Underlying principles and basic methodology

Underlying principles

By carefully controlling the stimulus it is possible to study the H reflex of single motor units. An ingenious (but demanding) method has been described by Shindo *et al.* (1994), utilising essentially the same principles as those used for threshold tracking of the compound H reflex (cf. p. 11), but doing so for a single motor unit and estimating the size of the test Ia EPSP necessary to reach firing threshold for that unit.

Recording

The EMG potential of a single motor unit discharging in the H reflex is recorded with a needle electrode. This constitutes a 'unitary' H reflex, a single soleus motor unit potential contributing to the compound soleus H reflex.

Stimulation

The posterior tibial nerve is stimulated to produce an H reflex. The excitability of a single motoneurone is assessed as the stimulus intensity that activates the unit at rest with a 50% probability, referred to as the 'critical firing stimulus' (CFS). This stimulus intensity

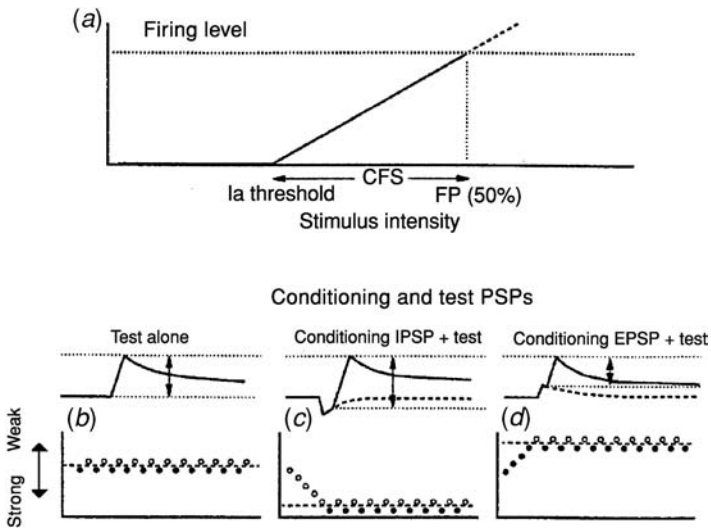


Fig. 1.17. The principle of the CFS method (unitary H reflex). (*a*) The size of the test EPSP increases almost linearly with the increase in stimulus intensity. The 'CFS' is the difference between the Ia threshold (measured as the weakest stimulus to produce a Ia peak in the PSTH of the voluntarily activated unit) and the stimulus necessary at rest to discharge the motoneurone in the H reflex with a firing probability of 50% ($FP_{50\%}$). (*b*)–(*d*) The size of the test Ia EPSP (top) and the resulting changes in the sequence of stimulation to reach $FP_{50\%}$ (bottom) in the control condition (*b*) in the presence of a conditioning IPSP (*c*) and a conditioning EPSP (*d*). The sizes of the test EPSPs (double-headed arrows in the top row of sketches in (*b*)–(*d*)) correspond to the CFS. Conditioning inhibition and facilitation are shown as increases and decreases in the CFS, respectively. Presence (●) and absence (❍) of discharge of the motor unit are shown in the bottom row. (*b*) In the control situation, the firing probability is 50%. (*c*) When there is a conditioning IPSP, the motor unit does not discharge (❍) until stimulus intensity is increased (downward) to reach $FP_{50\%}$. (*d*) When there is a conditioning EPSP, the motor unit discharges (●) and stimulus intensity has to be decreased (upward) to reach $FP_{50\%}$. Adapted from Shindo *et al.* (1994), with permission.

is expressed relative to the threshold intensity for the group Ia EPSP, which is estimated by measuring the threshold for the homonymous peak in PSTHs of the same unit when voluntarily activated. It is assumed that the latter threshold represents the threshold for the test EPSP in the motoneurone under study. At rest, the test stimulus intensity is determined automatically by computer. Repeated automatic adjustments of the test stimuli make the firing probability of the unit converge to 50% ($FP_{50\%}$) (❍ and ● showing the absence and the presence of firing of the unit, respectively, in the bottom rows of Fig. 1.17(*b*)–(*d*)). The stimulus intensity is increased if the unit fails to discharge in response to the preceding stimulus (❍ in *C*), and decreased if the unit does discharge (● in *D*).

Significance of changes in CFS produced by conditioning stimuli

Figure 1.17(*a*) shows diagrammatically the relationship between the intensity of the test stimulus and EPSP size within a single motoneurone. The Ia threshold indicates the weakest stimulus intensity that affects the discharge probability of the voluntarily activated motoneurone. The intensity that produces $FP_{50\%}$ corresponds to the weakest stimulus intensity that causes the motor unit to discharge with a 50% probability when at rest, and the difference between these intensities is the CFS, an indirect measure of the size of the test Ia EPSP necessary to make the motoneurone discharge when at rest. When conditioning stimuli hyperpolarise or

depolarise the motoneurone, there are appropriate changes in the CFS (double-headed arrows in the sketches in the top rows of Fig. 1.17(*b*)–(*d*)). The CFS for a motor unit should therefore be a function of the test Ia EPSP in the corresponding motoneurone, measured as the voltage excursion between the resting membrane potential and the firing threshold of the motoneurone. The relationship between the CFS and the size of the test EPSP is approximately linear, and the size of the CFS can be used as a measure of the size of the average test Ia EPSP. When conditioning stimuli produce an IPSP, the resulting hyperpolarisation prevents the unit from firing (○ in Fig. 1.17(*c*)). A stronger stimulus intensity is then required to produce an EPSP sufficiently large for the motoneurone to fire with a probability of 50%. Conversely, when conditioning stimuli produce depolarisation, the sum of the conditioning and test EPSPs causes the unit to fire with a probability greater than 50% (● in (*d*)), and the stimulus intensity must be reduced to produce the smaller test EPSP required to reach the $FP_{50\%}$ (Fig. 1.17(*d*)). The technique was validated by the demonstration that the sensitivity to femoral-induced heteronymous Ia facilitation was the same for the unitary and the compound soleus H reflexes.

Critique: limitations, advantages and conclusions

Advantages

(i) Conditioning effects may be explored avoiding any 'pool problems' (see pp. 16–20), and may be compared at rest and during contraction. (ii) As with the H reflex, and unlike the PSTH, varying the conditioning-test interval allows the full time course of an effect to be investigated without the risk that weak effects at long latency are obscured by the AHP or by recurrent inhibition elicited by a large conditioning monosynaptic discharge (Ia or corticospinal in origin) (see p. 37).

Limitations

(i) A single motor unit must be held for a long time using a needle electrode – first for a number of PSTHs (to document the threshold for the Ia EPSP) and then during the experimental studies.
(ii) The method can be applied only in muscles in which an H reflex is recordable at rest.
(iii) Only motor units of relatively low threshold can be studied.

Stimulation of the motor cortex

The development of techniques to stimulate the motor cortex through the intact scalp and skull allows studies of corticospinal function in intact co-operative human subjects, and has led to new diagnostic procedures and considerable advances in motor control physiology. Most of the pioneer work was undertaken by Marsden, Rothwell and colleagues, and this section is largely based on a comprehensive review by Rothwell (1997).

EMG responses evoked by cortical stimulation

Motor evoked potentials (MEPs) evoked by transcranial stimulation

These are recorded by surface electrodes over the corresponding muscle belly as is done for reflex studies. MEPs may be recorded at rest. However, as for the H reflex, a weak voluntary contraction raises the active motoneurone pool to firing threshold, thereby potentiating the response and helping to focus the MEP on the target muscle. In addition, the appropriate cortical circuits are facilitated by the voluntary activity, and this is particularly relevant when using magnetic stimulation, which activates the corticospinal system trans-synaptically (see below).

Surface electrodes are not selective

Surface electrodes can record EMG potentials generated at a distance. The detection of cross-talk is particularly important in the context of motor cortex stimulation, because: (i) the stimulus is not focal; (ii) even if it were, the response rarely involves a single

muscle; (iii) the effect observed following stimulation at a given site over the motor cortex depends on the existing level of background activity and can be reversed by switching voluntary activity from agonists to antagonists; (iv) reorganisation of the motor cortex may occur after neurological lesions. Crosstalk may be recognised by muscle palpation (except with near-threshold stimuli), and by the fact that the frequency content of EMG activity generated at a distance is narrower, the power spectrum being shifted to lower frequencies (see Capaday, 1997).

PSTHs

PSTHs of single motor units may be constructed after cortical stimulation. The intensity of the stimulation should then be set so that during voluntary activation of a unit cortical stimulation only changes its firing probability (i.e. the unit does not contribute to a compound MEP, or can be reliably recorded in isolation, usually with a needle electrode).

Mono- and non-monosynaptic transmission of corticospinal excitation

The sharp increase and short duration of the early peak in the PSTH of single units and its short latency (see Fig. 1.18(*f*)) strongly suggest that the onset of the excitation involves monosynaptic transmission, as might be expected from studies in higher primates. However there is considerable evidence (see Chapter 10) that, in human subjects, a significant component of the corticospinal excitation of upper limb motoneurones is relayed through propriospinal interneurones rostral to the motoneurone pool.

Electrical stimulation

The impetus for transcranial stimulation came from the studies of Merton and Morton (1980). They used a single high-voltage transcranial capacitive discharge and showed that stimulation over the motor cortex could produce a twitch of contralateral limb muscles.

Methodology

Anodal transcranial stimulation has a lower threshold than cathodal stimulation (Rothwell *et al.*, 1987; Burke, Hicks & Stephen, 1990). Merton and Morton used a bipolar electrode arrangement. For activation of hand muscles, the anode was placed 7 cm lateral to the vertex and the cathode at the vertex; for activation of the leg muscles, the anode was placed at the vertex and the cathode 6 cm anterior. Close bipolar stimulation with an inter-electrode distance 2 cm or less is more focal, but less effective, since higher stimulus intensities are needed to produce EMG responses (Cohen & Hallett, 1988), and this is more painful.

Multiple descending volleys elicited by cortical stimulation

In monkeys, a single stimulus applied at threshold intensity to the surface of the motor cortex activates pyramidal tract axons *directly*, eliciting a descending pyramidal volley termed the D wave ('D' for 'direct', due to direct stimulation of the corticospinal neurone or its axon). With higher stimulus intensities, the size of the D wave increases and the stimulus begins to recruit a series of subsequent volleys, 'I waves', which descend the pyramidal tract with the same velocity as the D wave, at intervals of ~1.5 ms (Patton & Amassian, 1954). I waves are due to transsynaptic activation of pyramidal tract neurones, and are so termed because the corticospinal neurones are activated 'indirectly'. Precisely how I waves are generated is unknown, i.e. whether they result from successive discrete excitatory inputs to the corticospinal neurone, whether they involve alternating excitatory and inhibitory inputs, or whether an essentially single input sets up a reverberating response from the neurone. The I waves are recruited in a particular order as stimulus intensity is increased. The reason for this is that the stimulus intensities necessary to recruit I waves are higher than those needed for D waves. Thus, at intensities above threshold for I waves, the stimulus will have already activated a number of corticospinal neurones in the preceding

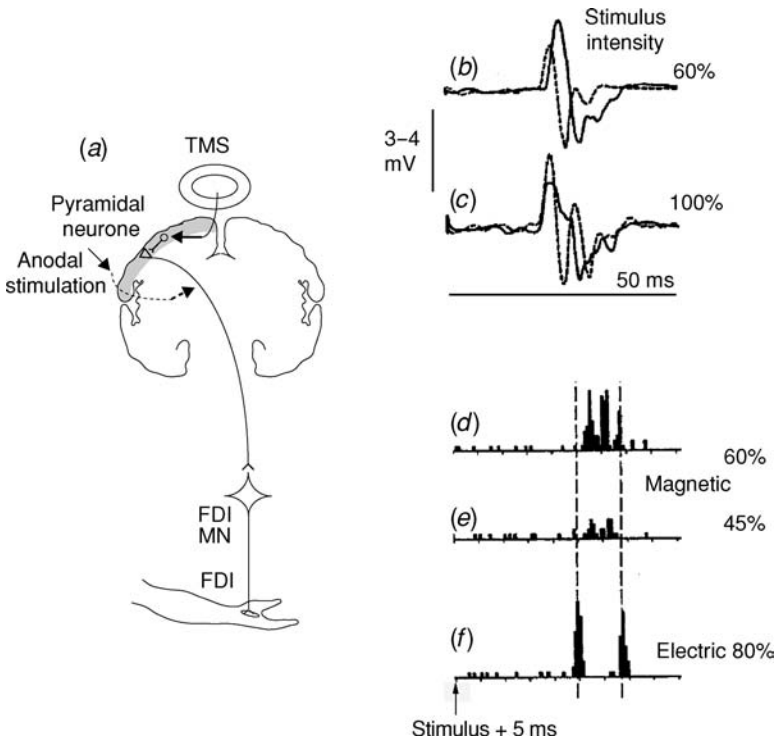


Fig. 1.18. Comparison of EMG responses evoked in human muscle by electrical and magnetic transcranial stimulation. (*a*) Sketch of the presumed pathways: a pyramidal neurone projecting to a first dorsal interosseus (FDI) motoneurone (MN) is activated at the level of its axon (dashed arrow) by anodal electrical stimulation, and trans-synaptically (continuous arrow) by transcranial magnetic stimulation (TMS). (The grey matter is only sketched in the motor area of the stimulated hemisphere.) (*b*), (*c*) Surface EMG responses in pre-activated FDI muscle after different intensities of stimulation (60% (*b*), and 100% (*c*)) following electrical stimulation (anodal, dashed lines) and TMS (induced current flowing in posterior-anterior direction over the lateral part of the motor strip, continuous lines) (from Day *et al.*, 1989). (*d*)–(*f*) Comparison of the effects of anodal electrical stimulation (*f*) and TMS (at intensities of 60% and 45% (*d*), (*e*)) on the PSTH of the same FDI motor unit (calibration 2.5 ms). The two peaks in (*f*) are thought to be due to corticospinal D and I waves. Adapted from Rothwell (1997), with permission.

D wave. These may be refractory during the first I-wave input and only able to respond in the second or the third I wave. In human subjects, the recruitment of D and I waves after transcranial electric stimulation seems very similar to that seen after direct stimulation of the exposed motor cortex in monkeys. Intra-operative recordings during scoliosis surgery from the spinal epidural space of descending volleys produced by transcranial stimulation show initial recruitment of an early rapidly conducted D wave followed by a series of I waves that have a similar conduction velocity as the D wave (Boyd *et al.*, 1986; Burke, Hicks & Stephen, 1990). From a practical point of view, only with relatively weak transcranial electrical stimuli does the D wave arise at cortical level: with relatively strong stimuli, the shortest latency component of the D wave produced by scalp stimulation probably arises from the decussation of the pyramids (Rothwell *et al.*, 1994). At threshold, D wave responses to transcranial electrical stimulation probably arise from the axon, several nodes distant to the cell body (see Rothwell, 1997).

Motor evoked potentials (MEPs) elicited by electric stimulation

Figure 1.18(*b*), (*c*) (dashed line) shows the EMG potential produced in the first dorsal interosseus (FDI) muscle by anodal electrical stimulation of the brain. The latency of EMG responses elicited by electrical stimulation is short, and the calculated central motor conduction time from the cortex to spinal motoneurones (using F wave estimates of peripheral conduction times) is about 4 ms for biceps motoneurones at C5 and 5 ms for C8 hand muscles (see Rothwell *et al.*, 1991). Such short latencies suggest that at least the onset of the MEP is produced by activity in the fast-conducting corticospinal axons, probably the monosynaptic component of the corticospinal tract.

Changes induced in the PSTH of single units

The PSTH of a FDI unit in Fig. 1.18(*f*) shows that anodal electrical stimulation produces an early peak with a sharp increase and short duration, probably due to the D wave activating the motoneurone monosynaptically (Day *et al.*, 1989). Increasing the stimulus intensity recruits further peaks which follow the initial peak at intervals of ∼1.5 ms, and are thought to be due to the arrival at the motoneurone pool of I-wave volleys. This is illustrated in Fig. 1.18(*f*), where the initial peak is followed ∼4 ms later by a second peak due to the I_2 wave (pyramidal neurones being refractory at the latency of the I_1-wave, cf. above).

Disadvantages

The major problem with transcranial electrical stimulation is that only a small fraction of the current flows into the brain. Much of the current flows between the electrodes on the scalp and produces strong discomfort, local pain and contraction of the scalp muscles.

Magnetic stimulation

Like electrical stimulation, transcranial magnetic stimulation of the motor cortex (TMS) readily evokes EMG responses in contralateral muscles. However, the magnetic field can penetrate scalp and skull with minimal discomfort, perhaps only that due to the contraction of scalp muscles. TMS is therefore now used exclusively for clinical studies and almost exclusively in research studies. In general, electrical stimulation is only used (with TMS) when testing the excitability of corticospinal neurones (cf. p. 44). Because the responses in arm muscles appear to behave differently to those in the leg, they will be considered separately.

General methodology

The magnetic stimulation coil

This consists of coils of wire connected to a large electrical capacitance. When the capacitance is discharged, a large but transient current flows through the coil, some several thousand ampères within 200 μs. The current produces a magnetic field of up to 3 tesla oriented perpendicular to the coil (see Barker, Jalinous & Freeston, 1985). The skull presents a low impedance to magnetic fields of this frequency, and the magnetic field induces eddy currents in superficial layers of the brain at right angles to the field. It is these which stimulate the neural tissue, specifically the axons of cortical neurones. It is worth noting that the neural tissue is stimulated electrically with both forms of transcranial stimulation. What differs is the method of delivery.

Electrical currents induced by the magnetic field

These flow parallel to the surface of the brain. The magnetic field falls off rapidly with distance from the coil: with a typical 12 cm-diameter round coil, the strength falls by half at a distance of 4–5 cm from the coil surface (Hess, Mills & Murray, 1987). Experiments in monkeys suggest that, even at the highest stimulus intensities, there is no significant activation of corticospinal fibres outside the grey matter (Edgley *et al.*, 1990).

Stimulation using different coils

With standard round coils, the induced current in the brain flows from an annulus underneath the

coil, which is usually some 8–12 cm in diameter. The direction of current flow in the coil is optimal for stimulation of the left hemisphere when counter-clockwise and the right when clockwise. Coils wound in a figure-of-8 shape provide a more focal stimulus, and the lowest threshold occurs when the induced current in the brain flows from posterior to anterior at an angle approximately perpendicular to the line of the central sulcus (Mills, Boniface & Schubert, 1992). Cone-shaped coils are now often used to evoke responses in foot, leg or thigh muscles.

Responses in upper limb muscles

Longer latency of EMG responses evoked by magnetic stimulation

When current in the coil flows in an antero-medial to a latero-posterior direction (i.e. in the direction opposite to that of the induced current in the brain), the latency of EMG responses evoked in active muscles is 1–2 ms longer than those evoked by threshold transcranial electrical stimulation (Day *et al.*, 1989). This holds for both the MEP (Fig. 1.18(*b*)) and the earliest peak in the PSTHs from single units (Fig. 1.18(*d*)–(*f*)).

Trans-synaptic activation of pyramidal tract neurones by cortical stimulation

The most likely explanation for the difference in latency of the EMG responses in human hand muscles is that originally put forward by Day *et al.* (1989): magnetic stimulation at threshold activates pyramidal tract neurones trans-synaptically (continuous horizontal arrow in the sketch in Fig. 1.18(*a*)) to produce I waves in the pyramidal tract, whereas electrical stimulation activates axons directly to produce D waves (dashed horizontal arrow in Fig. 1.18(*a*)). This view has been confirmed by epidural recordings in conscious co-operative patients of the corticospinal volleys produced by transcranial electrical and magnetic stimulation (di Lazzaro *et al.*, 1998). Thus, the latency difference between EMG responses produced by the two techniques is the time taken for trans-synaptic activation of pyramidal neurones following excitation of cortical elements oriented parallel to the surface, such as stellate cells or cortico-cortical connection fibres (see Rothwell, 1997).

TMS can also activate pyramidal axons directly

A D wave is produced in corticospinal axons to upper limb motoneurones when the coil is rotated or the intensity of stimulation is increased significantly (e.g. see Fig. 1.18(*c*); Werhahn *et al.*, 1994). Direct recordings of descending activity obtained in anaesthetised human subjects during surgery have shown that TMS can produce D waves with a lower threshold than I waves (Burke *et al.*, 1993), but: (i) the combination of relaxation and deep anaesthesia is then likely to depress the synaptic activity responsible for generating I waves (Hicks *et al.*, 1992); (ii) the threshold for recruiting such D waves in the pyramidal tract in unconscious individuals is usually two or more times higher than the usual threshold for producing EMG responses in normal active muscles (Berardelli *et al.*, 1990; Burke *et al.*, 1993; Fujiki *et al.*, 1996). The situation has, however, been complicated by further recordings of corticospinal volleys in two unanaesthetised subjects using epidural leads: stimulation using clockwise current through a large circular coil appeared to be more diffuse than with a figure-of-8 coil and induced D waves preferentially in one of the two subjects (Di Lazzaro *et al.*, 2002), much as occurs regularly in the anaesthetised patients.

Responses in leg muscles

The responses evoked by either anticlockwise transcranial magnetic or anodal electrical stimulation of the leg area are of equal latency in the tibialis anterior (Priori *et al.*, 1993). This was thought to indicate that both activate pyramidal axons at the same site, at a point near the cortical surface, where they bend to leave the cortex and curve towards the internal capsule (Priori *et al.*, 1993). The implication is that magnetic stimulation of the leg area readily produces D-wave activity. An alternative possibility was raised by Nielsen, Petersen and Ballegaard (1995). They found that the EMG responses evoked

by anodal stimulation 2–3 cm lateral to the vertex occurred 1–2 ms earlier than those evoked from the vertex, and they interpreted this as direct stimulation of corticospinal axons deep to cortex. In accordance with this interpretation, epidural recordings of corticospinal volleys in awake co-operative human subjects have revealed that both anodal stimulation at the vertex and magnetic stimulation produce I waves at threshold; however, electrical stimulation consistently evoked D waves only when the anode was shifted 2 cm lateral to the vertex (Di Lazzaro *et al.*, 2001).

Critique: advantages, limitations, conclusions

Cortical stimulation may be used to evoke test responses and conditioning stimuli

Test responses

During voluntary contraction, the recruitment sequence in a voluntarily activated motoneurone pool is similar for Ia and corticospinal inputs (cf. below). The H reflex and the MEP should therefore be modified similarly by conditioning stimuli, unless the conditioning volley alters (i) motor cortex excitability (see below); (ii) presynaptic inhibition of Ia terminals mediating the afferent volley of the test reflex (Chapter 8, pp. 343–4); or (iii) transmission of that part of the corticospinal volley transmitted through an interneuronal relay (Chapter 10). A practical consequence of the difference in the sites of activation in the hand area is that threshold responses to electrical stimulation (due to direct activation of corticospinal axons) should be less affected by changes in cortical excitability than those evoked by magnetic stimulation (due to trans-synaptic activation of pyramidal neurones). This has been used as a method for suggesting that changes in the MEP observed in various experimental situations reflect changes in excitability of cortical neurones: e.g. cutaneous modulation of the MEP in the tibialis anterior (Chapter 9, pp. 422–4).

Conditioning stimulation

Subliminal transcranial magnetic stimulation has been used extensively to investigate the corticospinal control of all spinal cord circuits for which there are reliable methods of investigation (cf. Chapters 3–10).

Limitations

Diffuse stimulation

It is impossible to focus the magnetic field in order to restrict the extent of the induced current flow only to specific cortical areas and, at rest, TMS induces responses in several muscles. A good way of focusing the stimulation on one muscle is to record the response from a voluntarily activated muscle, but it is then impossible to investigate changes in transmission produced by a voluntary contraction. It is essential that the position of the coil on the scalp is stable throughout an experiment, and different methods have been proposed to ensure this. Manual fixation against a reference grid marked on the scalp is the simplest way (see Capaday, 1997). Alternatively the position of the coil may be secured by a harness (Schubert *et al.*, 1997). In any event, because the focusing of the response on a particular muscle is dependent on the position of the coil over the scalp, it is important that the subject does not move the neck during the session. Long experiments can become uncomfortable.

Input–output relationship within the motoneurone pool

As for the H reflex, the input–output relationship within the motoneurone pool is sigmoid, and it is important to set the stimulus intensity within the range corresponding to the steep (roughly linear) part of the relationship (see Capaday, 1997).

Motoneurones responsible for the MEP

During voluntary contractions, the recruitment sequence in the activated motoneurone pool is

the same for Ia and corticospinal inputs, i.e. from small slow-twitch to large fast-twitch units (Bawa & Lemon, 1993). However, with the technique of the unitary H reflex, it has been shown that, in ECR *at rest*, H reflexes and MEPs of similar size do not necessarily recruit the same population of motoneurones (Nielsen *et al.*, 1999). This could be because the component of the corticospinal excitation transmitted through the propriospinal relay is distributed evenly across motoneurones in the pool (see Chapter 10, pp. 469–71). The consequence of this is that a different modulation of the MEP and the H reflex *at rest* should be confirmed in single motor units with the technique described pp. 37–9 before inferring a specific effect on the volley mediating either response.

Multiple corticospinal volleys

The multiple volleys set up by a single stimulus produce temporal summation in the motoneurone pool, and it may be difficult to define the exact arrival time of the first corticospinal volley. This is particularly so in a muscle at rest where it is usual for motoneurone discharge to depend on summation of subliminal EPSPs.

Conclusions

The ability to study the effects of corticospinal volleys in awake subjects has been a major breakthrough in human motor control physiology (and pathophysiology), because this has made it possible to investigate: (i) the transmission of corticospinal excitation to motoneurones, and (ii) the corticospinal control of spinal pathways.

Spatial facilitation

Underlying principles

Excitatory convergence

In animal experiments, the indirect 'spatial facilitation technique' has been used to demonstrate the existence of: (i) interneurones interposed in a given pathway (R. M. Eccles & Lundberg, 1957), and (ii) convergence from two different fibre systems onto common interneurones (e.g. I and II in Fig. 1.19(*a*); cf. Lundberg, 1975). The intensity of the stimuli is adjusted so that separate stimulation of either I or II does not elicit a post synaptic potential (PSP) in the motoneurone (first two rows in Fig. 1.19(*c*)) indicating that the volleys were subthreshold in the interneurone (first two rows in Fig. 1.19(*b*)). If combined stimulation of I and II then produces an EPSP in the motoneurone (last row in Fig. 1.19(*c*)), there must have been excitatory convergence onto common excitatory interneurones projecting to the motoneurone. In order to be sure that stimuli are sufficient to create EPSPs in the interneurones, it has proved convenient to use stimuli that separately excite at least a few interneurones, thus evoking small EPSPs in the motoneurone. When EPSPs from different sources are evoked simultaneously in one motoneurone the resulting EPSP can, at most, be equal to their algebraic sum (see Eccles, 1964, his Fig. 13*(J), (M)*). Thus, excitatory convergence onto common interneurones can be inferred when the EPSP on combined stimulation is larger than the algebraic sum of the EPSPs evoked by separate stimuli. The method can also be used to show convergence of two excitatory inputs onto common inhibitory interneurones, recording the resultant IPSP in the motoneurone.

Convergence of excitation and inhibition onto common interneurones

A modification of the technique is used to establish convergence of excitation and inhibition onto common interneurones. Activation of system I evokes a test PSP (either EPSP or IPSP) in motoneurones, whereas activation of system II is without effect in the motoneurone by itself. If the test PSP is decreased or abolished with combined stimulation, the conditioning stimulus II probably had an inhibitory effect on the interneurones, provided that it did not change membrane conductance of the motoneurone or produce presynaptic inhibition of the primary afferents of system I (cf. Lundberg, 1975).

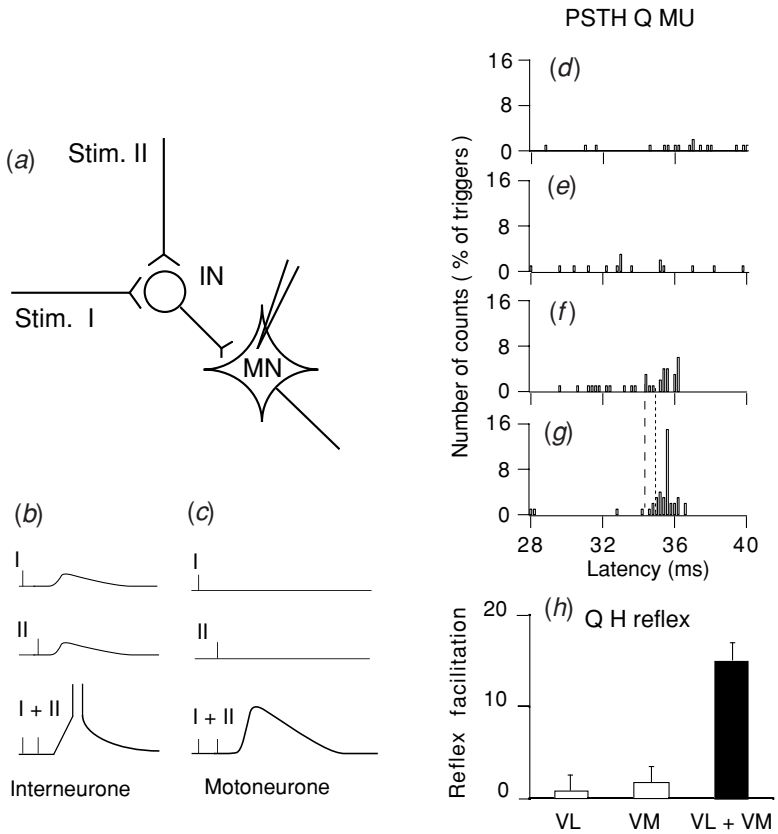


Fig. 1.19. Spatial facilitation. (*a*) Diagram showing convergence of two inputs (stimulus [Stim.] I and II) onto common interneurones (IN), while recording intra-cellularly from one motoneurone (MN). (*b*) Either input by itself evokes a subliminal EPSP in INs, but combined stimulation (I + II) summates the EPSPs and fires the INs. (*c*) Neither input by itself has an effect on the MN, but combined stimulation evokes an EPSP in the MN. (*d*)–(*g*) PSTHs in a quadriceps (Q) unit (0.2 ms bins, latency after TMS even when peripheral stimulation is given alone) showing: the background firing (*d*), the effect of common peroneal nerve stimulation by itself ((*e*) 0.7 × MT), the effect of TMS by itself ((*f*) 26% of the maximal stimulator output), the effect of combined stimulation ((*g*) 11 ms ISI). Dashed and dotted vertical lines in (*f*), (*g*): onset of the corticospinal peak and of the extra facilitation on combined stimulation, respectively. (*h*) Amount of facilitation (conditioned – control reflex as a percentage of control reflex) of the quadriceps (Q) H reflex after separate (□) and combined (■) stimulation of the vastus lateralis (VL) and vastus medialis (VM) nerves (0.4 × MT, 8 and 9 ms ISI, respectively). Adapted from Baldissera, Hultborn & Illert (1981) ((*a*)–(*c*)), Marchand-Pauvert, Simonetta-Moreau & Pierrot-Deseilligny (1999) ((*d*)–(*g*)) and Fournier *et al.* (1986) (*h*), with permission.

Spatial facilitation judged in the PSTH of single units recordings

Here spatial facilitation involves comparing the effects of two volleys delivered separately and together on the PSTHs of a single motor unit.

Summation of two PSPs at a premotoneuronal level

Summation of EPSPs

This is illustrated in Fig. 1.19(*d*)–(*g*). In this quadriceps unit, the background firing (*d*) was not modified by a common peroneal nerve volley (*e*), and TMS at

threshold only evoked a small peak of corticospinal excitation (*f*). However, when the two stimuli were combined (*g*), there was a large facilitation of the corticospinal peak (Marchand-Pauvert, Simonetta-Moreau & Pierrot-Deseilligny, 1999).The summation of two excitatory inputs in a motoneurone produces little more than the sum of their effects in the PSTH (cf. below), and such a large extra facilitation therefore implies spatial facilitation of the two inputs at an interneuronal level (Pauvert, Pierrot-Deseilligny & Rothwell, 1998). Convergence of the two volleys onto interneurones is further supported by the absence of extra facilitation in the first bins of the corticospinal peak (between vertical dotted and dashed lines in (*f*), (*g*)). This is what would be expected if cortical and peripheral volleys converged onto common interneurones rather than directly onto the motoneurone. Because of the synaptic delay at the interneurone, this input would arrive at the motoneurone after the direct monosynaptic corticomotoneuronal input. Thus facilitation transmitted through an interneuronal relay should not affect the onset of the corticospinal response, and 'initial sparing' should be demonstrable, as it was.

Convergence in inhibitory pathways

This may be demonstrated with a similar method. Thus, Fig. 1.7(*c*)–(*f*) reveals that separate stimulation of the deep peroneal and femoral nerves produced facilitation, but combined stimulation resulted in a suppression of the peak of femoral excitation. Here again, the convergence at interneuronal level was confirmed by the finding that suppression on combined stimulation spared the initial bins of the peak of excitation.

Limitations

Under resting conditions, the summation of EPSPs in a motoneurone is linear (cf. p. 45). However, when using the PSTH method described in this chapter, there may be facilitation on combined stimulation if the two stimuli are delivered appropriately early in the AHP. Two monosynaptic EPSPs can be evoked at a point in the recovery from the post-spike AHP where a single EPSP would cause the motoneurone to fire only occasionally, but where a combination of two EPSPs would often produce a discharge. As a result the effect on combined stimulation would be greater than the sum of effects of separate stimuli. However, this problem can be identified because: (i) the facilitation affects the whole peak of excitation in the PSTH, including its initial part, i.e. there is no 'initial sparing' (Pauvert, Pierrot-Deseilligny & Rothwell, 1998); (ii) there should be few or no counts in PSTH bins preceding the peaks produced by each input alone and when they are given together (see p. 34).

Spatial facilitation judged from monosynaptic test reflexes

Method

The principles of spatial facilitation can also be applied when using a monosynaptic reflex to assess the excitability of the motoneurone pool: the excitatory effects of two conditioning stimuli (I and II) are measured when applied separately and together, and summation of excitatory effects elicited by the two inputs in common interneurones is likely when facilitation of the reflex on combined stimulation is larger than the algebraic sum of the facilitations evoked by separate stimuli. Thus, Fig. 1.19(*h*) shows that weak conditioning stimuli to the vastus lateralis and vastus medialis nerves evoked significant reflex facilitation when applied together (■), much greater than the sum of the individual effects shown in the open columns (Fournier *et al.*, 1986). This suggests that the two conditioning volleys converged onto common interneurones.

Limitations

Because the H reflex assesses the excitability of a motoneurone pool, the extra facilitation on combined stimulation could also result from non-linearity or inhomogeneity within the pool. Such possibilities must be ruled out before inferring summation at a premotoneuronal level.

(i) At low reflex amplitudes the sensitivity of the H reflex to facilitation increases with increasing size of the control reflex (see pp. 16–18). An excitatory conditioning stimulus increases the size of the test reflex and, if the reflex is small, this enhances its susceptibility to facilitation by the second stimulus. Such problems can be avoided by adjusting the strength of the conditioning stimuli so that at least one of them does not evoke any H reflex facilitation by itself (Fournier *et al.*, 1986).

(ii) Inhomogeneity would occur if the distribution of the conditioning EPSPs within the pool was different from that of the test Ia EPSPs (which excite preferentially slow motoneurones, see pp. 3–4). Each conditioning EPSP might then excite preferentially fast motoneurones but insufficiently to allow them to be recruited by the test reflex, thus giving no demonstrable effect with separate stimuli. On combined stimulation, summation of conditioning EPSPs in these fast motoneurones would increase their excitability enough to fire them in the test reflex, producing an extra facilitation at motoneurone level. Experiments on single motor units are required to eliminate this possibility.

Conclusions

Spatial facilitation is an important technique because it allows one to study interneuronal circuits in human subjects by providing evidence for convergence of different inputs (e.g. peripheral and corticospinal) onto common interneurones. However, the results of such studies need to be interpreted with caution, because false-positive results can occur due to non-linear summation in the pool of motoneurones, and there may be problems even in a single active motoneurone.

Coherence analysis between EMG/EMG or EEG/EMG signals

Traditional techniques for studying neural circuitry underlying motor commands in man involve conditioning stimuli which generate artificially synchronised signals in the central nervous system. Recent methodological advances based on frequency (Fourier) analysis (calculation of spectra, cross-spectra, coherence and phase between simultaneously recorded natural EMG/EMG and/or EMG/EEG inputs) allow the motor system to be studied without the use of artificial inputs (see Farmer *et al.*, 1997; Brown *et al.*, 1998). However, these methods are now developing and require further clarification before being applied in routine clinical or physiological studies, and they will only be considered briefly in this edition of the book.

Cross-correlation

Valuable information about the organisation of the synaptic input to motoneurones during motor behaviour may be obtained from analysing the coupling between motor units in the active muscles. The framework for this has been established over the past 15–20 years (Amjad *et al.*, 1989; Halliday *et al.*, 1995; Farmer *et al.*, 1997). Based on theoretical considerations and experimental data, it may be concluded that two neurones receive a common drive from branches of common last-order neurones when the discharges of the two neurones are tightly coupled within a few milliseconds of each other (Sears & Stagg, 1976). Such short-term synchrony is observed for the discharges of pairs of human motor units recorded from the same or synergistic muscles (Bremner, Baker & Stephens, 1991a,b). The duration of the short-term synchrony is usually longer than required to reject other mechanisms, but it is generally accepted that a common drive from last-order neurones, is of major importance for its occurrence (see Farmer *et al.*, 1997).

Coherence techniques

It is also possible to demonstrate coupling of motor unit activity in the frequency domain (Davey *et al.*, 1994; Farmer *et al.*, 1993, 1997; Halliday *et al.*, 1995).

Generally, coherence is observed in a frequency band between 15 and 30 Hz, although coherence peaks may also be seen around 40–60 Hz (Farmer *et al.*, 1993, 1997; McAuley, Rothwell & Marsden, 1997; Brown *et al.*, 1998). The coherence peaks reflect the frequency content of the last-order input to the spinal motoneurones, and in the case of the coherence between 15 and 30 Hz, the evidence suggests that it depends on intact transmission in the pyramidal tract (cf. Farmer *et al.*, 1993, 1997).

General conclusions

Methods

A number of methods have been developed to investigate the changes in excitability of human motoneurones after a conditioning volley. The simplest one is the modulation of the on-going EMG, which provides rapidly a full-time course of the changes in motoneuronal excitability. This is a distinct advantage when investigating patients, but the temporal resolution of the method is weak. Because the H reflex enables a comparison of the results obtained at rest and during movement, it remains the only available method with which it is possible to investigate how transmission in spinal pathways is changed by motor tasks in human subjects. The technique of the H reflex is simple but, besides changes in motoneuronal excitability, the size of the reflex depends on mechanisms acting on the afferent limb of the reflex and on 'pool problems'. The drawbacks related to the complexity of the so-called monosynaptic reflex pathway can usually be controlled by parallel investigations on single motor units (using post-stimulus time histograms for voluntarily activated units, or the unitary H reflex). Such studies should be performed systematically when studying motor control physiology in human subjects, keeping in mind the fact that the recordings provide data only for the lowest-threshold motoneurones in the pool, and that the fractionation and focusing of voluntary drives necessary for PSTHs may result in an unnaturally biased input to the pool. The F wave provides a flawed measure of the excitability of the motoneurone pool and has little place as a research tool. Cortical stimulation has made it possible to investigate corticospinal excitation of motoneurones and the corticospinal control of spinal pathways. However, a single stimulus can generate multiple corticospinal volleys and this complicates the interpretation of the results. Spatial facilitation is an indirect technique used to demonstrate the convergence of two inputs onto common interneurones projecting to the motoneurone(s) being tested, and is an indispensable tool for probing interneuronal circuits in human subjects.

Development

There has been considerable development of methods available to explore spinal pathways in human subjects since the first investigations performed with the H reflex in the 1950s: PSTHs of single units, spatial facilitation techniques, cortical stimulation. These developments have resulted in considerable advances in motor control physiology and in new diagnostic procedures. An important principle is that, in human experiments, conclusions are more firmly based when supported by evidence using more than one technique.

Résumé

Monosynaptic reflex

Initial studies

The monosynaptic reflex was introduced in animal studies in the early 1940s as a tool for investigating excitability changes in the motoneurone pool. In human subjects, the first motoneurones discharging in the soleus H reflex elicited by electrical stimulation of the posterior tibial nerve have been shown to do so at a latency consistent with a monosynaptic pathway.

Underlying principles

Ia afferents have monosynaptic excitatory projections onto homonymous motoneurones, and this pathway is responsible for the tendon jerk. In the control reflex, a group Ia volley causes some motoneurones to discharge and creates EPSPs in other motoneurones which, though they do not discharge, are slightly depolarised. If motoneurones are facilitated by a conditioning volley, the size of the test reflex increases because some of these subliminally excited motoneurones will discharge in response to the summation of conditioning and test EPSPs. Conversely, if motoneurones receive conditioning IPSPs, the test Ia volley will no longer be able to discharge the motoneurones last recruited into the control reflex, and the size of the test reflex will be decreased.

Basic methodology

(i) H reflexes can be recorded at rest from soleus, quadriceps, semitendinosus, and FCR, and from virtually all limb muscles during weak voluntary contractions.

(ii) Reflexes are recorded through bipolar surface electrodes placed over the corresponding muscle belly. Reflex latency is measured to the first deflection of the H wave from baseline, and its amplitude usually assessed peak-to-peak. Contamination of the recording by the EMG of another muscle may occur due to spread of the test or conditioning stimuli, volume conduction of the conditioning potential, or to the fact that the reflex response occurs in a number of muscles, not just the one being studied. Palpation of muscle tendons may help identify this problem. Another simple way of ensuring that the reflex response originates from the muscle over which it is recorded is to check that it increases during voluntary contraction of that muscle.

(iii) H reflexes are obtained by percutaneous electrical (or magnetic) stimulation of Ia afferents in the parent nerve. The optimal stimulus duration for eliciting the H reflex is long (1 ms). The best method involves placing the cathode over the nerve and the anode on the opposite side of the limb. However, in areas where there are many nerves, bipolar stimulation should be used to avoid encroachment of the stimulus upon other nerves. Reflex attenuation due to post-activation depression is sufficiently small after 3–4 s to allow routine testing at 0.2–0.3 Hz for relaxed muscles.

(iv) H and M recruitment curves: when increasing the intensity of the electrical stimulus to the parent nerve, there is initially a progressive increase in the reflex amplitude. When the threshold of motor axons is exceeded, a short-latency direct motor response (M wave) appears in the EMG. Further increases in stimulus intensity cause the M wave to increase and the H reflex to decrease. The test reflex should never be on this descending part of the recruitment curve. Finally, when the direct motor response is maximal (M_{max}), the reflex response is totally suppressed, because the antidromic motor volley set up in motor axons collides with and eliminates the reflex discharge. M_{max} provides an estimate of the response of the entire motoneurone pool and must always be measured, and the amplitudes of the reflexes should be expressed as a percentage of M_{max}. The constancy of a small M wave may be used to monitor the stability of the stimulation conditions.

(v) Tendon jerks may be convenient for testing the excitability of motoneurones of proximal muscles, although this introduces two complications: the mechanical delay due to the tendon tap, and the possibility that changes in γ drive might alter the sensitivity of muscle spindle primary endings to percussion (however, see Chapter 3).

(vi) Control and conditioned reflexes should be randomly alternated, because this prevents the subject from predicting the reflex sequence, and regular alternation produces erroneously large results.

(vii) The H reflex technique underestimates the central delay: in individual motoneurones, the rise time of the EPSP ensures that the spike evoked by the monosynaptic input in the last recruited motoneurones occurs sufficiently late to be altered by a disynaptic PSP. An EPSP elicited by a conditioning volley entering the spinal cord after the test volley may summate with the test Ia EPSP and cause the motoneurone to discharge 'too early'. In the motoneurone pool, the test reflex discharge is desynchronised.

(viii) The recovery cycle of the H reflex is the result of too many phenomena to allow useful physiological insights.

(ix) With threshold tracking, test stimuli are varied to maintain an H reflex of constant size. Reflex facilitation produces a decrease in the current required to produce the test reflex. There are advantages of threshold tracking over the conventional technique of amplitude tracking: less variability, constant population of motoneurones contributing to the test response, avoiding the problem of size-related changes in test reflex sensitivity, and the dynamic range of threshold tracking is wide. There are also disadvantages: changing stimulus intensity changes the intensity of the afferent volley, and the reflex size also depends on mechanisms acting on the afferent volley (see below); when excitability changes, there is a delay before a new threshold can be reached.

Reflex size also depends on mechanisms acting on the afferent volley

As a result, many mechanisms other than changes in motoneurone excitability can alter reflex size.

(i) Changes in the excitability of Ia afferent axons will occur when there is a change in the discharge rate of those axons. An increased discharge rate will produce 'activity-dependent hyperpolarisation' of the active axons. When axons hyperpolarise, a constant stimulus will produce a smaller afferent volley.

(ii) Changes in presynaptic inhibition of Ia terminals must always be considered when there is a change in the amplitude of the monosynaptic reflex. To that end, several methods have been developed (see Chapter 8).

(iii) Post-activation depression of the monosynaptic reflex is due to reduced transmitter release from previously activated Ia afferents, and is prominent at short intervals of 1–2 s or less (see Chapter 2). The depressive effects of stimulus rate on the reflex size are generally taken into account in reflex studies, but post-activation depression occurs under any circumstance that activates the Ia afferents responsible for the test reflex, and this is often ignored. Misinterpretations have arisen when comparing test reflexes recorded at rest and during or after a voluntary contraction because this phenomenon was neglected.

(iv) Autogenetic inhibition elicited by the test volley helps limit the size of the reflex. The quadriceps H reflex may be suppressed by conditioning volleys that, by themselves, do not depress the on-going EMG or the background firing of single motor units. The suppression is due to convergence between the conditioning volleys and group I (Ib) afferents in the test volley for the H reflex onto inhibitory interneurones mediating disynaptic group I inhibition. This helps limit the size of the H reflex, and creates a problem for H reflex studies, because the reflex cannot be considered exclusively monosynaptic. Only those changes that affect the entire monosynaptic excitatory peak in the PSTH of single units to the same extent, and specifically those that affect the initial 0.5–1.0 ms of the peak, can be considered to have affected the monosynaptic pathway.

'Pool problems'

(i) Expressing the changes in the H reflex size as a percentage of control values causes changes to appear much larger with the smaller test H reflexes. This is a mathematical consequence of normalising to control H reflexes of different size, and can be avoided by expressing the results as a percentage of M_{max}.

(ii) Size-related sensitivity of the test reflex (non-linearity within the motoneurone pool). Because the

input–output relationship in the motoneurone pool is sigmoid, when the conditioning input is strong, the number of additional motoneurones recruited (or de-recruited) by a constant input increases with increasing size of the control test reflex and then decreases. When the effect of the conditioning input is more modest, the relationship is relatively flat between the two phases of increase and decrease. The input–output relationship must be taken into account when the size of the control H reflex evoked by a constant test stimulus is different (e.g. when comparing rest and contraction). To set the test stimulus intensity so that the reflex remains within the linear range may be a solution when the conditioning effect is moderate. Otherwise, the intensity of the test stimulus may be adjusted so that the size of the unconditioned reflex is the same in the two situations, but this introduces problems because changing the intensity of the test stimulus alters the afferent volley responsible for the reflex.

(iii) Changes in the recruitment gain of the reflex. Despite a control reflex of constant size, a greater change in the H reflex could occur (e.g. during movement) if the conditioning input had different effects on low- and high-threshold motoneurones, thus compressing the range of thresholds in the motoneurone pool and increasing the slope of the input–output relationship for the test reflex (i.e. altering the 'recruitment gain' of the reflex). As a result, a constant conditioning volley would then recruit more motoneurones than in the control situation, even though there was no change in the specific pathway explored. The only way to control for this possibility is to investigate whether the conditioning EPSP is changed in single motor units.

(iv) Plateau potentials can develop in motoneurones, and may be triggered by peripheral inputs and/or voluntary effort. The triggering of 'plateaux' would greatly distort the input–output relationship of the pool.

Normative data

Reflex amplitude varies widely in normal subjects, and amplitude measurements in patients are of little value except when pathology is asymmetrical. Reflex latency has a strong correlation with height and a weak but significant correlation with age.

Conclusions

The H reflex technique is attractively simple, but strict methodology is required for valid results. The reflex pathway is not as simple as it first seems, but most of the complexities may be controlled by parallel investigations on the discharge of single motor units. The H reflex enables a comparison of results obtained at rest and during movement, and it therefore remains the standard method for investigating how transmission in spinal pathways is changed during motor tasks in human subjects.

F wave

Principles of the method and basic methodology

A supramaximal electrical shock delivered to a nerve will elicit, in addition to the M_{max} response, a late response, termed the F wave. The pathway involves an antidromic volley in motor axons, 'backfiring' of motoneurones and conduction of an orthodromic volley to the muscle. For many muscles, F waves occur in high-threshold motoneurones preferentially.

Characteristics

F waves can be recorded from any muscle. They typically vary from trial to trial in amplitude, latency and shape. The persistence is the percentage of stimuli that produce F waves. The latency of the F wave is roughly similar to that of the H reflex, and its amplitude is normally below 5% of M_{max}. Its sensitivity to changes in motoneurone excitability is low and it has little place as a research tool.

F wave studies

These are useful clinically in detecting acquired demyelinating polyneuropathies, where the latency of the F wave may be quite prolonged, and in suspected proximal nerve lesions that are otherwise inaccessible to routine testing.

Modulation of the on-going EMG

Principles of the method and basic methodology

The on-going EMG during a steady voluntary contraction is full-wave rectified, averaged, and plotted against the conditioning stimulus. An excitatory input to motoneurones will facilitate the on-going EMG activity, and an inhibitory one will suppress it. The central delay of a conditioning effect can be calculated from the expected time of arrival of the conditioning volley at the segmental level of the tested motoneurone pool.

Changes in the on-going EMG do not necessarily parallel those in the H reflex

This is because: (i) the on-going EMG is more sensitive to inhibition than the monosynaptic reflex, and (ii) mechanisms that can alter the efficacy of the group I test volley can alter the H reflex.

Critique: advantages, limitations, conclusions

Advantages

The full time course of the changes in motoneuronal excitability can be recorded more easily and more rapidly than when using the monosynaptic reflex; comparing the modulation of the on-going EMG during various motor tasks may give a general idea of the different patterns elicited by a given stimulus in these tasks; the absence of test stimulation avoids problems due to instability of the stimulating electrodes for the test volley during movement.

Limitations

The technique can be used only in an active motoneurone pool; the temporal resolution of the method is limited; when there is an initial facilitation, the subsequent post-spike AHP and recurrent inhibition can obscure late synaptic events; the type of motor unit involved in the EMG modulation cannot be specified.

Conclusions

Modulation of on-going EMG activity has the advantages of simplicity and speed, and this is an asset particularly in studies on patients. However, the technique can only provide a general idea of the response of the motoneurone pool to a stimulus.

Post-stimulus time histograms (PSTHs) of the discharge of single motor units

Almost by definition, the 'pool problems' inherent in the compound H reflex are not an issue when studying the responses of single motor units.

Underlying principles

The effect of a particular input to a single motoneurone can be determined by constructing a histogram of the timing of motoneurone spikes following repeated presentation of an appropriate stimulus. This procedure extracts from the naturally occurring spike train only those changes in firing probability that are time-locked to the stimulus.

Basic methodology

Recording

A prerequisite for PSTH investigations is the isolation of a single motor unit during voluntary contraction. This is possible with a window discriminator with variable upper and lower levels, and has been made easier with sophisticated template-matching paradigms that allow automatic recognition of the

shape of motor units. The background discharge of the unit must be stable to avoid false peaks or troughs in the PSTH.

Stimulation

Stimuli may be delivered randomly, or with respect to the discharge of the motor unit, each stimulus then being triggered at a fixed delay after the preceding motoneurone discharge. The latter allows one to avoid the AHP or conversely to use the AHP to attenuate the monosynaptic discharge of the motor unit. The intensity of the stimulation should be subliminal for the compound response.

Assessment of the timing of the changes in firing probability

The recording window usually begins after a fixed delay following the stimulus, when stimulus artefact and the M wave have disappeared. The latency of the first bin of a group of consecutive bins with a significant change in firing probability is taken as the latency of the effect. The time resolution of the method is excellent, dependent only on the bin width. The onset of a period of increased (EPSP) or decreased (IPSP) firing probability may be identified from a cumulative sum (CUSUM) display by the onset of a positive (or negative) slope. CUSUMs commonly allow more confident estimates of latency than can reasonably be achieved using raw histograms which inevitably contain irregular bin-to-bin fluctuations. To estimate the central delay of an effect, it is convenient to compare the latency of the peak (or trough) to that of homonymous monosynaptic Ia excitation in the same unit.

Assessment of the size and significance of the peaks and troughs in the PSTH

When stimulation is delivered randomly with respect to the discharge of the motor unit, the background firing is calculated during the period immediately preceding the stimulation. When stimulation is triggered by the previous motor unit discharge, the probability of firing is affected by the AHP following this discharge. To take the gradual recovery of membrane potential during the inter-spike interval into account, a histogram of firing probability is constructed under control conditions without stimulation, control and conditioned situations being randomly alternated in the same sequence. The control histogram is then subtracted from the conditioned one. To normalise the results it is convenient to express the number of counts in each bin as a percentage of the number of triggers. The PSTH method may be used to calculate the conduction velocity of the Ia afferents.

Conclusions

The PSTH is a valuable method, which allows the investigation of single motonerones in human subjects with good time resolution. It can be applied in virtually all muscles, and the use of needle electrodes allows studies on high-threshold motor units. It is an indispensable complement of the H reflex in avoiding 'pool problems'. The most important limitation is that it requires a voluntary contraction of the tested muscle.

Unitary H reflex

Methodology

A 'unitary' H reflex is the H reflex of a single motor unit and is recorded with a needle electrode. Using a threshold tracking technique, measurements are made of the current required to just discharge the motoneurone at rest and of the current required to produce a liminal homonymous Ia peak in PSTHs for the unit. The difference between these values has been termed the 'critical firing stimulus' (CFS) and represents the size of the EPSP needed to produce a discharge of the single motoneurone.

The CFS size

This can be used as a measure of the size of the test Ia EPSP necessary to activate the motoneurone. When conditioning stimuli produce an IPSP or EPSP within

a motoneurone, stronger or weaker test stimuli are required to discharge the motoneurone, and the CFS changes accordingly.

Conclusions

Advantages

Conditioning effects may be explored avoiding 'pool problems' at rest and during contraction; varying the ISI allows the investigation of the full time course without risk that a large early facilitation obscures weak effects of longer latency.

Limitations

The method requires holding a single motor unit with a needle electrode for a long time; it can be used only in muscles in which the H reflex is recordable at rest; only motor units with a relatively low firing threshold can be examined.

Stimulation of the motor cortex

EMG responses evoked by cortical stimulation

Transcranial stimulation of the motor cortex produces motor evoked potentials (MEPs) which can be recorded by surface electrodes placed over the corresponding muscle belly. MEPs can be recorded at rest, but a weak voluntary contraction potentiates the response and helps focus the MEP on the target muscle. The detection of cross-talk is particularly important, because the response is rarely restricted to a single muscle, and the effect observed following simulation at a given site over the motor cortex can be reversed merely by switching activity from agonists to antagonists. Cross-talk may often be recognised by muscle palpation. PSTHs of single units may be constructed after cortical stimulation, the stimulus intensity then being set so that during voluntary activation of the unit cortical stimulation does not affect the unit, other than to change its firing probability.

Multiple cortical volleys

A single anodal electrical stimulus at threshold intensity activates pyramidal tract axons directly, eliciting the D wave. At higher stimulus intensities, the stimulus recruits a series of subsequent volleys (I waves), which are due to trans-synaptic activation of pyramidal tract neurones.

Transcranial magnetic stimulation (TMS)

Magnetic stimulation is now used almost exclusively because the discomfort is minimal compared with that caused by electrical stimulation. The magnetic stimulator consists of coils of wire connected to a large electrical capacitance. When the capacitance is discharged, a large current flows through the coil, and this produces a magnetic field oriented perpendicularly to the coil. The magnetic field induces eddy currents which stimulate the axons of cortical neurones. A number of different coils is available. The latency of EMG responses evoked by magnetic stimulation in upper limb muscles is 1–2 ms longer than those evoked by threshold transcranial electrical stimulation. This is probably due to a difference in the point at which the two methods of stimulation activate the corticospinal pathways: magnetic stimulation at threshold tends to activate pyramidal tract neurones trans-synaptically (producing I waves in the pyramidal tract) whereas electrical stimulation tends to activate axons directly producing D waves. The abrupt increase and short duration of the early peak in the PSTH of single units strongly suggests monosynaptic onset of corticospinal excitation in motoneurones. The EMG responses evoked by transcranial magnetic and electrical stimulation in leg muscles have similar latency in tibialis anterior, probably because they both produce D waves, activating corticospinal axons at the same site, near the cortical surface (however, see pp. 43–4).

Critique: advantages, limitations, conclusions

(i) Cortical stimulation may be used to produce a test response: motoneurone excitability tested by the

H reflex and the MEP should be similarly modified by conditioning stimulation, unless the conditioning volley alters presynaptic inhibition of Ia terminals mediating the afferent volley of the test H reflex, or transmission of that part of the corticospinal volley which traverses an interneuronal relay. On the other hand, the difference in sites of activation of pyramidal neurones in the hand area to electrical and magnetic stimulation may be used as a method to determine whether changes in the MEP result from changes in motor cortex excitability.

(ii) Cortical stimulation may also be used as a conditioning stimulus to investigate the corticospinal control of spinal pathways (see Chapters 3–10).

(iii) Limitations: at rest, TMS induces responses in several muscles, and H reflexes and MEPs of similar size do not necessarily recruit the same population of motoneurones.

(iv) Conclusions: The ability to evoke corticospinal volleys in awake subjects has been a major breakthrough in human motor control physiology (and pathophysiology), because this has made it possible to investigate corticospinal control of spinal pathways, and the transmission of corticospinal excitation to motoneurones.

Spatial facilitation

Principles of the method

The spatial facilitation technique was developed in animal experiments to document the existence of interneurones by demonstrating convergence between two excitatory inputs on the putative interneurones while recording any resulting PSP (either EPSP or IPSP) in a motoneurone. Spatial summation at a premotoneuronal level is inferred when the PSP on combined stimulation is larger than the sum of PSPs evoked by separate inputs.

Spatial facilitation judged in single motor unit recordings

Summation of two excitatory inputs at a premotoneuronal level produces significant extra facilitation on combined stimulation such that the peak of excitation in the PSTH is significantly greater than the sum of the effects of separate stimuli. The extra facilitation will not involve the initial part of the peak produced by combined stimulation if the onset of the synaptic effect in the motoneurone involves a monosynaptic pathway.

Spatial facilitation judged from monosynaptic test reflexes

The excitatory effects of two conditioning stimuli are measured when applied separately and together. Summation in common interneurones is considered likely when facilitation of the reflex on combined stimulation is greater than the sum of the facilitations produced by separate stimuli. However, because the H reflex assesses the excitability of a motoneurone pool, the extra facilitation on combined stimulation could also result from non-linearity or inhomogeneity within the pool. Concordant results from experiments on single motor units are required to eliminate this possibility.

Coherence analysis in EMG/EMG or EEG/EMG signals

Recent advances based in frequency analysis (calculation of spectra, cross-spectra, coherence and phase between simultaneously recorded natural EMG and/or EEG inputs) allow the motor system to be studied under natural conditions, without artificial inputs. However, these recently developed methods require further clarification before being applied routinely.

REFERENCES

Abbruzzese, M., Ratto, S., Abbruzzese, G. & Favale, E. (1985). Electroneurographic correlates of the monosynaptic reflex: experimental studies and normative data. *Journal of Neurology, Neurosurgery and Psychiatry*, **48**, 434–44.

Aimonetti, J. M., Vedel, J. P., Schmied, A. & Pagni, S. (2000). Distribution of presynaptic inhibition on type-identified motoneurones in the extensor carpi radialis pool in man. *Journal of Physiology (London)*, **522**, 125–35.

Amjad, A. M., Breeze, P., Conway, B. A., Halliday, D. M. & Rosenberg, J. R. (1989). A framework for the analysis of neuronal networks. *Progress in Brain Research*, **80**, 243–55 (discussion 239–42).

Araki, T., Eccles, J. C. & Ito, M. (1960). Correlation of the inhibitory post-synaptic potential of motoneurones with the latency and time course of inhibition of monosynaptic reflexes. *Journal of Physiology (London)*, **154**, 354–77.

Ashby, P. & Labelle, K. (1977). Effects of extensor and flexor group I afferent volleys on the excitability of individual soleus motoneurones in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 910–19.

Ashby, P. & Zilm, D. (1982a). Relationship between EPSP shape and cross correlation profile explored by computer simulation for studies on human motoneurons. *Experimental Brain Research*, **47**, 33–40.

(1982b). Characteristics of postsynaptic potentials produced in single human motoneurones by homonymous group I volleys. *Experimental Brain Research*, **47**, 41–8.

Awiszus, F. (1997). Spike train analysis. *Journal of Neuroscience Methods*, **74**, 155–66.

Aymard, C., Katz, R., Lafitte, C. *et al.* (2000). Presynaptic inhibition and homosynaptic depression : a comparison between lower and upper limbs in normal subjects and patients with hemiplegia. *Brain*, **123**, 1688–702.

Baldissera, F., Hultborn, H. & Illert, M. (1981). Integration in spinal neuronal systems. In *Handbook of Physiology*, section I, *The Nervous System*, vol. II, *Motor Control*, ed. V. B. Brooks, pp. 508–95. Bethesda, MD: American Physiological Society.

Baldissera, F., Cavallari, P. & Dworzak, F. (1994). Motor neuron 'bistability'. A pathogenetic mechanism for cramps and myokymia. *Brain*, **117**, 929–39.

Barker, A. T., Jalinous, R. & Freeston, I. L. (1985). Non-invasive magnetic stimulation of the human motor cortex. *Lancet*, **I**, 1106–7.

Bathien, N. & Morin, C. (1972). Variations comparées des réflexes spinaux au cours de l'attention intensive et sélective. *Physiology and Behaviour*, **9**, 533–8.

Bawa, P. & Lemon, R. N. (1993). Recruitment of motor units in response to transcranial magnetic stimulation in man. *Journal of Physiology (London)*, **471**, 445–64.

Berardelli, A., Inghilleri, M., Cruccu, G. & Manfredi, M. (1990). Descending volley after electrical and magnetic transcranial stimulation in man. *Neuroscience Letters*, **112**, 54–8.

Bostock, H., Cikurel, K. & Burke, D. (1998). Threshold tracking techniques in the study of human peripheral nerve. *Muscle and Nerve*, **21**, 137–58.

Boyd, S. G., Rothwell, J. C., Cowan, J. M. A. *et al.* (1986). A method of monitoring function of cortical pathways during scoliosis surgery with a note on motor conduction velocities. *Journal of Neurology, Neurosurgery and Psychiatry*, **49**, 251–7.

Bremner, F. D., Baker, J. R. & Stephens, J. A. (1991a). Correlation between the discharge of motor units from the same and from different finger muscles in man. *Journal of Physiology (London)*, **432**, 355–80.

Bremner, F. D., Baker, J. R. & Stephens, J. A. (1991b). Variation in the degree of synchronization exhibited by motor units lying in different finger muscles in man. *Journal of Physiology (London)*, **432**, 381–99.

Brown, P., Salenius, S., Rothwell, J. C. & Hari, R. (1998). Cortical correlate of the Piper rhythm in humans. *Journal of Neurophysiology*, **80**, 2911–17.

Brunia, C. H. M. (1971). The influence of a task on the Achilles tendon reflexes during a fixed foreperiod of one second. *Physiology and Behaviour*, **6**, 367–73.

Buchthal, F. & Schmalbruch, H. (1970). Contraction times of twitches evoked by H-reflexes. *Acta Physiologica Scandinavica*, **80**, 378–82.

Burke, D., Gandevia, S. C. & McKeon, B. (1984). Monosynaptic and oligosynaptic contributions to human ankle jerk and H-reflex. *Journal of Neurophysiology*, **52**, 435–48.

Burke, D., Adams, R. W. & Skuse, N. F. (1989). The effect of voluntary contraction on the H reflex of various muscles. *Brain*, **112**, 417–33.

Burke, D., Hicks, R. G. & Stephen, J. P. H. (1990). Corticospinal volleys evoked by anodal and cathodal stimulation of the human motor cortex. *Journal of Physiology (London)*, **425**, 283–99.

Burke, D., Hicks, R., Gandevia, S. C., Stephen, J. Woodforth, I. & Crawford, M. (1993). Direct comparison of corticospinal volleys in human subjects to transcranial magnetic and electrical stimulation. *Journal of Physiology (London)*, **470**, 383–93.

Burke, D., Fuhr, P., Hallett, M. & Pierrot-Deseilligny, E. (1999). H reflexes of the median and tibial nerves. In *Recommendations on the Practice of Clinical Neurophysiology*, ed. G. Deuchl & A. Eisen, pp. 259–62. Amsterdam: Elsevier.

Capaday, C. (1997). Neurophysiological methods for studies of the motor system in freely moving human subjects. *Journal of Neuroscience Methods*, **74**, 201–18.

Chan, J. H. L., Lin, C. S.-Y., Pierrot-Deseilligny, E. & Burke, D. (2002). Excitability changes in stimulated axons may influence responses to paired-pulse transcranial magnetic stimulation in human subjects. *Journal of Physiology (London)*, **542**, 951–61.

Cohen, L. G. & Hallett, M. (1988). Methodology for non-invasive mapping of human motor cortex with electrical

stimulation. *Electroencephalography and Clinical Neurophysiology*, **69**, 403–11.

Collins, D. F., Burke, D. & Gandevia, S. C. (2001). Large involuntary forces consistent with plateau-like behavior of human motoneurons. *Journal of Neuroscience*, **21**, 4059–65.

Collins, D. F., Burke, D. & Gandevia, S. C. (2002). Sustained contractions produced by plateau-like behaviour in human motoneurones. *Journal of Physiology (London)*, **538**, 289–301.

Crone, C. & Nielsen, J. (1989). Methodological implications of the post-activation depression of the soleus H-reflex in man. *Experimental Brain Research*, **78**, 28–32.

Crone, C., Hultborn, H., Mazières, L., Morin, C., Nielsen, J. & Pierrot-Deseilligny, E. (1990). Sensitivity of monosynaptic test reflexes to facilitation and inhibition as a function of the test reflex size: a study in man and the cat. *Experimental Brain Research*, **81**, 35–45.

Davey, P. H., Ellaway, P. H., Baker, J. R. & Friedland, C. L. (1993). Rhythmicity associated with a high degree of short-term synchrony of motor unit discharge in man. *Experimental Physiology*, **78**, 649–61.

Day, B. L., Dressler, D., Hess, C. W. *et al.* (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology (London)*, **412**, 449–73.

Day, B. L., Riescher, H., Struppler, A., Rothwell, J. C. & Marsden, C. D. (1991). Changes in the response to magnetic and electrical stimulation of the motor cortex following muscle stretch in man. *Journal of Physiology (London)*, **433**, 41–57.

Deschuytere, J., Rosselle, N. & DeKeyser, C. (1976). Monosynaptic reflexes in the superficial forearm flexors in man and their clinical significance. *Journal of Neurology, Neurosurgery and Psychiatry*, **39**, 555–65.

Di Lazzaro, V., Oliviero, A., Profice, P. *et al.* (1998). Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. *Electroencephalography and Clinical Neurophysiology*, **109**, 397–401.

(2001). Descending spinal cord volleys evoked by transcranial magnetic and electrical stimulation of the motor cortex leg area in conscious humans. *Journal of Physiology (London)*, **537**, 1047–58.

Di Lazzaro, V., Oliviero, A., Pilato, F. *et al.* (2002). Descending volleys evoked by transcranial magnetic stimulation of the brain in conscious humans: effects of coil shape. *Clinical Neurophysiology*, **113**, 114–19.

Eccles, J. C. (1964). *The Physiology of Synapses*. 316 pp. Berlin: Springer Verlag.

Eccles, R. M. & Lundberg, A. (1957). Spatial facilitation in the direct inhibitory pathways. *Nature*, **179**, 1305–6.

Edgley, S. A., Eyre, J. A., Lemon, R. N. & Miller, S. (1990). Excitation of the corticospinal tract by electromagnetic stimulation of the scalp on the macaque monkey. *Journal of Physiology (London)*, **425**, 301–20.

Eisen, A. & Fisher, M. (1999). The F wave. In *Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology*, ed. G. Deuschl & A. Eisen, pp. 255–7. Amsterdam: Elsevier.

Eisen, A. & Odusote, K. (1979). Amplitude of the F-wave: a potential means of documenting spasticity. *Neurology*, **29**, 1306–9.

Ellaway, P. H. (1978). Cumulative sum technique and its application to the analysis of peristimulus time histogram. *Electroencephalography and Clinical Neurophysiology*, **45**, 302–4.

Espiritu, M. G., Lin, C. S.-Y. & Burke, D. (2003). Motoneuron excitability and the F wave. *Muscle and Nerve*, **27**, 720–7.

Farmer, S. F., Bremner, F. D., Halliday, D. M., Rosenberg, J. R. & Stephens, J. A. (1993). The frequency content of common synaptic inputs to motoneurones studied during voluntary isometric contraction in man. *Journal of Physiology (London)*, **470**, 127–55.

Farmer, S. F., Halliday, D. M., Conway, B. A., Stephens, J. A. & Rosenberg, J. R. (1997). A review of recent applications of cross-correlation methodologies to human motor unit recording. *Journal of Neuroscience Methods*, **74**, 175–87.

Fisher, M. A. (1992). H-reflexes and F-waves: physiology and clinical indications. *Muscle and Nerve*, **15**, 1223–33.

Forget, R., Pantieri, R., Pierrot-Deseilligny, E., Shindo, M. & Tanaka, R. (1989). Facilitation of quadriceps motoneurones by group I afferents from pretibial flexors in man. 2. Possible interneuronal pathway. *Experimental Brain Research*, **78**, 10–20.

Fournier, E., Katz, R. & Pierrot-Deseilligny, E. (1984). A reevaluation of the pattern of group I fibre projections in the human lower limb on using randomly alternated stimulations. *Experimental Brain Research*, **56**, 193–6.

Fournier, E., Meunier, S., Pierrot-Deseilligny, E. & Shindo, M. (1986). Evidence for interneuronally mediated Ia excitatory effects to human quadriceps motoneurones. *Journal of Physiology (London)*, **377**, 143–69.

Fujiki, M., Isono, M., Mori, S. & Ueno, S. (1996). Corticospinal direct responses to transcranial magnetic stimulation in humans. *Electroencephalography and Clinical Neurophysiology*, **101**, 48–57.

Gassel, M. M. (1963). A study of femoral nerve conduction time. *Archives of Neurology*, **9**, 607–14.

Gassel, M. M. & Ott, K. (1969). A novel and accelerated method of evaluating motoneuron excitability. *Transactions of the American Neurological Association*, **94**, 269–70.

(1970). Local sign and late effects on motoneuron excitability of cutaneous stimulation in man. *Brain*, **93**, 95–106.

Gerilovsky, L., Ysvetinov, P. & Trenkova, G. (1989). Peripheral effects on the amplitude of monopolar and bipolar H-reflex potentials from the soleus muscles. *Experimental Brain Research*, **76**, 173–81.

Gorassini, M., Bennett, D. J. & Yang, J. F. (1998). Self-sustained firing of human motor units. *Neuroscience Letters*, **247**, 13–16.

Gorassini, M., Yang, J. F., Siu, M. & Bennett, D. J. (2002). Intrinsic activation of human motoneurons: possible contribution to motor unit excitation. *Journal of Neurophysiology*, **87**, 1850–8.

Gustafsson, B. & McCrea, D. (1984). Influence of stretch-evoked synaptic potentials on firing probability of cat spinal motoneurones. *Journal of Physiology (London)*, **347**, 431–51.

Halliday, D. M., Rosenberg, J. R., Amjad, A. M., Breeze, P., Conway, B. A. & Farmer, S. F. (1995). A framework for the analysis of mixed time series/point process-data theory and application to the study of physiological tremor, single motor unit discharges and electromyography. *Progress in Biophysics and Molecular Biology*, **64**, 237–78.

Henneman, E. & Mendell, L. M. (1981). Functional organization of motoneurone pool and its inputs. In *Handbook of Physiology, Section I, The Nervous System*, vol. II, *Motor Control*, Part 1, ed. V. B. Brooks, pp. 423–507. Bethesda, MD: American Physiological Society.

Hess, C. W., Mills, K. R. & Murray, N. M. F. (1987). Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology (London)*, **388**, 397–419.

Hicks, R., Burke, D., Stephen, J., Woodforth, I. & Crawford, M. (1992). Corticospinal volleys evoked by electrical stimulation of human motor cortex after withdrawal of volatile anaesthesics. *Journal of Physiology (London)*, **456**, 393–404.

Hodes, R. & Dement, W. C. (1964). Depression of electrically induced reflexes in man during low voltage EEG. *Electroencephalography and Clinical Neurophysiology*, **17**, 617–29.

Hoffmann, P. (1918). Über die Beriehungen der Sehnenreflexe zur willkürlichen Bewegung und zum Tonus. *Zeitschrift für Biologie*, **68**, 351–70.

(1922). *Untersuchungen über die Eigenreflexe (Sehnen reflexe) menschlischer Muskeln*. Berlin: Springer.

Hugon, M. (1973). Methodology of the Hoffmann reflex in man. In *New Developments in Electromyography and Clinical Neurophysiology*, Vol. 3, ed. J. E. Desmedt, pp. 277–293. Basel: Karger.

Hultborn, H. (1999). Plateau potentials and their role in regulating motoneuronal firing. *Progress in Brain Research*, **123**, 39–48.

Hultborn, H. & Nielsen, J. B. (1995). H-reflexes and F-responses are not equally sensitive to changes in motoneuronal excitability. *Muscle and Nerve*, **18**, 1471–4.

Hultborn, H., Illert, M., Nielsen, J., Paul, A., Ballegaard, M. & Wiese, H. (1996). On the mechanism of the post-activation depression of the H-reflex in human subjects. *Experimental Brain Research*, **108**, 450–62.

Hultborn, H., Enriquez-Denton, M. E., Wienecke, J. & Nielsen, J. B. (2003). Variable amplification of synaptic input to cat spinal motoneurones by dendritic persistent inward current. *Journal of Physiology (London)*, **552**, 945–52.

Hunt, C. C. (1955). Monosynaptic reflex response of spinal motoneurones to graded afferent stimulation. *Journal of General Physiology*, **38**, 813–53.

Hutton, R. S., Roy, R. R. & Edgerton, V. R. (1988). Coexistent Hoffmann reflexes in human leg muscles are commonly due to volume conduction. *Experimental Neurology*, **100**, 265–73.

Katz, R., Morin, C., Pierrot-Deseilligny, E. & Hibino, R. (1977). Conditioning of H-reflex by a preceding subthreshold tendon reflex stimulus. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 575–80.

Katz, R., Meunier, S. & Pierrot-Deseilligny, E. (1988). Changes in presynaptic inhibition of Ia fibres in man while standing. *Brain*, **111**, 417–37.

Kernell, D. & Hultborn, H. (1990). Synaptic effects on recruitment gain: a mechanism of importance for the input-output relations of motoneurone pools? *Brain Research*, **507**, 176–9.

Kiernan, M. C., Mogyoros, I., Hales, J. P., Gracies, J. M. & Burke, D. (1997). Excitability changes in human cutaneous afferents induced by prolonged repetitive axonal activity. *Journal of Physiology (London)*, **500**, 255–64.

Kimura, J., Yanagisawa, H., Yamada, Y., Mitsudome, A., Sasaki, H. & Kimura, A. (1984). Is the F wave elicited in a select group of motoneurons? *Muscle and Nerve*, **7**, 382–99.

Kirkwood, P. A. & Sears, T. A. (1978). The synaptic connections to intercostal motoneurones as revealed by the average common excitation potentials. *Journal of Physiology (London)*, **275**, 103–34.

(1982). Excitatory post-synaptic potentials from single muscle spindle afferents in external intercostal motoneurones of the cat. *Journal of Physiology (London)*, **322**, 287–314.

Lamy, J. C., Wargon, I., Baret, M. *et al.* (2005). Post-activation depression in various spinal pathways in humans. *Experimental Brain Research*, submitted.

LeFever, R. S. & De Luca, C. J. (1982). A procedure for decomposing the myoelectric signal into its constituent action potentials. *IEEE Transactions of Biomedical Engineering*, **29**, 158–64.

Lin, C. S.-Y., Chan, J. H. L., Pierrot-Deseilligny, E. & Burke, D. (2002). Excitability of human muscle afferents studied using threshold tracking of the H reflex. *Journal of Physiology (London)*, **545**, 661–9.

Lloyd, D. P. C. (1941). A direct central inhibitory action on dromically conducted impulses. *Journal of Neurophysiology*, **4**, 184–90.

Lundberg, A. (1975). The control of spinal mechanisms from the brain. In *The Nervous System. The Basic Neurosciences*, vol. 1, ed. B. Tower, pp. 253–65. New York: Raven Press.

McAuley, J. H., Rothwell, J. C. & Marsden, C. D. (1997). Frequency peaks of tremor, muscle vibration and electromyographic activity at 10 Hz, 20 Hz and 40 Hz during human muscle finger contraction may reflect rhythmicities of central neural firing. *Experimental Brain Research*, **114**, 525–41.

Magladery, J. W. & McDougal, D. B. (1950). Electrophysiological studies of nerve and reflex activity in normal man. I. Identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibers. *Bulletin of the Johns Hopkins Hospital*, **86**, 265–90.

Magladery, J. W., Porter, W. E., Park, A. M. & Teasdall, R. D. (1951a). Electrophysiological studies of nerve and reflex activity in normal man. IV. Two-neurone reflex and identification of certain action potentials from spinal roots and cord. *Bulletin of the Johns Hopkins Hospital*, **88**, 499–519.

Magladery, J. W., Teasdall, R. D., Park, A. M. & Porter, W. E. (1951b). Electrophysiological studies of nerve and reflex activity in normal man. V. Excitation and inhibition of two-neurone reflexes by afferent impulses in the same nerve trunk. *Bulletin of the Johns Hopkins Hospital*, **88**, 520–37.

Magladery, J. W., Teasdall, R. D., Park, A. M. & Languth, H. W. (1952). Electrophysiological studies of reflex activity in patients with lesions of the nervous system. I. A comparison of spinal motoneurone excitability following afferent nerve volleys in normal persons and patients with upper motor neurone lesions. *Bulletin of the Johns Hopkins Hospital*, **91**, 219–43.

Malmgren, K. & Pierrot-Deseilligny, E. (1988). Evidence for non-monosynaptic Ia excitation of wrist flexor motoneurones, possibly via propriospinal neurones. *Journal of Physiology (London)*, **405**, 747–64.

Mao, C. C., Ashby, P., Wang, M. & McCrea, D. (1984). Synaptic connections from large muscle afferents to the motoneurones of various leg muscles in man. *Experimental Brain Research*, **56**, 341–50.

Marchand-Pauvert, V., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (1999). Cortical control of spinal pathways mediating group II excitation to thigh motoneurones. *Journal of Physiology (London)*, **517**, 301–13.

Marchand-Pauvert, V., Nicolas, G. & Pierrot-Deseilligny, E. (2000). Monosynaptic Ia projections from intrinsic hand muscles to forearm motoneurones in humans. *Journal of Physiology (London)*, **525**, 241–52.

Marchand-Pauvert, V., Nicolas, G., Burke, D. & Pierrot-Deseilligny, E. (2002). Suppression of the H reflex by disynaptic autogenetic inhibitory pathways activated by the test volley. *Journal of Physiology (London)*, **542**, 963–76.

Marque, P., Nicolas, G., Marchand-Pauvert, V., Gautier, J., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (2001). Group I projections from intrinsic foot muscles to motoneurones of leg and thigh muscles in humans. *Journal of Physiology (London)*, **536**, 313–27.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and their Central Actions*. London: Arnold.

(1996). Relationship of firing intervals of human motor units to the trajectory of post-spike after-hyperpolarization and synaptic noise. *Journal of Physiology (London)*, **492**, 597–628.

Mazevet, D. & Pierrot-Deseilligny, E. (1994). Pattern of descending excitation of presumed propriospinal neurones at the onset of voluntary movement in man. *Acta Physiologica Scandinavica*, **150**, 27–38.

Meinck, H. M. (1980). Facilitation and inhibition of the human H-reflex as a function of the amplitude of the control reflex. *Electroencephalography and Clinical Neurophysiology*, **48**, 203–11.

Merton, P. A. & Morton, H. B. (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature*, **285**, 227.

Meunier, S., Penicaud, A., Pierrot-Deseilligny, E. & Rossi, A. (1990). Monosynaptic Ia excitation and recurrent inhibition from quadriceps to ankle flexors and extensors in man. *Journal of Physiology (London)*, **423**, 661–75.

Miles, T. S. (1997). Estimating post-synaptic potentials in tonically discharging human motoneurons. *Journal of Neuroscience Methods*, **74**, 167–74.

Miles, T. S., Le, T. H. & Türker, K. S. (1989). Biphasic inhibitory responses and their IPSPs evoked by tibial nerve stimulation in human soleus motor neurones. *Experimental Brain Research*, **77**, 637–45.

Milner-Brown, S. H., Stein, R. E. & Yemm, R. (1973). The orderly recruitment of human motor units during voluntary isometric contractions. *Journal of Physiology (London)*, **230**, 359–70.

Mills, K. R., Boniface, S. J. & Schubert, M. (1992). Magnetic brain stimulation with a double coil: the importance of coil orientation. *Electroencephalography and Clinical Neurophysiology*, **85**, 17–21.

Mogyoros, I., Kiernan, M. C., Gracies, J. M. & Burke, D. (1997). The effect of stimulus duration on the latency of submaximal nerve volleys. *Muscle and Nerve*, **19**, 1354–6.

Nielsen, J. & Kagamihara, Y. (1993). Differential projection of the sural nerve on early and late recruited human tibialis anterior motor units: change of recruitment gain. *Acta Physiologica Scandinavica* **147**, 385–401.

Nielsen, J., Petersen, N. & Ballegaard, M. (1995). Latency of effect evoked by electrical and magnetic brain stimulation in lower limb motoneurones in man. *Journal of Physiology (London)*, **484**, 791–802.

Nielsen, J., Morita, H., Baumgarten, J., Petersen, N. & Christensen, L. O. (1999). On the comparability of H-reflexes and MEPs. *Electroencephalography and Clinical Neurophysiology*, **51**, 93–101.

Paillard, J. (1955). *Réflexes et régulations d'origine proprioceptive chez l'Homme*. Thèse de Sciences. Paris: Arnette.

Panizza, M. E., Nilsson, J. & Hallett, M. (1989). Optimal stimulus duration for the H reflex. *Muscle and Nerve*, **12**, 576–9.

Panizza, M. E., Nilsson, J., Roth, B. J., Basser, P. J. & Hallett, M. (1992). Relevance of stimulus duration for activation of motor and sensory fibers: implications for the study of H-reflexes and magnetic stimulation. *Electroencephalography and Clinical Neurophysiology*, **85**, 22–9.

Patton, H. D. & Amassian, V. E. (1954). Single and multiple unit analysis of cortical stage of pyramidal tract activation. *Journal of Neurophysiology*, **17**, 345–63.

Pauvert, V., Pierrot-Deseilligny, E. & Rothwell, J. C. (1998). Role of spinal premotoneurones in mediating corticospinal input to forearm motoneurones in man. *Journal of Physiology (London)*, **508**, 301–12.

Petersen, N., Morita, H. & Nielsen, J. (1998). Evaluation of reciprocal inhibition of the soleus H-reflex during tonic plantar flexion in man. *Journal of Neuroscience Methods*, **84**, 1–8.

(1999). Modulation of reciprocal inhibition between ankle extensors and flexors during walking in man. *Journal of Physiology (London)*, **520**, 605–19.

Pierrot-Deseilligny, E. & Mazevet, D. (2000). The monosynaptic reflex: a tool to investigate motor control in humans. Interest and limits. *Clinical Neurophysiology*, **30**, 67–80.

Pierrot-Deseilligny, E., Morin, C., Bergego, C. & Tankov, N. (1981). Pattern of group I fibre projections from ankle flexor and extensor muscles in man. *Brain Research*, **42**, 337–50.

Poliakov, A. & Miles, T. S. (1992). Quantitative analysis of reflex responses in the averaged surface electromyogram. *Journal of Neuroscience Methods*, **43**, 195–200.

Priori, A., Bertolasi, L., Dressler, D. *et al.* (1993). Transcranial electric and magnetic stimulation of the leg area of the human motor cortex : single motor unit and surface EMG responses in the tibialis anterior muscle. *Electroencephalography and Clinical Neurophysiology*, **89**, 131–7.

Renshaw, B. (1940). Activity in the simplest spinal reflex pathways. *Journal of Neurophysiology*, **3**, 373–87.

Rothwell, J. C. (1997). Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *Journal of Neuroscience Methods*, **74**, 113–22.

Rothwell, J. C., Thompson, P. D., Day, B. L. *et al.* (1987). Motor cortex stimulation in intact man. I. General characteristics of EMG responses in different muscles. *Brain*, **110**, 1173–90.

Rothwell, J. C., Thompson, P. D., Day, B. L., Boyd, S. & Marsden, C. D. (1991). Stimulation of the human motor cortex through the scalp. *Experimental Physiology*, **76**, 159–200.

Rothwell, J. C., Burke, D., Hicks, R., Stephen, J., Woodforth, I. & Crawford, M. (1994). Transcranial electrical stimulation of the motor cortex in man: further evidence for the site of activation. *Journal of Physiology*, **481**, 243–50.

Schieppati, M. (1987). The Hoffmann reflex: a means of assessing spinal reflex excitability and its descending control in man. *Progress in Neurobiology*, **28**, 345–76.

Schimsheimer, R. J., Ongerboer de Visser, B. W., Kemp, B. & Bour, L. J. (1987). The flexor carpi radialis H-reflex in polyneuropathy: relations to conduction velocities of the median nerve and the soleus H-reflex latency. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 447–52.

Schubert, M., Curt, A., Jensen, L. & Dietz, V. (1997). Corticospinal input in human gait: modulation of magnetically-evoked motor responses. *Experimental Brain Research*, **115**, 244–6.

Sears, T. A. & Stagg, D. (1976). Short-term synchronization of intercostal motoneurone activity. *Journal of Physiology (London)*, **263**, 357–81.

Shindo, M., Yanagawa, S., Morita, H. & Hashimoto, T. (1994). Conditioning effect in single human motoneurones: a new method using the unitary H reflex. *Journal of Physiology (London)*, **481**, 469–77.

Stephens, J. A., Usherwood, T. P. & Garnett, R. (1976). Technique for studying synaptic connections of single motoneurones in man. *Nature*, **263**, 343–4.

Táboríková, H. & Sax, D. S. (1968). Motoneurone pool and the H reflex. *Journal of Neurology, Neurosurgery and Psychiatry*, **31**, 354–61.

(1969). Conditioning H reflex by preceding subthreshold H reflex stimulus. *Brain*, **92**, 203–12.

Trontelj, J. V. (1973). A study of the F response by single fibre electromyography. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 318–22. Basel: Karger.

Türker, K. S. & Powers, R. K. (1999). Effects of large excitatory and inhibitory inputs on motoneuron discharge rate and probability. *Journal of Neurophysiology*, **82**, 829–40.

(2003). Estimation of postsynaptic potentials in rat hypoglossal motoneurones: insights for human work. *Journal of Physiology (London)*, **551**, 419–31.

Vagg, R., Mogyoros, I., Kiernan, M. C. & Burke, D. (1998). Activity-dependent hyperpolarization of motor axons produced by natural activity. *Journal of Physiology (London)*, **507**, 919–25.

Werhahn, K., Fong, J. K. Y., Meyer, B. U. *et al.* (1994). The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseus muscle. *Electroencephalography and Clinical Neurophysiology*, **93**, 138–48.

Wood, S. A., Gregory, J. E. & Proske, U. (1996). The influence of muscle spindle discharge on the human H reflex and the monosynaptic reflex in the cat. *Journal of Physiology (London)*, **497**, 279–90.

Yates, S. K. & Brown, W. F. (1979). Characteristics of the F response: a single motor unit study. *Journal of Neurology, Neurosurgery and Psychiatry*, **42**, 161–70.

Zhu, Y., Starr, A., Su, S. H., Woodward, K. G. & Haldeman, S. (1992). The H-reflex to magnetic stimulation of lower-limb nerves. *Archives of Neurology*, **49**, 66–71.

2

Monosynaptic Ia excitation and post-activation depression

The extent to which the spinal stretch reflex is involved in normal motor control and the contribution of monosynaptic Ia connections in its generation are not yet completely clarified. Regardless of these uncertainties, there is continuing interest in the reflex connections of the primary endings of muscle spindles, as detailed below.

Muscle synergies laid down in the spinal cord

The execution of even the simplest movement involves a large number of muscles, but the pattern of muscle activity is consistent for any given type of movement (see Illert, 1996). Beevor (1904, cited by Illert, 1996) claimed that the neuronal arrangements for stereotyped movements are laid down in the spinal cord. The various muscle synergies could thus be represented by different sets of spinal connections, which have been termed 'spinal functional units' (Baldissera, Hultborn & Illert, 1981), and are thought to be mobilised during voluntary movements, as was postulated long ago by Forster (1879, cited by Hultborn, 2001). One objective in the study of reflexes is to identify the pattern of connections underlying a particular form of behaviour. This entails tracing the effects of a given input to see how widely it is distributed to excite or inhibit different neurones. The classical example of such a study was provided by Sherrington (1910), who detailed the muscles that contract or relax in the flexor reflex (see Chapter 9). In this respect, monosynaptic excitatory effects conveyed by Ia afferents occupy a unique place, because the monosynaptic action on motoneurones occurs without a complicating interneurone. Thus, 'all that need be sought is the simple wiring diagram of which motoneurones are supplied by the Ia fibres of each individual muscle, and how powerfully' (Matthews, 1972). Of course this does not mean that the strength of the monosynaptic Ia excitation is fixed by hardwired connections. Presynaptic inhibition of Ia terminals (see Chapter 8) and post-activation depression (see pp. 96–101) are mechanisms capable of modulating transmission of Ia excitation within the spinal cord.

Phylogenetic adaptation of reflex pathways

This adaptation may also be studied easily by documenting the evolution of heteronymous Ia connections. As emphasised by Hongo *et al.* (1984), limb muscles are similar in cats, monkeys and humans, despite the considerable change from digitigrade to plantigrade walking and from quadrupedal to bipedal upright stance and the differences in size of the different species. Evolutionary changes in the use of the limbs are therefore likely to depend largely on changes in the central nervous system, and to involve either altered use of existing pathways or changed connections to motoneurones. It is a challenging problem to determine how the different feedback systems have become adapted to the evolutionary demands for changed movement patterns, and here again investigations of distribution of monosynaptic Ia connections provide the easiest way to approach the issue. The differences in the distribution of heteronymous monosynaptic Ia excitation are relatively

small between cats and baboons but become more prominent between baboons and humans, as is discussed on p. 93. The fact that these adaptations have occurred indicates that the reflex assistance provided by the widespread Ia connections is functionally important in human subjects.

Ease to investigation

Because the synaptic input from Ia afferents is the first to arrive at motoneurones after peripheral nerve stimulation and can be evoked at the lowest threshold, it is technically the easiest to explore. This explains why the reflex effects of the group Ia fibres have lent themselves to more detailed study than any other group of afferent fibres, both in animals and humans.

Fusimotor drive

The existence of a separate efferent innervation of intrafusal fibres (the γ-efferent or fusimotor innervation) that can modulate the sensitivity of spindle endings and thereby alter Ia feedback implies that modulating fusimotor drive can effectively alter the Ia support to movements (see Chapter 3).

Post-activation depression at the Ia afferent-motoneurone synapse

A reduction in post-activation depression may be an important spinal mechanism underlying spasticity. Post-activation depression following repetitive activation of a synapse is a general phenomenon in the nervous system, but again monosynaptic Ia connections on motoneurones provide the most convenient way to study the phenomenon, both in animals and humans (see pp. 96–100).

Background from animal experiments

Initial findings

Since the clinical description of the tendon jerk at the end of the nineteenth century, it took a long time: (i) to recognise the reflex origin of the response (Jolly, 1911, cited by Matthews, 1972), (ii) to demonstrate that it had a monosynaptic pathway (Lloyd, 1943b), and (iii) to establish conclusively that Ia fibres form the afferent limb of the reflex pathway (Lundberg & Winsbury, 1960). The history of the laborious demonstration of the pathway of the tendon jerk is documented in Matthews (1972). Lloyd demonstrated that a peripheral group I volley evokes, in addition to the homonymous reflex response (1943a), subthreshold facilitation of motoneurones of synergistic muscles acting at the same joint (1946). A wider distribution of monosynaptic Ia excitation was subsequently documented (Eccles, Eccles & Lundberg, 1957).

Pathway of monosynaptic Ia excitation

Ia afferents

Ia afferents originate from muscle spindle primary endings, which are on the central region of both bag and chain fibres. They are sensitive mechanoreceptors, responsive to the static and dynamic components of muscle stretch and also to high-frequency vibration (see Matthews, 1972). The non-linear characteristics of the primary ending enable it to signal the very initiation of a length change. Ia afferents are the largest and most rapidly conducting peripheral nerve fibres, with conduction velocities up to $\sim$120 m s^{-1} for the cat hindlimb, but up to only $\sim$70 m s^{-1} in humans (see Chapter 3). Group Ia afferents bifurcate on entering the spinal cord through the dorsal root and run in both the rostral and caudal directions in the dorsal columns (Fig. 2.1). Several collaterals from each Ia fibre leave the dorsal columns and enter the ventral horn to make contact with motoneurones of the homonymous and synergistic muscles (see Fig. 2.1 and below). The rostrocaudal spread of individual collaterals within the ventral horn is limited, and it is unlikely that more than a single collateral of a Ia fibre has access to a given motoneurone. All dendritic regions accessible to investigation as well as the soma receive monosynaptic connections (see Henneman & Mendell, 1981).

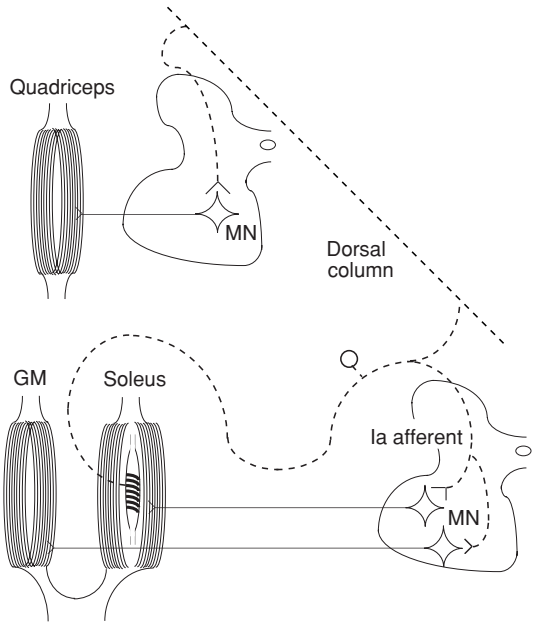


Fig. 2.1. Connections of monosynaptic Ia excitation. Ia afferents (dashed lines) originating from muscle spindle primary endings of the soleus have monosynaptic projections to homonymous soleus motoneurones (MNs), and to heteronymous MNs supplying its close synergist, the gastrocnemius medialis (GM), located at the same S1 segmental level and also, after running in the dorsal column, to MNs of the quadriceps located more rostrally in L4. The particular projections sketched here have been observed in human experiments (Meunier, Pierrot-Deseilligny & Simonetta, 1993).

Strength of monosynaptic Ia projections to individual motoneurones

Homonymous and heteronymous motoneurones

Monosynaptic Ia excitation is generally stronger in homonymous than heteronymous motoneurones (see Henneman & Mendell, 1981) and, accordingly, reflex responses can be recorded at rest only in the homonymous muscle. This is because each Ia fibre sends terminals to all or nearly all of its homonymous motoneurones but only to some synergistic motoneurones. However, heteronymous Ia EPSPs may be larger than the homonymous ones in some motor nuclei (e.g., in the baboon flexor digitorum communis, Clough, Kernell & Phillips, 1968).

A further factor influencing the size of Ia EPSPs is the type of motoneurone

EPSPs are largest in small motoneurones innervating slow-twitch motor units (Eccles, Eccles & Lundberg, 1957), and monosynaptic Ia EPSPs evoked on maximal stimulation of the homonymous nerve scale quite precisely with motor unit type. There is thus a direct correlation with the fatigue resistance and an inverse correlation with the tetanic force produced by the motor unit and with the size of the motoneurone (see R. E. Burke, 1981). This is in accord with Henneman's size principle (Chapter 1, pp. 3–4). The mechanism underlying this particular distribution has been extensively debated. Apart from the fact that small motoneurones have a higher input resistance, it has been assumed that invasion of Ia terminals is a graded process that is generally more complete in the terminal arborisations on small motoneurones because they have fewer branch points (see Henneman & Mendell, 1981). Whatever the underlying mechanism, this particular distribution favours the units that are commonly involved in postural reflexes.

Distribution of heteronymous monosynaptic Ia excitation

Hindlimb

Whereas early studies emphasised the homonymous nature of monosynaptic Ia excitation, the technique of facilitating the monosynaptic reflex allowed Lloyd (1946) to reveal effects from synergistic (heteronymous) muscles acting at the same joint. This led him to propose the concept of the 'myotatic unit' in which all muscles acting at the same joint with the same function are welded into a functional unit by monosynaptic Ia excitation with reciprocal Ia inhibition of antagonists. Later investigations with intracellular recording techniques revealed that the Ia synergism is by no means restricted to the

mechanical agonists operating at the same joint, but may include distant muscles operating at different joints, e.g. bidirectional excitatory connections between quadriceps and adductor femoris, and unidirectional projections from quadriceps to soleus (Eccles, Eccles & Lundberg, 1957; R. M. Eccles & Lundberg, 1958). These heteronymous Ia connections were believed to have evolved to assist feline locomotion (R. M. Eccles & Lundberg, 1958; Engberg & Lundberg, 1969), and differences found between the cat and baboon hindlimb Ia connections support this view (Hongo *et al.*, 1984).

Cat forelimb

The above data promoted the view that the Ia synergism is rather rigid and that, by not allowing much flexibility, it is optimised for assisting the flexion–extension movements of locomotion (cf. Illert, 1996). However, the cat forelimb has a less stereotyped movement repertoire than the hindlimb and a more extensive distribution of Ia connections, with many transjoint connections from proximal to distal muscles. It has been argued that this system should be capable of coping with and assisting the larger repertoire of manipulatory paw movements (Fritz *et al.*, 1989; Illert, 1996).

The stretch reflex

Monosynaptic Ia excitation contributes to the stretch (or 'myotatic') reflex described in the decerebrate cat (Liddell & Sherrington, 1924). Reflex responses arising from Ia afferents during locomotion have been studied in detail in many 'reduced' animal preparations in which walking can be elicited. Thus, it was shown in the 'mesencephalic' cat that, during selective peripheral nerve block of fusimotor axons, the EMG activity of the triceps surae was reduced by half (Severin, 1970). This indicates that muscle spindle afferents contribute significantly to muscle activation during locomotion (however, see Chapter 3, p. 114), but it gives no quantitative insights into the functional relevance of the stretch reflex, in terms of force production. Recently, it has been shown that, in the high decerebrate cat, muscle reflexes due to group I volleys evoked by *length* changes during the stance phase of walking produce over one third of the force of ankle extension (Stein, Misiaszek & Pearson, 2000). However, the relative contributions of Ia and Ib afferents is unknown: the inhibitory effect of Ib afferents may be reversed to facilitation during locomotion (Chapter 6, p. 248).

Methodology

Underlying principles

Stimulation of Ia afferents elicits in motoneurones an excitation that can be assessed in human subjects using the H reflex, the PSTHs of single motor units or the modulation of the on-going voluntary EMG. Several properties may be used to confirm that a response results from monosynaptic Ia excitation: (i) a central delay consistent with monosynaptic transmission; (ii) a low electrical threshold of the responsible afferents; (iii) a similar effect produced by a tendon tap, and (iv) the first response to be blocked by ischaemia.

Homonymous monosynaptic Ia excitation

Homonymous monosynaptic Ia excitation provides the excitatory drive responsible for motoneurones discharging in the H reflex and the tendon jerk, and is the sole input contributing to the onset of the early low-threshold peak of homonymous excitation in the PSTHs of single motor units.

Evidence for a two-neurone arc in the human soleus

Soleus H reflex

As discussed in Chapter 1, percutaneous electrical stimulation of the posterior tibial nerve below $1 \times$ MT produces a synchronised response in the

soleus muscle, a response that has become known as the Hoffmann reflex or H reflex. Monosynaptic transmission from Ia afferents to motoneurones was confirmed for human subjects by intrathecal recordings of the afferent and efferent volleys of the soleus H reflex by Magladery *et al.* (1951). They showed that, at the lower end of the spinal cord, the ventral root deflection (reflex) was separated from the dorsal root volley (elicited by the lowest threshold group I afferents) by only 1.5 ms. When allowance was made for the conduction in proximal portions of roots and within cord itself, the time left was too short for interneuronal transmission. This indicates that the first motoneurones discharging in the soleus H reflex do so at a latency consistent with a monosynaptic pathway. In support of this view, the variability in latency of a single motor unit in the H reflex is low, consistent with the existence of only a single central synapse (Trontelj, 1973). The conclusion that the latency of the soleus H reflex is determined by monosynaptic transmission has been confirmed by Ertekin, Mungan & Uludag (1996), again using intrathecal recordings of the dorsal and ventral root volleys associated with the soleus H reflex.

Monosynaptic Ia excitation of soleus motoneurones may also be demonstrated using the PSTH method

Stimulation of Ia afferents in the posterior tibial nerve consistently evokes a peak of homonymous monosynaptic excitation in soleus motor units at the same latency as the H reflex (Ashby & Labelle, 1977; Mao *et al.*, 1984). The equivalence of the latencies with the two methods is illustrated in Fig. 2.2, taking into account the trigger delay of the unit in the PSTH (Chapter 1, pp. 32–3). The H reflex at rest (*b*) and the posterior tibial-induced discharge of a single unit during voluntary contraction (*c*) occur at virtually the same latency, and this is the latency of the first bin of the peak of excitation in PSTHs from the unit ((*d*), (*e*)). This therefore reflects monosynaptic excitation (cf. Magladery *et al.*, 1951, and above). The duration of the peak (1.1 ms in Fig. 2.2(*e*)) corresponds to the rise-time of the composite monosynaptic EPSP (Burke, Gandevia & McKeon, 1984; Mao *et al.*, 1984).

Initial bins of the peak

However only the first 0.7 ms of the peak (i.e. the interval between the two vertical dashed lines in Fig. 2.2(*e*)) may be attributed unequivocally to monosynaptic excitation. The later bins of the peak can be contaminated by oligosynaptic pathways (see Chapter 1, pp. 14–16). Similarly, when the H reflex is of reasonable size, only with the first recruited motoneurones will the monosynaptic Ia EPSP not be contaminated by oligosynaptic inputs (Burke, Gandevia & McKeon, 1984).

Ia origin of the afferent limb of the homonymous monosynaptic pathway of the soleus

Apart from the monosynaptic transmission, several other arguments support the view that Ia fibres form the afferent limb of the monosynaptic pathway.

Effect of tendon taps

A broader peak of facilitation is produced in the PSTHs of soleus motoneurones by percussion on the Achilles tendon (Birnbaum & Ashby, 1982; Burke, Gandevia & McKeon, 1983), a potent stimulus for muscle spindle primary endings (Lundberg & Winsbury, 1960). The onset of the peak of excitation in single soleus motor units occurs about 5–6 ms later with tendon percussion than with electrical stimulation, a difference consistent with the time required for receptor activation and afferent conduction to the popliteal fossa (Burke, Gandevia & McKeon, 1983).

Low electrical threshold

In agreement with the finding that Ia afferents are the largest afferent fibres in the cat, the afferent volley of the soleus H reflex is produced by the afferents of the very low electrical threshold (0.67 × MT, Fukushima, Yamashita & Shimada, 1982). The threshold of the

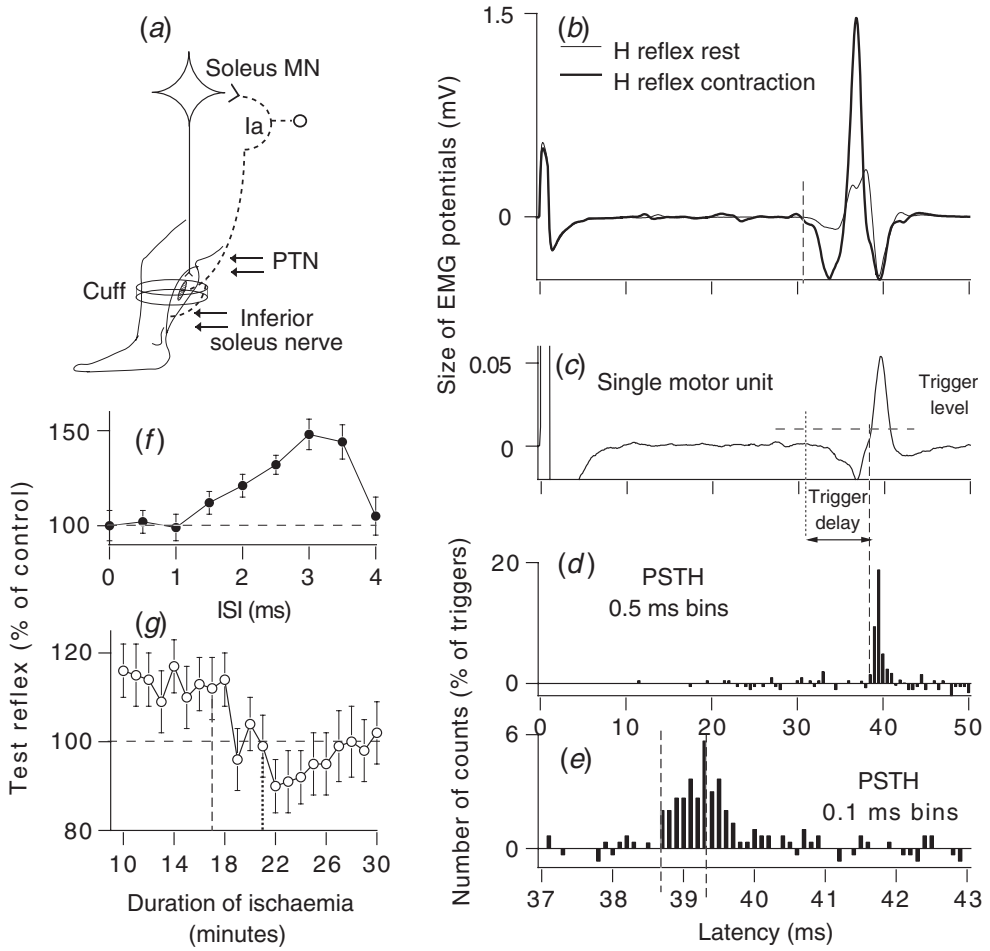


Fig. 2.2. Methods of investigating homonymous monosynaptic Ia excitation. (*a*) Sketch of the pathway of homonymous monosynaptic Ia excitation of soleus (Sol) motoneurones (MN). Stimulation is applied to the posterior tibial nerve (PTN) or the inferior soleus (Inf Sol) nerve. A sphygmomanometer cuff is positioned around the upper part of the leg (below the electrode eliciting the H reflex, but above that eliciting the Inf Sol nerve volley). (*b*)–(*e*) Results obtained from a single subject during the same experiment. (*b*) Sol H reflex elicited by PTN stimulation at 1 × MT at rest (thin line) and during weak Sol voluntary contraction (thick line). The latency of the H reflex (30.6 ms) is indicated by the vertical dashed line. (*c*) Potential from a single voluntarily activated Sol motor unit elicited by PTN stimulation at 0.7 × MT (subthreshold for the compound H reflex). The dashed horizontal line indicates the trigger level of the window discriminator, and the interval between the latency of the unit (30.8 ms, dotted vertical line) and when the rapidly rising phase of the potential crosses the trigger level (38.7 ms, dashed vertical line) represents the trigger delay of the unit (7.9 ms, double headed horizontal arrow). (*d*), (*e*) PSTHs (after subtraction of the background firing) of the unit illustrated in (*c*) following PTN stimulation at 0.7 × MT, using 0.5 and 0.1 ms bin widths ((*d*) and (*e*), the latter with an expanded abscissa). The two vertical dashed lines in *E* indicate the first 0.7 ms of the peak (i.e. its purely monosynaptic part). (*f*), (*g*) The Sol H reflex (expressed as a percentage of its unconditioned value) was conditioned by stimulation of the Inf Sol nerve at 0.8 × MT and is plotted against the ISI (*f*) and the time after the onset of ischaemia ((*g*), 3.5 ms ISI). (*g*) 17 minutes after the onset of ischaemia the Achilles tendon jerk started to decrease (indicated by the vertical dashed line) and disappeared 4 minutes later (vertical dotted line), while the maximal M response was not modified, indicating that α motor fibres were not blocked. The suppression of the tendon jerk may therefore be attributed to the blockade of Ia afferents, as also may be the facilitation of the H reflex induced by Inf Sol stimulation. Each symbol represents the mean of 10 (*f*) and 5 (*g*) measurements. Vertical bars ±1 SEM. Modified from Pierrot-Deseilligny *et al.* (1981) ((*f*), (*g*)), with permission.

monosynaptic homonymous peak observed in the PSTHs of single motor units is even lower (~0.5–0.6 × MT, Mao *et al.*, 1984; Meunier *et al.*, 1990), because the excitation is (i) then subthreshold for the compound H reflex, and (ii) obtained in a motoneurone whose excitability has been raised by voluntary activation.

Facilitation by a homonymous volley

It is possible to stimulate selectively the inferior branch of the soleus nerve on the lower border of the soleus muscle (Pierrot-Deseilligny *et al.*, 1981). Such stimulation facilitates the soleus H reflex with the time course shown in Fig. 2.2(*f*). The facilitation has a low threshold with respect to motor fibres (<0.4 × MT), probably because α motor fibres have branched at this distal site, whereas there is almost no branching of Ia afferents (see the discussion in Pierrot-Deseilligny *et al.*, 1981). Activation of Ia fibres by the conditioning stimulus could render some fibres refractory to the more proximal test stimulus. Even so, the Ia facilitation can manifest itself because only some of the Ia afferents recruited by the conditioning stimulus are activated by the test stimulus (probably because of their location within the posterior tibial nerve; Meunier & Pierrot-Deseilligny, 1989).

Effect of ischaemia

Ischaemia affects large fibres preferentially (Magladery, McDougal & Stoll, 1950), and is often used to demonstrate that an excitation is due to Ia afferents. Thus, to provide further evidence for the Ia origin of the inferior soleus-induced facilitation of the soleus H reflex, a sphygmomanometer cuff was inflated at the upper part of the leg below the electrode eliciting the test reflex but above that eliciting the conditioning volley (Fig. 2.2(*a*)). Figure 2.2(*g*) shows that the facilitation of the H reflex produced by inferior soleus stimulation was suppressed at the same time as the Achilles tendon jerk. This supports the view that the homonymous facilitation of the soleus H reflex is Ia in origin (Pierrot-Deseilligny *et al.*, 1981).

Homonymous monosynaptic Ia excitation in other muscles

Diagnostic studies

There are a number of advantages to testing the reflex pathway during a weak voluntary contraction (cf. Burke, Adams & Skuse, 1989). The contraction will potentiate the reflex by raising the excitability of the active motoneurone pool close to firing threshold and possibly by diminishing the limitation placed on reflex size by Ib afferents in the test volley (Chapter 6, pp. 268–71). During a voluntary contraction, (i) H reflexes may be recorded in virtually all accessible limb muscles; (ii) 'clamping' motoneurone excitability at a standard level eliminates the component of latency variability due to the rise-time of the composite EPSP responsible for the H reflex; (iii) responses can be obtained with a lower threshold and, as a result, the onset of the H wave can be distinguished more easily from the end of the M wave, and latency measurements can be made more accurately in proximal muscles; (iv) higher stimulus rates can be used because the attenuation of reflex amplitude with rate is greatly diminished (see p. 99); (v) the contraction 'directs' the reflex response to the active motoneurone pool so that specific reflex arcs (and specific segmental levels) can be investigated. For different limb muscles, superficial nerves are activated most conveniently by electrical stimulation, even when proximal. For example, group Ia afferents from biceps brachii are conveniently activated electrically at Erb's point (Miller, Mogyoros & Burke, 1995). Deep nerves are more of a problem, but may be accessed using magnetic stimulation (Zhu *et al.*, 1992).

Homonymous peak in the PSTHs of single motor units

For all limb muscles tested, stimulation of the parent nerve evokes an early peak with all the characteristics of homonymous monosynaptic Ia excitation – same latency as the H reflex after allowance for the trigger delay of the unit; low electrical threshold; elicitation by tendon taps (see references concerning the

different motor nuclei on p. 79). As discussed in Chapter 1 (p. 34), it is convenient to calculate the central delay of any given effect with respect to the latency of the homonymous monosynaptic Ia peak.

Critique

(i) The same arguments (low electrical threshold, elicitation by a tendon tap, early blockade by ischaemia) demonstrate that Ia afferents are the afferent limb of the H reflex and of the early low-threshold peak in the PSTHs of single units of other muscles. The latency of both the H reflex and the early Ia peak is consistent with monosynaptic transmission, when the afferent and efferent conduction times are taken into account. Given that homonymous monosynaptic Ia EPSPs exist in all cat and baboon motor nuclei, the existence of homonymous monosynaptic Ia excitation in motoneurones of human limbs is likely. However, so far, unequivocal evidence for a 'two-neurone-arc' in human subjects has been reported only for soleus. (ii) The amplitude of the H reflex cannot be used to assess the absolute strength of Ia connections within a given motoneurone pool, i.e. the effectiveness of a given Ia input in discharging motoneurones, because the amplitude of the H reflex is affected by other factors (cf. pp. 79–81).

Heteronymous monosynaptic Ia excitation

Heteronymous facilitation of the H reflex cannot provide unequivocal data

Monosynaptic excitation cannot be inferred from the timing of the H reflex facilitation

In humans, heteronymous monosynaptic Ia projections were first studied from quadriceps to soleus, using the H reflex method (Bergmans, Delwaide & Gadea-Ciria, 1978). However, monosynaptic connections cannot be demonstrated unequivocally with this technique, as illustrated in Fig. 2.3(*d*)–(*f*). Stimulation of the femoral nerve facilitates the soleus H reflex, and this appears at low threshold (0.6 × MT, (*e*), (*f*)), consistent with a group Ia effect (cf. p. 75). However, Fig. 2.3(*d*) shows that the reflex facilitation appears at the –6.8 ms ISI, i.e. earlier than the expected synchronous arrival of the two volleys at motoneuronal level (see the arrow at the –5.4 ms ISI in Fig. 2.3(*d*) corresponding to the difference in conduction times of the conditioning and test Ia volleys, and legend of Fig. 2.3(*c*); Hultborn *et al.*, 1987). This facilitation of the H reflex is 'too early' because of the poor time resolution of the H reflex technique (as discussed in Chapter 1, pp. 9–10).

Contamination by oligosynaptic effects

In addition, Fig. 2.3(*e*) shows that at the –6.5 ms ISI, i.e. 0.3 ms after the onset of reflex facilitation, increasing the conditioning stimulus intensity from 0.5 to 0.9 × MT resulted in a continuous increase in the soleus H reflex facilitation. With a longer ISI (–5.5 ms, Fig. 2.3(*f*)), the reflex stopped increasing for conditioning stimuli beyond 0.8 × MT, indicating contamination of the volley by Ib afferents, producing non-reciprocal group I (Ib) inhibition (see Chapter 6). In another paradigm, gastrocnemius medialis facilitation of the quadriceps H reflex, Pierrot-Deseilligny *et al.* (1981) found that non-reciprocal group I inhibition starts to appear 0.8 ms after the onset of the presumably monosynaptic Ia facilitation, again indicating that only the first 0.7 ms of the Ia excitation is not significantly contaminated by subsequent oligosynaptic effects.

PSTH method

A more valid method for demonstrating heteronymous Ia monosynaptic projections relies on the comparison in the PSTHs of single motor units of the difference in the latencies of the peaks of homonymous and heteronymous Ia excitations with the difference in afferent conduction times for the two volleys.

Principle of the procedure

The principle has been established in the experimental paradigm from quadriceps to soleus

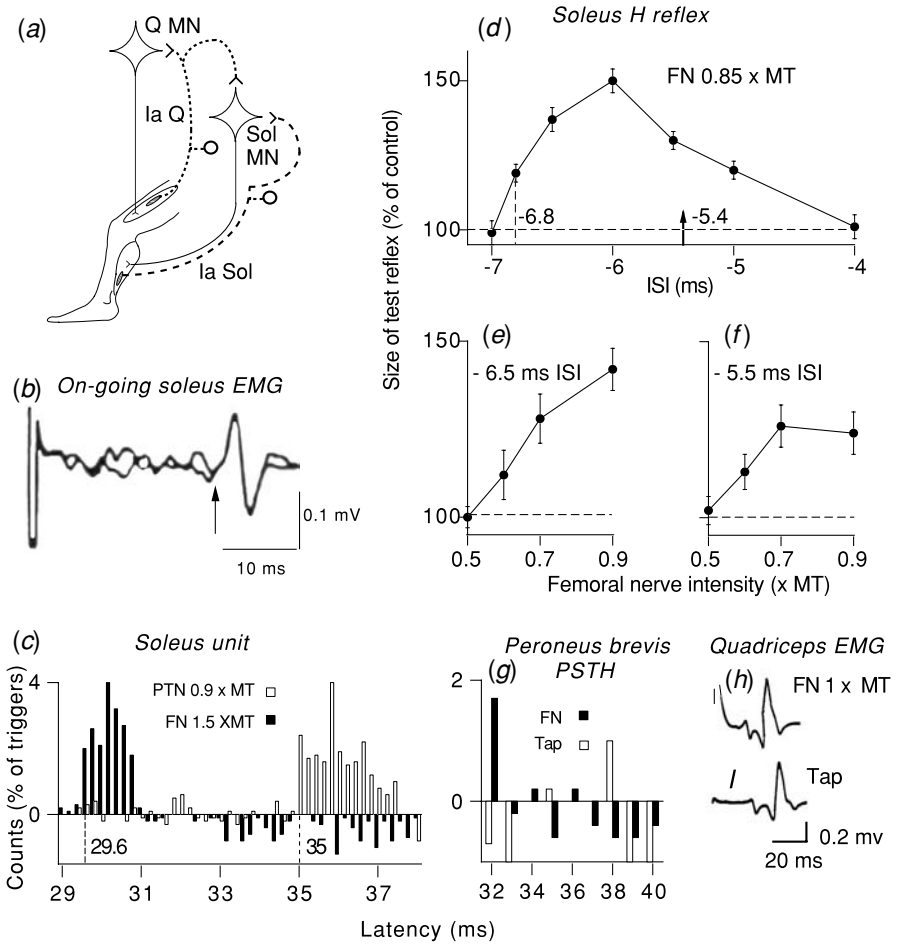


Fig. 2.3. Methods to investigate heteronymous monosynaptic Ia connections from quadriceps. (*a*) Sketch of the pathways (dashed and dotted lines) of homonymous and heteronymous monosynaptic Ia excitations from quadriceps (Q) to a soleus (Sol) motoneurone (MN). (*b*) Facilitation of the averaged on-going *unrectified* voluntary Sol EMG (128 sweeps, contraction 20 % MVC, one trace recorded at 1 Hz and the other at 3 Hz), after stimulation of the femoral nerve (FN) at 1.4 × MT (the arrow indicates the onset of the excitation at 28.5 ms). (*c*) PSTH (after subtraction of the background firing, 0.2 ms bin width) of a single Sol unit to stimulation of the posterior tibial nerve (PTN, 0.9 × MT, □) and of the FN (1.5 × MT, ■). The 5.4 ms difference in latencies of the two peaks (35 ms – 29.6 ms) corresponds exactly to the difference in afferent conduction times. (Distances from stimulation sites to motoneuronal level of 0.66 and 0.29 m and conduction velocities of 64 and 59 m s^{-1} for PTN and FN Ia volleys, respectively, produce a difference of 5.4 ms: 10.3 [0.66/64] – 4.9 [0.29/59]). (*d*)–(*f*) Amplitude of the Sol H reflex conditioned by FN stimulation and expressed as a percentage of its unconditioned value. (*d*) Time course after FN stimulation at 0.85 × MT; the vertical arrow at the –5.4 ms ISI indicates the synchronous arrival of the two volleys at motoneuronal level; the negative value results from the more proximal position of the conditioning electrode. (*e*), (*f*) The abscissa is the FN intensity ((*e*) – 6.5 ms ISI, (*f*) – 5.5 ms ISI). (*g*) PSTH (after subtraction of the background firing, 1 ms bin width) of a single peroneus brevis unit after stimulation of the FN (1 × MT, ■) or a Q tendon tap (□), evoking an H reflex (*h*) or a tendon jerk (*i*) of similar size in the Q EMG. Estimate of the afferent conduction times showed that the FN-induced peak in (*g*) occurred at a latency (32 ms) consistent with a monosynaptic linkage. The peak elicited by the tendon tap appeared 6 ms later, and this corresponds to the difference in the latencies of the Q H (*h*) and tendon (*i*) reflexes. Modified from Meunier *et al.* (1996) (*b*), Hultborn *et al.* (1987a) ((*c*)–(*f*)), Meunier, Pierrot-Deseilligny & Simonetta-Moreau (1994) ((*g*)–(*i*)), with permission.

(Hultborn *et al.*, 1987). Thus, in the PSTH of Fig. 2.3(*c*), the difference in the latencies of the early facilitation evoked in the same soleus motor unit by stimulation of the homonymous posterior tibial nerve (35 ms) and the heteronymous femoral nerve (29.6 ms) was 5.4 ms. Because the efferent conduction time and the trigger delay were the same, the difference between the two latencies must reflect the difference in the afferent conduction times and/or the central (synaptic) delay of the effects evoked by the two volleys. If the heteronymous excitation was mediated through a monosynaptic pathway, much as is the homonymous Ia excitation of soleus motoneurones (see above), the difference between the latencies of the two peaks should be entirely explained by the difference in afferent conduction times.

Estimate of the afferent conduction times

Afferent conduction times for the fastest homonymous and heteronymous Ia volleys can be estimated from: (i) the distance from stimulation sites to the entrance of the afferent volleys to the spinal cord (L2 and C7 vertebrae in the lower and upper limb, respectively) measured on the skin, and (ii) the conduction velocity of Ia afferents. The latter can be calculated from the latency of the monosynaptic Ia peaks measured in the PSTH of the same unit after stimulation of homonymous Ia afferents at two levels (Chapter 1, p. 36). In the experiment illustrated in Fig. 2.3(*c*), the distances from stimulation sites to motoneurone pool were 0.66 m and 0.29 m, and the conduction velocities for the posterior tibial and femoral volleys were 64 and 59 m s^{-1}, respectively. The difference in afferent conduction times was 5.4 ms (i.e. 10.3 ms (0.66/64) – 4.9 ms (0.29/59)). Thus the difference in afferent conduction times was identical to the difference in latencies of the homonymous and heteronymous peaks in the PSTHs of Fig. 2.3(*c*). This allows no time for transmission across an interneurone and indicates that the onset of the heteronymous excitation, like that of the homonymous one, is presumably monosynaptic.

Critique

The validity of the conclusion depends on the accuracy of latency measurements, the reliability of the estimates of Ia conduction velocities, the accuracy of distance measurements, and the possible contribution of oligosynaptic pathways.

(i) Because of the trigger delay, there is some uncertainty in the absolute latency of the peaks, but the trigger delay is the same for homonymous and heteronymous peaks in a given unit, when they are investigated in the same sequence. This will therefore not alter the difference in latencies of the two peaks, and this is the critical measurement in these experiments. The shorter the bin width, the better the time resolution of the method. Notwithstanding, because the central delay of the earliest disynaptic group I effects in humans is 0.7 ms longer than that of the monosynaptic Ia excitation (see above), 0.5 ms bins should allow a disynaptic effect to be detected.

(ii) The longer the distance between the two points of stimulation of Ia fibres, the greater the precision of the measurement of the Ia afferent conduction velocity. The calculated velocity is that of the fastest Ia afferents, but the onset of the aggregate EPSP underlying the monosynaptic Ia EPSP in individual motoneurones is given by the fastest Ia afferents, and this same issue applies to both homonymous and heteronymous pathways, while the critical measurement in these experiments is the difference between the two pathways.

(iii) A greater source of uncertainty is the measurement of conduction distances. When the homonymous and heteronymous volleys are in the same nerve (e.g. Ia volleys from the FCR and intrinsic hand muscles in the median nerve), the difference in the distances to the spinal cord can be measured accurately. This is not the case when the two volleys are in nerves located on different aspects of the limb (e.g. the median and the radial nerve), or *a fortiori* for the posterior tibial and femoral nerves where the common 'intra-abdominal part' of the two nerves can be measured only approximately. However, a 3-cm error in this segment would alter the difference between heteronymous and homonymous afferent

conduction times by only 0.1 ms, and this is the critical measurement in these experiments (see Meunier *et al.*, 1990).

Evidence drawn from bidirectional connections

Underlying principle

To eliminate uncertainties associated with the estimates of peripheral afferent conduction times, studies have been performed on Ia connections linking a pair of muscles in both directions (i.e. bidirectional connections; Meunier, Pierrot-Deseilligny & Simonetta, 1993). Two motor units in different muscles were investigated in the same experiment, using the same stimulation sites for the two units, so that the homonymous volley for one unit was the heteronymous volley for the other unit and vice versa. Because of this, the absolute value of the difference in afferent conduction times between the homonymous and heteronymous volleys was the same for the two units, and the conclusions do not depend on peripheral afferent conduction times.

Cogent evidence for monosynaptic connections

If the heteronymous connection is monosynaptic for both units of the pair, the difference (Δ) between the latencies of the homonymous and heteronymous peaks for each unit will depend only on the difference in afferent conduction times for the homonymous and heteronymous Ia volleys. Because the homonymous volley for one unit is the heteronymous volley for the other, the algebraic sum of these two differences should be nil. This appears to be so for the pair of units illustrated in Fig. 2.4, one in the soleus ((*b*), (*c*)), the other in the peroneus brevis ((*d*), (*e*)). After stimulation of the posterior tibial ((*b*), (*e*)) and superficial peroneal ((*c*), (*d*)) nerves, the differences in latencies of the homonymous and heteronymous peaks were –1 and 1 ms, respectively. Similar results have been found for units in soleus and quadriceps, and this represents a powerful argument for heteronymous Ia monosynaptic connections. The calculations underlying the technique as they apply to the units in Fig. 2.4 are elaborated further in the figure legend.

Validation of other results

It is of particular interest that the evidence for heteronymous monosynaptic connections drawn from bidirectional connections supports conclusions from studies relying on calculations of afferent conduction times. Indeed, the afferent conduction time was 0.9 ms longer for the superficial peroneal volley than for the posterior tibial volley (cf. legend of Fig. 2.4), while the PSTHs in Fig. 2.4 show that, for the two units of the pair, the latencies of the superficial peroneal peaks, whether heteronymous (soleus) or homonymous (peroneus brevis), were 1 ms longer than the posterior tibial peaks (i.e. virtually identical to the difference in afferent conduction times). Hence, the results in these bidirectional studies suggest that any errors in the estimates of afferent conduction times were not significant and validate the conclusions based upon those estimates.

Facilitation of the on-going voluntary EMG

Heteronymous monosynaptic Ia connections described in PSTH experiments may be demonstrable by averaging the rectified on-going voluntary EMG activity. This is the case for the median-induced excitation of biceps brachii (Miller, Mogyoros & Burke, 1995), the femoral-induced excitation of soleus (Fig. 2.3(*b*)) or tibialis anterior (Meunier *et al.*, 1996), and the ulnar (at the wrist)-induced excitation of wrist flexors (G. Lourenço, C. Iglesias, E. Pierrot-Deseilligny & V. Marchand-Pauvert, unpublished data). The averages cannot prove monosynaptic transmission but, if on other grounds such a connection is known to exist, averaging the EMG represents a simple method for demonstrating such activity in routine studies.

Evidence that monosynaptic heteronymous excitation is Ia in origin

In addition to the evidence for the monosynaptic transmission obtained in PSTH experiments using

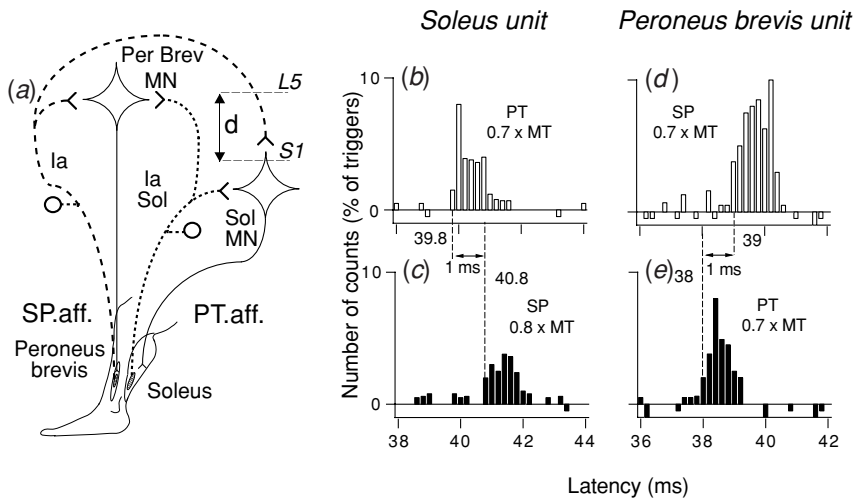


Fig. 2.4. Bidirectional monosynaptic Ia connections between soleus and peroneus brevis. (*a*) Sketch of the Ia pathways from soleus (Sol) and peroneus brevis (Per brev) (dotted and dashed lines) to motoneurones (MN) of Sol and Per Brev. Note the extra intra-spinal distance (d) between the L5 and S1 segments. (*b*)–(*e*) PSTHs (after subtraction of the background firing, 0.2 ms bin width) for a Sol unit ((*b*), (*c*)) and a Per Brev unit ((*d*), (*e*)) to stimulation of the posterior tibial (PT) and the superficial peroneal (SP) nerves during the same experimental session (□, ■ homonymous and heteronymous peaks). Homonymous stimulation for the Sol unit (PT, (*b*)) was heteronymous for the Per Brev unit (*e*), and homonymous stimulation for the Per Brev unit (SP, (*d*)) was heteronymous for the Sol unit (*c*). For the Sol unit the latency of the homonymous peak ((*b*), 39.8 ms) was 1 ms shorter than that of the heteronymous peak ((*c*), 40.8 ms). For the Per Brev unit the latency of the homonymous peak ((*d*), 39 ms) was 1 ms longer than that of the heteronymous peak ((*e*), 38 ms). Stimulation of the PT nerve was more proximal than that of the SP nerve: given distances from stimulation sites to motoneuronal level of 0.70 m and 0.61 m, and conduction velocities of 68 m s^{-1} and 65 m s^{-1} for SP and PT volleys, respectively, the difference in afferent conduction times was 0.9 ms (10.3 ms [0.70/68] – 9.4 ms [0.61/65]). The differences in latencies of the homonymous and heteronymous peaks in both units (1 ms) therefore correspond almost exactly to the differences in afferent conduction times of the homonymous and heteronymous volleys. However, with bidirectional connections, evidence for monosynaptic connectivity is independent of estimates of afferent conduction times. Indeed, the difference in the latencies of the two peaks (Δ = homonymous latency *minus* heteronymous latency) depends on two factors: (i) the difference in peripheral afferent conduction times (PT.aff. and SP.aff.) from stimulation sites to the entrance in the spinal cord; (ii) the supplementary central delay that has to be added if the heteronymous connection is not monosynaptic (d1 and d2 for each member of the pair, respectively). (The intraspinal conduction time taken by the heteronymous superficial peroneal volley to run caudally along the distance [d] can be omitted, because it has been estimated to be only 0.1 ms [Meunier *et al.*, 1990]). Thus, one has:

$-\Delta 1$ (soleus) = PT.aff. – (SP.aff. + d1) = PT.aff. – SP.aff. – d1

$-\Delta 2$ (peroneus brevis) = SP.aff. – (PT.aff. + d2) = SP.aff. – PT.aff. – d2

Adding these equations gives:

$\Delta 1 + \Delta 2$ = PT.aff. – SP.aff. – d1 + SP.aff. – PT.aff. – d2 = – d1 – d2.

If heteronymous projections are monosynaptic in both directions, i.e. when d1 and d2 are nil, this sum ($\Delta 1 + \Delta 2$) must be nil, as it is ($-1 + 1$). Modified from Meunier, Pierrot-Deseilligny & Simonetta (1993), with permission.

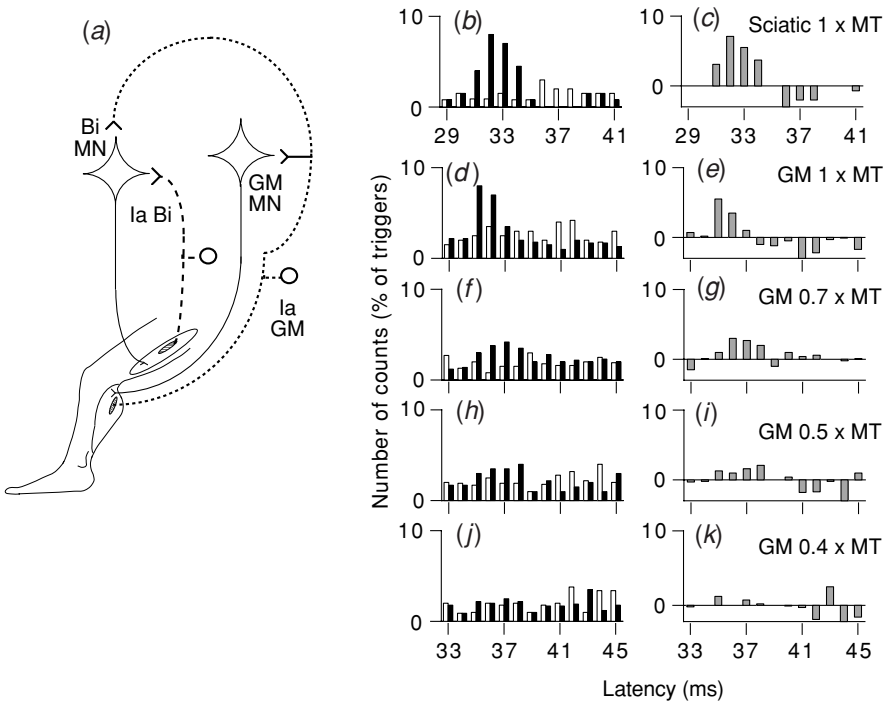


Fig. 2.5. Low electrical threshold for monosynaptic Ia excitation from gastrocnemius medialis to biceps femoris. (*a*) Sketch of the pathway (dashed and dotted lines) of homonymous and heteronymous monosynaptic Ia excitations to biceps femoris (Bi) motoneurones (MN), the latter from gastrocnemius medialis (GM). (*b*), (*d*), (*f*), (*h*), (*j*) PSTHs (1 ms bin width), for a biceps femoris unit, with (■) and without stimulation (□). (*c*), (*e*), (*g*), (*i*), (*k*) Difference between control and conditioned histograms. (*b*), (*c*) Stimulation of the sciatic nerve (1 × MT). (*d*)–(*k*) Stimulation of the nerve of the GM muscle at 1 × MT ((*d*)–(*e*)), 0.7 × MT ((*f*)–(*g*)), 0.5 × MT ((*h*)–(*i*)), and 0.4 × MT ((*j*)–(*k*)). The difference in latencies of the homonymous and heteronymous peaks corresponds to the difference in afferent conduction times. Modified from Meunier, Pierrot-Deseilligny & Simonetta (1993), with permission.

the methods described above, a number of findings indicate that the heteronymous excitation is due to Ia afferents.

Low electrical threshold

When the connection is strong, its electrical threshold is as low as that of homonymous monosynaptic Ia excitation (Meunier, Pierrot-Deseilligny & Simonetta, 1993). Thus Fig. 2.5 shows, for a motor unit in biceps femoris, that the heteronymous excitation produced by stimuli of different intensity to the gastrocnemius medialis nerve ((*d*)–(*k*)) appeared with an intensity of 0.5 × MT. This corresponds to the lowest threshold that has been observed for homonymous Ia excitation (Mao *et al.*, 1984; Meunier *et al.*, 1990), other than stimulation of the inferior branch of the soleus nerve (cf. p. 69).

Tendon tap

Heteronymous monosynaptic excitation may also be produced by a tendon tap which, at rest, strongly activates muscle spindle primary endings and Ia afferents (see p. 67). Thus Fig. 2.3(*g*)–(*i*) shows that monosynaptic excitation is evoked in the PSTH of a peroneus brevis unit (*g*) by femoral volleys produced by electrical stimulation ((*h*), 1 × MT) and by

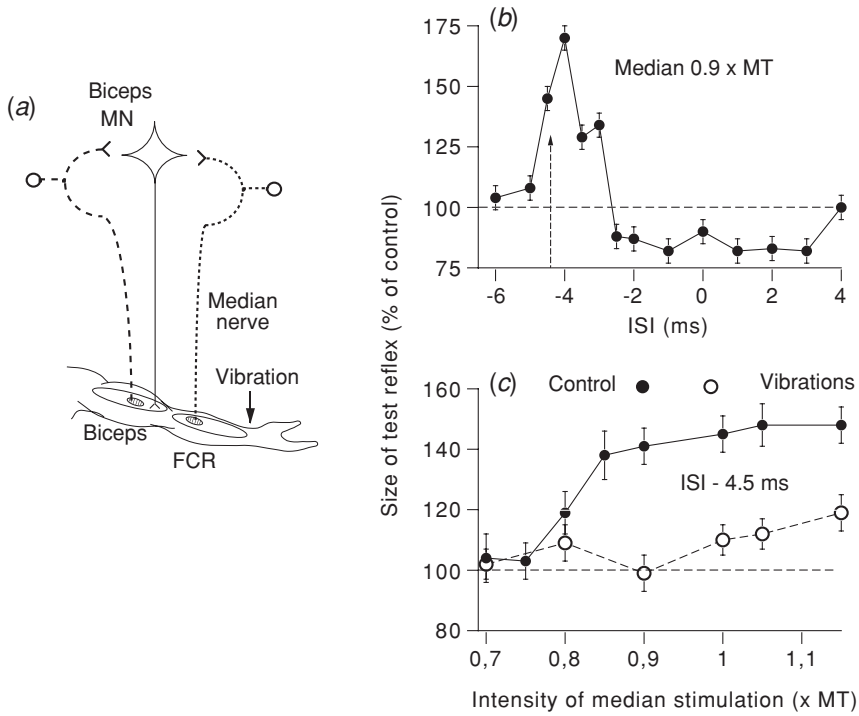


Fig. 2.6. Increasing the electrical threshold for median-induced monosynaptic Ia excitation of biceps brachii motoneurones by prolonged vibration to the tendon of flexor carpi radialis. (*a*) Sketch of the pathway (dashed and dotted lines) of homonymous and heteronymous (from FCR) monosynaptic Ia excitations to biceps brachii motoneurones (MN). (*b*), (*c*) The size of the biceps tendon jerk conditioned by a median nerve volley is plotted against the ISI (*b*) or the intensity of the conditioning stimulus (*c*). (*b*) Because of the mechanical delay introduced by the tap, the synchronous arrival of the two volleys at motoneurone level (vertical arrow at the –4.5 ms ISI) occurs when the conditioning stimulus is delivered after the test tap (negative ISIs). Parallel PSTH experiments, analogous to that in Fig. 2.3(*c*), have shown that the facilitation is monosynaptic. (*c*) At the –4.5 ms ISI, changes in the test reflex when the stimulus intensity is increased are compared in the control situation (●) and following long-lasting vibration (○, 166 Hz, for 25 minutes) to the FCR tendon (arrow in (*a*)). Modified from Cavallari & Katz (1989), with permission.

percussion on the patellar tendon (*i*), evoking reflex responses of similar size in the quadriceps EMG.

Effects of long-lasting tendon vibration

High-frequency vibration constitutes a potent stimulus for muscle spindle primary endings (see p. 64). In the cat prolonged vibration raises the electrical threshold of the responding Ia afferents because it produces activity-dependent hyperpolarisation of the activated Ia fibres (Coppin, Jack & MacLennan, 1970; Fetz *et al.*, 1979). This technique may also be used in humans (Heckman *et al.*, 1984). The results shown in Fig. 2.6 illustrate monosynaptic Ia projections from FCR to biceps brachii (Cavallari & Katz, 1989). Median nerve stimulation at 0.9 × MT facilitated the biceps tendon jerk (Fig. 2.6(*b*)). The facilitation appeared at the –4.5 ms ISI and was shown to be monosynaptic in parallel PSTH experiments. At this early ISI, the threshold for the facilitation was significantly increased (Fig. 2.6(*c*)) and its extent significantly decreased after prolonged vibration applied to the FCR tendon, evidence that it was due to activation of Ia afferents.

Absence of early excitation from cutaneous afferents

In the human upper limb, the conduction velocity of the fastest cutaneous afferents is not significantly slower than that of the fastest Ia fibres (Macefield, Gandevia & Burke, 1989). It is therefore important that cutaneous stimulation that evoked the same sensations as elicited by the mixed nerve stimulation failed to reproduce the early peak of Ia excitation (as in the experiment illustrated in Fig. 2.9(*c*), (*d*)).

Conclusions

The best evidence for heteronymous Ia excitation is provided by demonstrating in PSTH experiments that the connection is monosynaptic. The most cogent arguments are drawn from experiments using bidirectional connections where the conclusions do not rely on peripheral afferent conduction times. Notwithstanding this, strong evidence is also provided by experiments showing that the differences in the latencies of the homonymous and heteronymous peaks can be explained by differences in afferent conduction times. Finally, the Ia origin of the heteronymous excitation is supported by (i) a low electrical threshold, (ii) elevation of the electrical threshold by long-lasting vibration to the tendon of the 'conditioning' muscle, and (iii) the demonstration that it can be elicited by tendon taps.

Range of electrical thresholds of Ia afferents when stimulating using surface electrodes

When stimulating peripheral nerves directly, as in cat experiments, the stimulus strength has to be increased to twice the threshold of the most excitable afferents to set up a maximal group I volley (Brock, Eccles & Rall, 1951). Given a threshold for human Ia afferents of ~0.5 × MT, one might expect a maximal group I volley with stimuli ~1 × MT. However, in many muscles other than the soleus, the H reflex appears and continues to increase at stimulus intensities well above 1 × MT provided that the reflex discharge is not occluded by the antidromic motor volley. The question then arises what is the range of the electrical thresholds of Ia afferents in humans when stimulating nerves through surface electrodes.

Growth of heteronymous Ia monosynaptic excitation

The growth of the Ia EPSPs has been estimated in the PSTHs of single motor units as the stimulus intensity was increased up to 4–5 × MT (Gracies, Pierrot-Deseilligny & Robain, 1994). Figure 2.7 illustrates the heteronymous facilitation evoked in a peroneus brevis unit after stimulation of the femoral nerve. The excitation was weak at 1 × MT ((*b*), (*c*)), but became clearer at 2–3 × MT at a latency of 31 ms ((*d*)–(*g*)), and increased further at 4–5 × MT, associated with a decrease in latency to 30.5 ms ((*h*)–(*k*)). Similar results were found with the femoral-induced excitation of tibialis anterior units and the superficial peroneal excitation of soleus units. Figure 2.7(*l*) shows that the mean amplitude of the excitation for 25 units increased with stimulus intensity to a maximum at 4 × MT. Given a threshold for Ia afferents of ~0.5 × MT (see above), full recruitment of Ia afferents at 4 × MT corresponds to 8 × Ia threshold. As in Fig. 2.7(*f*)–(*i*), there was often a decrease in latency of 1 bin (0.5 ms) with one of the step increases in intensity from, e.g. 3 to 4 × MT. The mean decrease in latency of the monosynaptic peak relative to the latency at 1 × MT is plotted against the stimulus intensity in *M.* It reached 0.53 ms at 4 × MT. The decrease in latency is probably due to two phenomena: stimulation of the afferents at more proximal nodes as stimulus intensity increased, so producing an effectively shorter afferent path, and a more rapidly rising EPSP as more group I afferents were recruited. The latter has been shown in the cat to produce a decrease in the latency of the corresponding peak in the PSTH of up to 0.35 ms (Fetz & Gustafsson, 1983). A greater latency shortening would be expected in humans because the extent of shortening will depend on the dispersion of the excitatory input and on the EPSP rise-time, both of which are greater in human subjects.

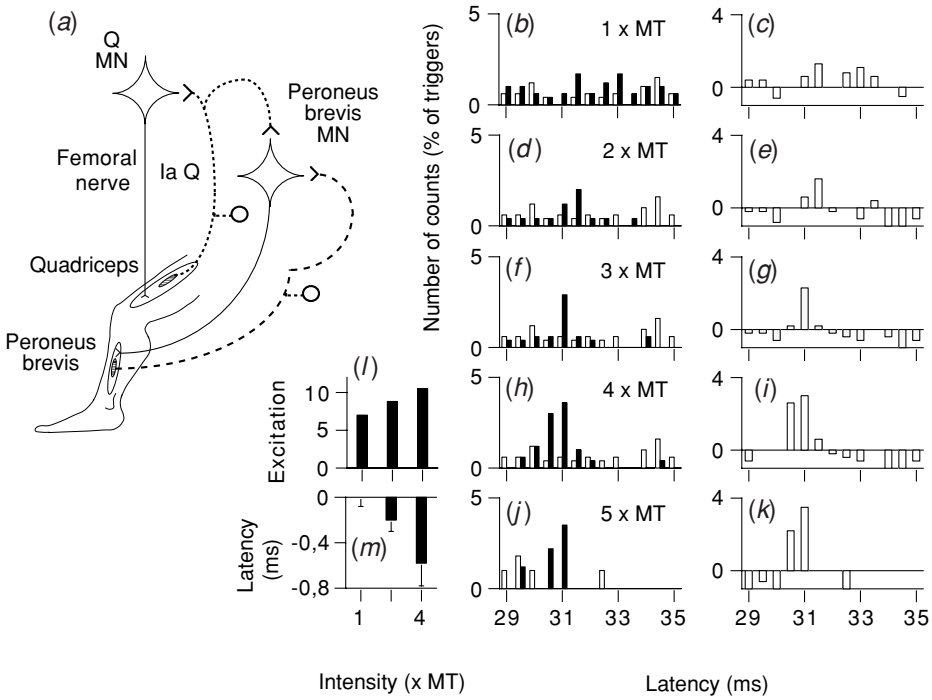


Fig. 2.7. Wide range of electrical thresholds for human Ia afferents. (*a*) Sketch of the pathway of heteronymous monosynaptic Ia excitation (dotted line) from quadriceps (Q) to a peroneus brevis motoneurone (MN). (*b*), (*d*), (*f*), (*h*), (*j*) PSTHs (0.5 ms bin width) for a peroneus brevis unit with (■) and without stimulation of the femoral nerve (□). (*c*), (*e*), (*g*), (*i*), (*k*) Difference between control and conditioned histograms. (*b*)–(*k*) Stimulation of the femoral nerve at 1 × MT ((*b*)–(*c*)), 2 × MT ((*d*)–(*e*)), 3 × MT ((*f*)–(*g*)), 4 × MT ((*h*)–(*i*)), and 5 × MT ((*j*)–(*k*)). (*l*), (*m*) Mean results from 25 motor units. (*l*) Mean amplitude of the excitation, expressed as the statistical significance (χ^2) of the difference between conditioned and control histograms during the first two bins of the peak, plotted against the intensity of stimulation. (*m*) Average decrease in latency of the monosynaptic peak (referenced to the latency at 1 × MT, which is the zero of the ordinate), plotted against the stimulus intensity. Modified from Gracies, Pierrot-Deseilligny & Robain (1994), with permission.

Difference between the full recruitment of Ia afferents in cat and human experiments

This difference (at 2 and 8 × Ia threshold, respectively) is probably due to the fact that in human experiments afferents are stimulated through electrodes on the skin surface, at a distance from the nerve. Human nerves have a larger diameter and the relevant fascicle may not always be optimally orientated to the surface. As a result, the threshold for a fibre will be determined as much by its distance from the stimulating electrodes as by its size.

Conclusions

Whatever the mechanism responsible for the wide range of electrical thresholds of Ia afferents, this factor needs to be taken into account for two reasons. (i) Reflex latency approaches the 'true monosynaptic latency' only at intensities far above motor threshold. (ii) If some Ia afferents are only activated by strong stimuli, the potential Ia reflex contribution may be underestimated in human experiments, which are generally performed with much lower stimulus intensities (≤1 × MT) in an attempt to activate group I afferents selectively.

Organisation and pattern of connections

The efficacy of a given Ia input in discharging a motoneurone is referred to as the 'strength of Ia excitation' in the following and depends on several factors: (i) the number of Ia afferents projecting to the tested motoneurone; (ii) the level of presynaptic inhibition and the level of post-activation depression at Ia terminals; (iii) any limitation produced by inhibitory circuits activated by the test volley, and (iv) the motoneurone type.

Homonymous monosynaptic Ia excitation

Evidence for homonymous Ia excitation in all motoneurone pools

H reflex

At rest, H reflexes can be recorded from the soleus, quadriceps and FCR in most healthy subjects (Fig. 2.8(*b*), (*d*), (*g*)), often from hamstrings (in thin subjects (*e*)), and rarely from other muscles ((*c*) , (*f*), (*h*)). However, an H reflex can be obtained in virtually all limb muscles during a weak voluntary contraction of the test muscle (see p. 69), without changing reflex latency significantly (see thick and thin lines in Fig. 2.8).

Homonymous monosynaptic Ia excitation in single motor units

Stimulation of the parent nerve evokes an early peak of increased probability of discharge in PSTHs of single motor units in all limb muscles tested, and this has the characteristics of homonymous monosynaptic excitation (see p. 69): soleus (Ashby & Labelle, 1977), tibialis anterior (Ashby & Zilm, 1982), gastrocnemius medialis (Mao *et al.*, 1984), peroneus brevis (Meunier, Pierrot-Deseilligny & Simonetta, 1993), quadriceps (Fournier *et al.*, 1986), hamstrings (Bayoumi & Ashby, 1989), intrinsic foot muscles (Marque *et al.*, 2001), biceps brachii (Cavallari & Katz, 1989), flexor carpi radialis (FCR) and flexor carpi ulnaris (FCU) (Malmgren & Pierrot-Deseilligny, 1988), deltoid, triceps brachii, extensor carpi radialis (ECR), flexor digitorum superficialis (FDS) and extensor digitorum (ED) (Gracies *et al.*, 1991), flexor pollicis longus (where the excitation is weak, Inglis *et al.*, 1997) and the intrinsic hand muscles (Marchand-Pauvert, Nicolas & Pierrot-Deseilligny, 2000). It must be emphasised that these investigations were performed during weak voluntary contractions (below 5% MVC), and the motor units studied were all in the low-threshold range.

Differences in the efficacy of homonymous Ia excitation in firing motoneurones

Estimate of the efficacy of the Ia input in firing homonymous motoneurones

This efficacy may be assessed by the ease with which the H reflex can be elicited at rest and by the size of the peak of excitation elicited in the PSTHs of single motor units by stimulation subthreshold for the compound H reflex (e.g. 0.7 × MT). Generally, these two measures are closely linked: e.g. in accordance with the ease with which the H reflex is obtained at rest in the soleus and FCR, the peak of homonymous Ia excitation elicited by a Ia input of comparable strength is significantly larger in soleus than in tibialis anterior (Mao *et al.*, 1984), and in the FCR than in the ECR (Chalmers & Bawa, 1997). The difficulty in activating some motoneurone pools reflexly cannot be attributed to low excitability of the motoneurone pool: tibialis anterior is more excitable to corticospinal inputs than soleus, while the reverse is true for Ia afferent inputs.

Preferential distribution of the monosynaptic Ia input to small motoneurones

In the cat, homonymous monosynaptic Ia EPSPs are maximal in small motoneurones innervating slow-twitch units (cf. p. 65). The size of the monosynaptic Ia peak should then decrease as larger motoneurones of higher threshold innervating

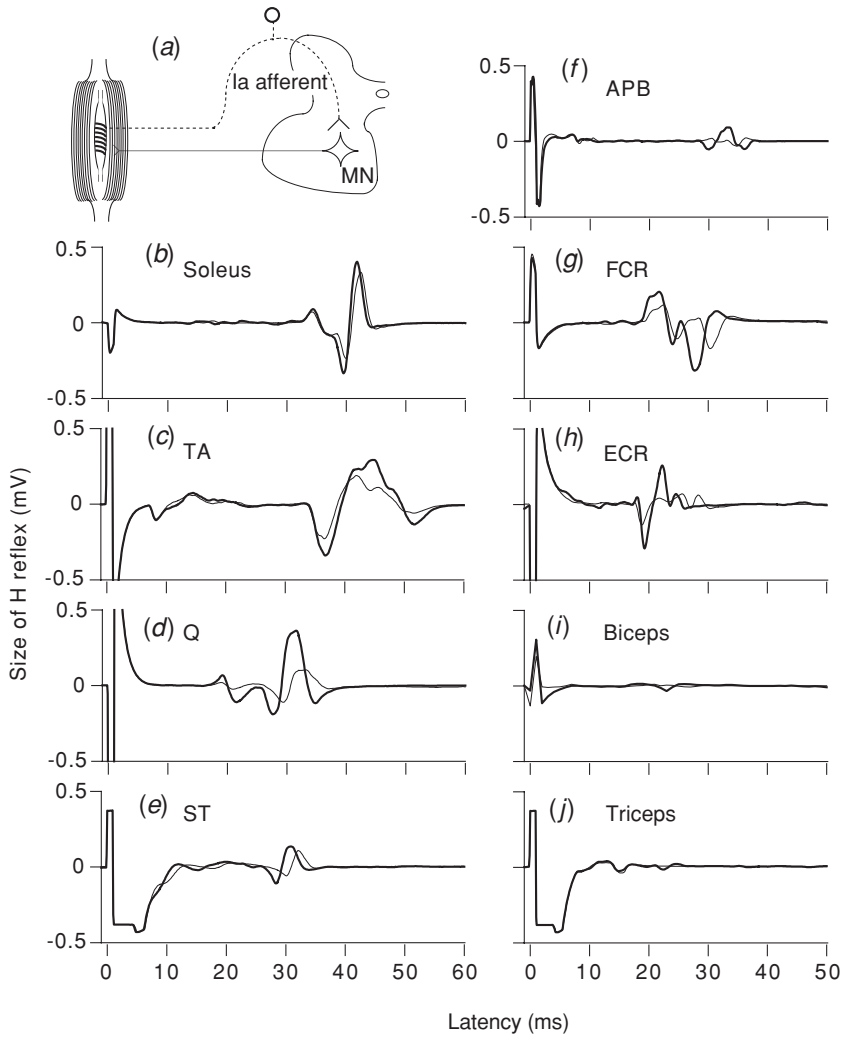


Fig. 2.8. H reflexes in different muscles. (*a*) Sketch of the monosynaptic pathway. (*b*)–(*j*) EMG recordings of the H reflex at rest (thin lines) and during voluntary activation of the tested muscle (thick lines) for the soleus (*b*), tibialis anterior ((*c*) TA), quadriceps ((*d*) Q), semitendinosus ((*e*) ST), abductor pollicis brevis ((*f*) APB), flexor carpi radialis ((*g*) FCR), extensor carpi radialis ((*h*) ECR), biceps brachii (*i*) stimulation at Erb's point), triceps brachii (*j*). All reflexes were obtained in the same subject (1.80 m tall).

units with larger and faster twitch contractions are recruited. This appears to be so in most muscles in which the different motor unit types have been investigated: second dorsal interosseus (Buller, Garnett & Stephens, 1980), soleus (Awiszus & Feistner, 1993), ECR (Fig. 8.5(*a*); Schmied *et al.*, 1997) and FCR (Nielsen & Pierrot-Deseilligny, unpublished data). Given this preferential distribution of Ia excitatory inputs to motoneurones innervating slow-twitch units, it is not surprising that the soleus H reflex may be obtained in all healthy subjects at rest, because the soleus is a homogeneous muscle

with mainly slow-twitch units (Edgerton, Smith & Simpson, 1975). However, in tibialis anterior (Ashby, Hilton-Brown & Stålberg, 1986; Semmler & Türker, 1994) and in abductor digiti minimi (Mazzocchio, Rothwell & Rossi, 1995), the largest responses to Ia input have not been found in low-threshold units.

Inhibitory mechanisms limiting the efficacy of the monosynaptic Ia input

Presynaptic inhibition of Ia terminals

This mechanism reduces the size of monosynaptic Ia EPSPs, and there is a tonic level of presynaptic inhibition of Ia terminals (see Chapter 8, pp. 353–4). The larger the maximal soleus H reflex at rest, the smaller the tonic on-going presynaptic inhibition of Ia terminals (Meunier & Pierrot-Deseilligny, unpublished data), and this supports the view that variations in the size of the maximal H reflex in different subjects (and perhaps in different muscles in the same subject) may reflect a different level of tonic presynaptic inhibition.

Contamination by oligosynaptic IPSPs

Non-reciprocal group I inhibition (so-called 'Ib' inhibition, see Chapter 6) can limit the size of the H reflex (Chapter 1, pp. 14–16). This limitation could also contribute to the absence of a recordable H reflex at rest in muscles, such as tibialis anterior, abductor pollicis brevis and ECR, though this would imply that the Ia/Ib balance was then shifted in favour of the Ib input. In these muscles, the appearance of an H reflex during a tonic voluntary contraction could involve depression of non-reciprocal group I inhibition to the active motoneurone pool (see Chapter 6, pp. 268–71), together with the increased excitability of the motoneurones.

Thresholds for α motor axons and Ia afferents

Alternatively, if the threshold for α motor axons was closer to that of Ia afferents, the maximal H reflex would probably be smaller and the reflex more difficult to obtain and, with single motor units, the peak of excitation seen in PSTHs to stimulation at 1 × MT would be smaller.

Heteronymous monosynaptic Ia excitation in the lower limb

Pattern and strength of distribution

In striking contrast with data for the cat and baboon hindlimb (see pp. 65–6), connections between some close synergists operating at the same joint are weak or absent in the human lower limb and trans-joint connections are almost the rule. Given the constraints raised above, the conclusions advanced below have generally been confirmed using more than one method.

General pattern of heteronymous Ia excitation

Table 2.1 shows the general pattern of heteronymous Ia excitation to leg and thigh muscles, estimated from PSTHs (Meunier, Pierrot-Deseilligny & Simonetta, 1993; Marque *et al.*, 2001). Grey cells represent muscle–nerve combinations with a statistically significant connection in humans. An attempt has been made to estimate the strength of the excitation (number of asterisks in each cell, see legend of Table 2.1), based on the average size of the heteronymous peak relative to that of the homonymous peak, both in response to stimulation at 1 × MT. As expected, the stronger the connection, the more frequently was it observed: e.g. the strongest connection (from gastrocnemius medialis to biceps femoris, five asterisks) was observed in 21/21 (100%) units and was, on average, 54% of the homonymous peak, whereas the weakest connection (from the intrinsic plantar muscles to biceps, one asterisk) was observed in only 27% of the units and had an average amplitude of 3% of the homonymous peak.

Connections between close synergists operating at the same joint

At knee level, strong connections exist between the two heads of the quadriceps (vastus lateralis and

Table 2.1. Monosynaptic heteronymous Ia excitation in the lower limb

Nerve / MN	Sol	GM	SP	DP	FN	TN
Sol		0	**	0	****	*
GM	**		**	*	**	*
Per Brev	**	0		**	**	*
TA	0	0	0		***	*
Q	**	**	0	*		*
Bi	***	*****	**	0	0	*
ST	**	**	*	**	0	*

Homonymous — No MS Ia — 0 — Cat

Heteronymous — Not explored — NE — Baboon (> 5% Homo)

Columns: nerve stimulated: Sol (inferior soleus), GM (nerve to the gastrocnemius medialis), SP (superficial peroneal), DP (deep peroneal), FN (femoral nerve), TN (tibial nerve at the ankle). Lines: motoneurone pools (MN) investigated with the PSTH method: Sol (soleus), GM (gastrocnemius medialis), Per Brev (peroneus brevis), TA (tibialis anterior), Q (quadriceps), Bi (biceps femoris), ST (semitendinosus). Grey cells indicate the existence of significant Ia excitation in humans (crossed cells correspond to homonymous pathways). The number of asterisks indicates the average size of the heteronymous peak relative to the homonymous peak (both recorded using stimulation at 1 × MT): * <10%; ** between 10 and 20%; *** between 20 and 30%, **** between 30 and 40%; ***** >40% (from Meunier, Pierrot-Deseilligny & Simonetta, 1993; Marque *et al.*, 2001; Marchand-Pauvert & Nielsen, 2002). Connections are compared to those described in the cat (cells with horizontal lines, Eccles, Eccles & Lundberg, 1957) and the baboon (cells with vertical lines, Hongo *et al.*, 1984). With the animal experiments, only connections with a heteronymous EPSP >5% of the homonymous EPSP are shown.

medialis), but are absent from semitendinosus to biceps, and doubtful from biceps to semitendinosus (Bayoumi & Ashby, 1989). At ankle level, there is weak Ia facilitation from gastrocnemius medialis to gastrocnemius lateralis (Mao *et al.*, 1984) and from soleus to gastrocnemius medialis (Meunier, Pierrot-Deseilligny & Simonetta, 1993). There is no Ia excitation from gastrocnemius medialis to soleus, a finding confirmed using different techniques: the modulation of the on-going EMG, the H reflex or PSTHs (Bouaziz, Bouaziz & Hugon, 1975; Pierrot-Deseilligny *et al.*, 1981; Mao *et al.*, 1984; Meunier, Pierrot-Deseilligny & Simonetta, 1993).

Connections linking ankle muscles that are not close synergists

There are bidirectional connections between soleus and peroneus brevis (Fig. 2.4), and from tibialis anterior to gastrocnemius medialis.

Transjoint connections exist between all muscle–nerve combinations tested

They can be very strong (e.g. gastrocnemius medialis to biceps). However, it should be emphasised that conclusions based on stimuli at 1 × MT underestimate the strength of the connections because, as discussed on pp. 77–8, not all Ia afferents are activated at this intensity. These connections are not confined to units in the low-threshold range investigated with the PSTH method. Many of the connections have also been observed with methods that explore a large fraction of the motoneurone pool, e.g. (i) modulation of the H reflex for the Ia excitation from gastrocnemius medialis to quadriceps and biceps motoneurones (Pierrot-Deseilligny *et al.*, 1981), and for the Ia excitation from quadriceps to soleus motoneurones (Bergmans, Delwaide & Gadea-Ciria, 1978; Hultborn *et al.*, 1987), and (ii) femoral modulation of the on-going EMG of soleus and tibialis anterior (Meunier *et al.*, 1996). An early peak of peroneal-induced monosynaptic Ia excitation has also been observed in the on-going quadriceps EMG of some subjects (Marchand-Pauvert & Nielsen, 2002). Proximal-to-distal transjoint connections can be explored safely only from the femoral nerve, because it does not contain afferents from distal muscles. Because of the difficulty in stimulating the nerves to hamstrings without encroaching upon afferents from foot and leg muscles in the sciatic nerve (or of stimulating the posterior tibial nerve without encroaching upon afferents from plantar foot muscles), it has not been possible to determine whether the connections from leg muscles to hamstrings (and from foot to proximal muscles) are bidirectional.

Projections to antagonists acting at another joint

A remarkable feature of these transjoint connections is that they often link a muscle or group of muscles to a pair of antagonistic muscles operating at another joint, e.g. quadriceps to all tested muscles acting at the ankle, soleus to quadriceps and hamstrings, and from intrinsic foot muscles to all leg and thigh muscles.

Phylogenetic adaptations

In Table 2.1, the connections in the human lower limb are compared to those in the hindlimb of the cat (cells with horizontal lines, Eccles, Eccles & Lundberg, 1957) and the baboon (cells with vertical lines, Hongo *et al.*, 1984).

Connections between close synergists

The absence of connections between some close synergists operating at the same joint in humans is predictable because of their weakness in the baboon. Thus, heteronymous Ia excitation from gastrocnemius medialis to soleus is absent in humans, very small in the baboon and large in the cat (the maximal heteronymous Ia EPSP is 3% of the maximal homonymous EPSP in the baboon and 41% in the cat). Similarly, the absence of heteronymous connections between medial and lateral hamstrings in humans is predictable because they are weaker in the baboon than in the cat.

Major differences in organisation

The most striking differences involve the presence of heteronymous connections that do not exist in the cat or the baboon or, when they exist, are <5% of the homonymous Ia EPSP (e.g. Ia connections from triceps surae onto quadriceps motoneurones, Edgley, Jankowska & McCrea, 1986; Hongo *et al.*, 1984). Thus, in human subjects, there are transjoint connections between all muscle–nerve combinations tested. The functional implications of these differences in organisation of Ia connections are considered on pp. 92–4. These ‘new’ connections raise questions about whether the term ‘synergists’ should be used functionally rather than anatomically.

Heteronymous monosynaptic Ia excitation in the upper limb

Connections between close synergists

Connections have been investigated at wrist level, using the PSTH method. There is bidirectional,

though asymmetrical, heteronymous Ia excitation between the two wrist flexors, FCR and FCU. Electrical stimuli at 1 × MT applied to the median nerve at elbow level often evoke monosynaptic Ia excitation of FCU units, whereas similar stimulation of the ulnar nerve rarely evokes significant excitation of FCR units (Malmgren & Pierrot-Deseilligny, 1988). An asymmetry has also been demonstrated using percussion of the tendons of FCR and FCU (Chalmers & Bawa, 1997), but this was less marked, possibly due to spread of the mechanical stimulus. Weak ECU facilitation by ED Ia afferents has been observed consistently but, in contrast with forearm flexors, there is no evidence for heteronymous Ia excitation at a latency consistent with a monosynaptic linkage between ECR and ECU (Chalmers & Bawa, 1997).

Transjoint connections and their phylogenetic adaptation

Table 2.2 is arranged qualitatively as is Table 2.1, and shows the pattern of transjoint heteronymous Ia excitation in the human upper limb, estimated from PSTHs.

Absence of proximal-to-distal projections

Again, there are striking differences from data in the cat (cells with horizontal lines, Fritz *et al.*, 1989). Connections from proximal to distal muscles are better developed in the cat forelimb (triceps to FCR and ECU, biceps to ECR) than in its hindlimb, but are absent in humans (Cavallari, Katz & Pénicaud, 1992). Because of the difficulty in stimulating the median and ulnar innervation of wrist muscles without encroaching upon afferents from hand muscles, it has not been possible to investigate projections from forearm muscles onto motoneurones innervating the intrinsic muscles of the hand. However, given the absence of other proximal-to-distal connections in the human upper limb, it is likely that projections from intrinsic hand muscle are probably also unidirectional (i.e. only distal-to-proximal, see below).

Table 2.2. Monosynaptic heteronymous Ia excitation in the upper limb

MN \ Nerve	MC	Tri	Med	Rad	Uln	Med & Uln (wrist)
Deltoid	*	*	0	**	0	NE
Bi		0	***	*	0	*
Tri	0		*	***	0	*
FCR	0	0		0	*	***
ECR	0	0	0		0	*
FCU	0	0	***	NE		*
ECU	0	0	NE	NE	NE	**
FDS	0	NE	NE	NE	NE	*
ED	0	NE	NE	NE	0	*
Hand	NE	NE	NE	NE	NE	

Homonymous | No MS: 0 | Cat

Heteronymous | Ia: NE

Columns: nerve stimulated: MC (musculo-cutaneous), Tri (nerve of the triceps brachii), Med (median), Rad (radial at the elbow), Uln (ulnar), Med & Uln (wrist) (median and ulnar at the wrist). Lines: motoneurone pools (MN) investigated with the PSTH method: Deltoid, Bi (biceps brachii), Tri (triceps brachii), FCR (flexor carpi radialis), ECR (extensor carpi radialis), FCU (flexor carpi ulnaris), ECU (extensor carpi ulnaris), FDS (flexor digitorum superficialis), ED (extensor digitorum), Hand (intrinsic hand muscles). Grey cells indicate the existence of significant Ia excitation in human subjects (crossed cells correspond to homonymous pathways). The number of asterisks represents the frequency of occurrence of the heteronymous peak: * <20%; ** between 20 and 60%; *** >60% (from Cavallari & Katz, 1989; Créange *et al.*, 1992; Cavallari, Katz & Pénicaud, 1992; Katz *et al.*, 1993; Mazevet & Pierrot-Deseilligny, 1994; Marchand-Pauvert, Nicolas & Pierrot-Deseilligny, 2000 and Lourenço, Iglesias, Pierrot-Deseilligny & Marchand-Pauvert unpublished data). Connections are compared to those described in the cat (cells with horizontal lines; Fritz *et al.*, 1989).

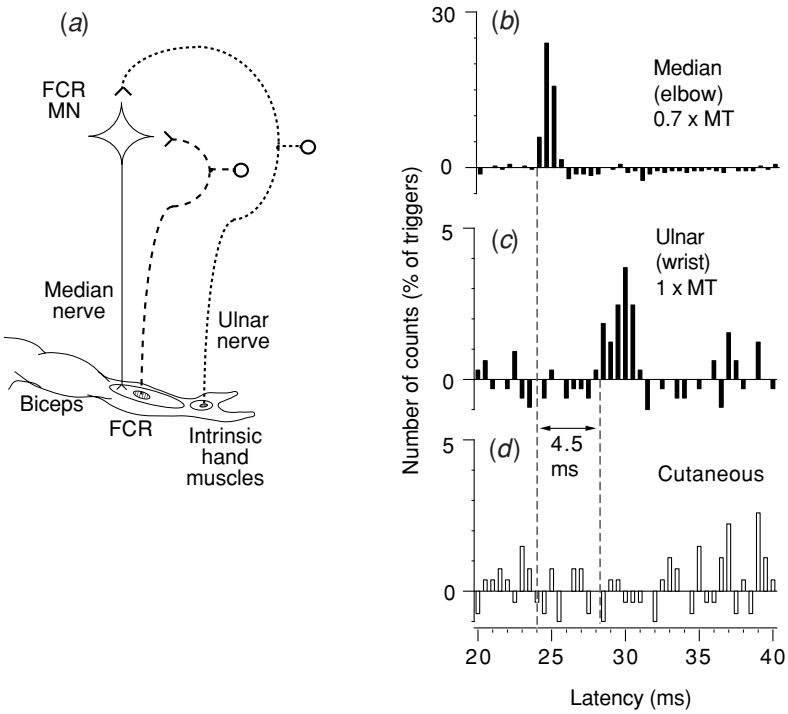


Fig. 2.9. Monosynaptic Ia excitation from intrinsic hand muscles to FCR motoneurones. (*a*) Sketch of the pathway (dashed and dotted lines) of homonymous and heteronymous monosynaptic Ia excitations to a FCR motoneurone (MN), the latter from intrinsic hand muscles innervated by the ulnar nerve. (*b*)–(*d*) PSTHs for a FCR unit (0.5 ms bin width, after subtraction of the background firing) are compared after stimulation of homonymous Ia afferents in the median nerve at elbow level ((0.7 × MT, (*b*)), of the ulnar nerve at wrist level (1 × MT (*c*)) and of the skin of the fourth and fifth fingers (*d*), mimicking the cutaneous sensation elicited by ulnar nerve stimulation, and making allowance for the extra peripheral conduction time. The difference between the latencies of the homonymous ((*b*) 24 ms) and heteronymous ((*c*) 28.5 ms) peaks is 4.5 ms, the distance between wrist and elbow electrodes, 29 cm, and the conduction velocity of the fastest Ia afferents 64 m s^{-1}. The supplementary peripheral conduction time along Ia afferents from wrist to elbow level (0.29/64 = 4.5 ms) accounts for the difference in the latencies of the two peaks of excitation (4.5 ms, (*b*), (*c*)), implying that the two excitations have a similar central linkage. Note the absence of effect of the cutaneous stimulation at the latency of the heteronymous peak (*d*). Modified from Marchand-Pauvert, Nicolas & Pierrot-Deseilligny (2000a,b), with permission.

Distal-to-proximal connections

Unidirectional connections from distal to proximal muscles are, if anything, better developed in the human upper limb than in the cat forelimb. This is so for forearm muscles to biceps and triceps motoneurones (Cavallari & Katz, 1989), and for projections from intrinsic hand muscles to motoneurones belonging to all proximal motor nuclei tested (biceps, triceps, FCR, FCU, FDS, ECR, and ED; Marchand-Pauvert, Nicolas & Pierrot-Deseilligny, 2000; Lourenço, Iglesias, Pierrot-Deseilligny & Marchand-Pauvert unpublished data). These projections can be quite strong (e.g. 12% of the number of triggers for the ulnar-induced monosynaptic excitation of the FCR unit illustrated in Fig. 2.9(*c*)).

Strength of the heteronymous excitation

An estimate of the strength of the heteronymous excitation relative to the homonymous excitation (as in the lower limb) cannot be made, because electrical stimuli below $1 \times$ MT activate only a small fraction of homonymous Ia afferents to proximal muscles operating at the elbow. The strength of the excitation, as indicated by number of asterisks in each cell of Table 2.2, is therefore based on the frequency of occurrence of the heteronymous excitation (see the legend of Table 2.2). Here again, results obtained for low-threshold motor units with the PSTH method have been confirmed by other methods: (i) modulation of the biceps and triceps tendon jerk by Ia afferent volleys from forearm muscles (Cavallari & Katz, 1989; Mazevet & Pierrot-Deseilligny, 1994), (ii) modulation of the FCR H reflex by Ia afferent volleys from intrinsic hand muscles (Marchand-Pauvert *et al.*, 2000a), and (iii) median-induced modulation of the on-going EMG of biceps (Miller, Mogyoros & Burke, 1995).

Conclusions

There are striking differences between different species, with transjoint monosynaptic Ia connections in all the combinations tested in the human lower limb. Ia projections from one muscle may be to antagonist muscles operating at another joint. In the human upper limb there are few or no transjoint proximal-to-distal connections, whereas the distal-to-proximal projections are strong, particularly those from intrinsic hand muscles.

Developmental changes in heteronymous Ia connections

Newborn

In newborn animals, there are dense monosynaptic Ia projections from homonymous muscles to direct antagonists as well as to synergists, but the former disappear during the first few post-natal days (kitten: R. M. Eccles, Sheally & Willis, 1963; rat: Saito, 1979).

It has been reported that, in the normal newborn baby, a tendon tap may elicit short-latency heteronymous excitatory responses in antagonistic muscles of the lower limb (soleus and tibialis anterior, quadriceps and hamstrings) at latencies consistent with a monosynaptic connection (Myklebust & Gottlieb, 1993). This 'reciprocal excitation' disappears during the first years of life. Similarly, in healthy human neonates, reflex responses at monosynaptic latency have been reported in the triceps brachii following a tap to the biceps brachii tendon (O'Sullivan, Eyre & Miller, 1991). This monosynaptic excitation of a direct antagonist disappears during the first four years of life (O'Sullivan *et al.*, 1998).

Ia excitation of antagonists in adults?

By cross-correlating the surface EMG with a series of 'pseudo-random taps', a similar 'monosynaptic excitatory response' from biceps to triceps has been reported in 14% of normal adults (McClelland, Miller & Eyre, 2001). This result is surprising, given that all normal adults manifest consistent and strong reciprocal Ia inhibition from biceps to triceps (cf. Katz, Pénicaud & Rossi, 1991; Chapter 5, p. 210). The problem with above results, including those in the newborn, is whether the response is due to field-spread of the EMG response of the agonist and/or to spread of the mechanical stimulus to spindles in the antagonist. Direct recordings from muscle spindle afferents have shown that vibration and percussion of the tendon of a muscle activates spindle endings in the antagonist (Burke *et al.*, 1976; Burke, Gandevia & McKeon, 1983). Thus, even with a very weak tap to the tibialis anterior tendon, it is impossible to eliminate completely spread of the vibration to soleus, and vice versa. This can produce an early, small and brief facilitation of the soleus H reflex occurring before the onset of presynaptic inhibition (see Hultborn *et al.*, 1987, and Fig. 8.2(*b*) in Chapter 8). To control for artefactual results due to spread of the mechanical stimulus, it is necessary to demonstrate that electrical stimulation of biceps Ia afferents facilitates the monosynaptic reflex of triceps.

Motor tasks and physiological implications

Homonymous monosynaptic Ia excitation. Stretch reflex responses

Abrupt stretch of an active muscle produces, in that muscle, a reflex response, that has three quite separate components (Fig. 2.11(*b*)–(*d*)): (i) the classical short-latency Ia spinal reflex (M1), (ii) the medium-latency component (M2), which is also automatic but of more complex origin (see Lee & Tatton, 1975; Marsden, Rothwell & Day, 1983; Schieppati & Nardone, 1999, and pp. 90–2), and, (iii) a long-latency response which occurs without thought but, because it is subject to will, can be considered quasi-voluntary (cf. p. 92). The latency of onset of the M1 response is compatible with monosynaptic Ia excitation. The extent to which oligosynaptic pathways contribute to this 'short-latency Ia stretch response' is unknown (cf. Jankowska & McCrea, 1983; Burke, Gandevia & McKeon, 1984).

The short-latency Ia spinal stretch reflex during natural motor tasks

Movements are controlled by motor programmes stored in the central nervous system and by spinal reflex mechanisms. These two means of control, once thought of as separate, are now known to interact (see Hultborn, 2001). The Ia stretch reflex has the simplest reflex pathway, and illustrates well the interactions between pre-programmed and reflex mechanisms during natural motor tasks. There is a considerable literature about the contribution of the short-latency Ia stretch reflex of triceps surae to various natural movements, but few data for other limb muscles.

Running

The contribution of the short-latency stretch reflex of *triceps surae* to a natural task was first established during the stance phase of running (Dietz, Schmidtbleicher & Noth, 1979; Fig. 2.10(*b*)). Before ground contact, gastrocnemius EMG activity slowly increases because of a centrally programmed activation and, after ground contact, there is an abrupt increase in activity. This increase was attributed to the short-latency Ia stretch reflex, because (i) its latency (35–45 ms) was consistent with transmission through the monosynaptic Ia pathway, and (ii) it was markedly reduced by a partial ischaemic block of group I afferents, sparing α motor axons (see p. 69). Thus, despite the increased presynaptic inhibition of Ia terminals that occurs during running (Chapter 8, p. 367), the spinal stretch reflex contributes to the muscle contraction during the pushing off of the foot in the stance phase. Because the stretch reflex enhances muscle stiffness, a considerable amount of elastic energy can be stored in tendons to be used during push off, and this probably leads to greater mechanical efficiency during running (Voigt *et al.*, 1995). To determine whether the stretch reflex contributes to automatic load compensation, the activity patterns have been compared when running on an even surface and when the leg was unexpectedly lifted or lowered (Dietz, 1981; Fig. 2.10(*b*)–(*d*)). When the leg was unexpectedly lifted, ground contact occurred earlier than expected, the dorsiflexion of the foot was slower and, as a result, the reflex response was smaller (*c*). In contrast, when the leg was lowered, ground contact occurred later, dorsiflexion was faster, and the stretch reflex response was larger (*d*). Thus, the spinal stretch reflex provides a mechanism through which rapid automatic resistance to an unexpected disturbance can be initiated. When running under normal gravitational conditions, there is a peak of EMG activity in vastus lateralis after ground contact, at a latency consistent with a short-latency Ia stretch reflex. Under simulated reduced gravity, there is a prominent decrease in this peak, in agreement with an anti-gravity role for the quadriceps (Ferris *et al.*, 2001, their Fig. 4).

Hopping

During hopping, abrupt passive ankle dorsiflexion occurs on landing, and this produces short-latency

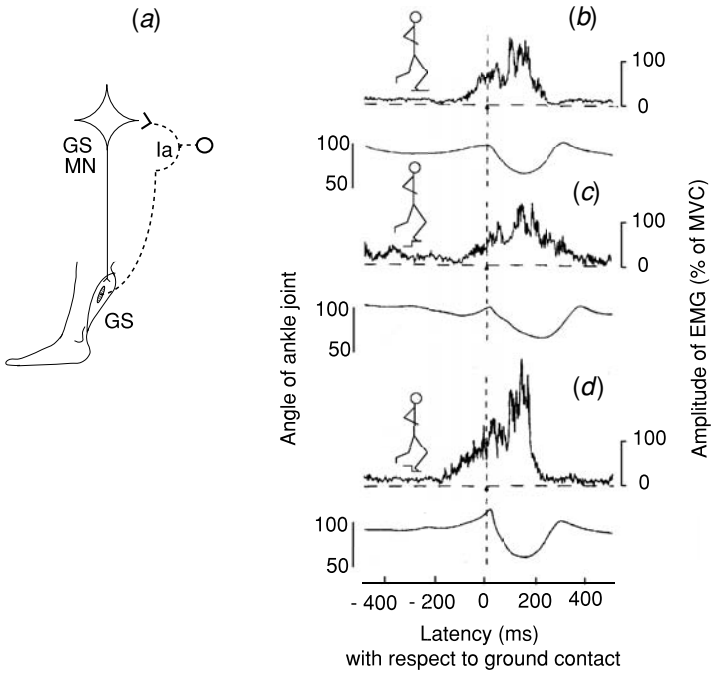


Fig. 2.10. Evidence for a contribution of the short-latency triceps surae stretch reflex to load compensation during running. (*a*) Sketch of the pathway of the triceps surae monosynaptic Ia stretch reflex. (*b*)–(*d*) Rectified and averaged ($n = 30$) on-going gastrocnemius EMG (upper traces, expressed as a percentage of MVC, right ordinate) together with the goniometer signal of the ankle position (lower traces, flexion downwards, left ordinate) during on-the-spot running. Results are compared when running on an even surface (*b*) and when the right leg was randomly lifted (*c*) or lowered (*d*), by adding or withdrawing a pedestal of 8 cm (see the sketches on the left of each trace). The vertical dashed line indicates ground contact. (Note that the peak of EMG activity during running may greatly exceed the EMG of a maximal tonic contraction, i.e. >100% MVC.) Modified from Dietz (1981), with permission.

stretch responses, consistently in soleus and to a lesser extent in gastrocnemius medialis, superimposed on centrally programmed activity (Voigt, Dyhre-Poulsen & Simonsen, 1998; Funase *et al.*, 2001). The absence of spinal stretch reflex responses previously reported by Melvill-Jones & Watt (1971a) might be due to an inappropriate method used by these authors to assess EMG activity (see the critique by Dietz, Schmidtbleicher & Noth, 1979).

Landing

Lower limb muscles

After the impact of landing, there is an EMG burst in the triceps surae, superimposed on activity pre-programmed during the fall. Its origin has been a matter of dispute, considered a stretch reflex response by Greenwood & Hopkins (1976) but centrally determined by others (Melvill-Jones & Watt, 1971b; Dyhre-Poulsen, Simonsen & Voigt, 1991). Ingenious experiments compared the responses following landing on a solid surface and on a false floor, thought to be solid. These experiments revealed robust evidence for strong short-latency stretch reflexes in soleus and medial gastrocnemius triggered by the impact of landing (Duncan & McDonagh, 2000). When the fall distance is sufficiently great, the flexion of the knee and hip increases and, as a result, there are also short-latency stretch responses in rectus femoris and biceps femoris.

These stretch responses increase with the distance fallen (Santello & McDonagh, 1998), and this suggests that they contribute to the automatic braking of the fall.

Upper limbs

In subjects falling intentionally forward onto their arms, there is an early EMG burst in the triceps brachii, the timing of which is compatible with a short-latency Ia stretch response after touchdown. When the subjects are blindfolded, these short-latency responses persist, even though the subjects lack knowledge about the depth of the fall. This indicates that a large part of the EMG activity after impact must be reactive rather than pre-programmed (Dietz, Noth & Schmidtbleicher, 1981).

Walking

Different results have been reported with two methods to stretch ankle extensors: no short-latency response was elicited by horizontal displacement of the body produced by sudden acceleration of a treadmill on which the subjects were walking (Berger, Dietz & Quintern, 1984), while a rapid imposed vertical rotation of the ankle has consistently produced such a reflex in the soleus (Yang, Stein & James, 1991; Sinkjaer, Andersen & Larsen, 1996; Grey *et al.*, 2001). This discrepancy is probably due to the fact that the vertical displacements produced a more rapid rotation of the ankle ($\sim 300^\circ\ s^{-1}$, in the experiments of Grey *et al.*, 2001) and, presumably, a greater Ia discharge. Only small and variable stretch-induced responses appear at monosynaptic Ia latency in the tibialis anterior, when it is active in the swing phase (Christensen *et al.*, 2001). Stretch-induced responses in the soleus only appear during the stance phase, and in particular in early stance, when the torque resulting from the soleus stretch reflex is greatest (Kearney, Lortie & Stein, 1999). This particular timing suggests that spinal reflexes play a role in the stabilisation of the supporting limb during walking rather than contributing to propulsion during late stance (Zehr & Stein, 1999). In contrast to the role of Ia spinal pathways when ankle extensors are unexpectedly stretched, suppression of the Ia feedback when they are unloaded in the stance phase of walking contributes little to the suppression of soleus EMG activity (Chapter 7, pp. 315–16). The explanation could be related to the strong presynaptic gating of Ia terminals on triceps surae motoneurones during gait (see Chapter 8, pp. 365–7). Presynaptic inhibition would not have the same effect on a reflex response produced by abrupt stretch, in which Ia afferents discharge at high frequency, and on the background discharge associated with the on-going movement, in which Ia afferent discharge rates are lower (see pp. 354–5).

Standing

Tilting the support toe-up or toe-down around the ankle joint occurs rarely in real life, but it has been used extensively in experimental studies, because it offers the possibility of testing the responses of ankle muscles to stretch in a stereotyped manner. Toe-up tilt of the upright stance in subjects standing on a rotating platform stretches soleus and evokes a short-latency response followed by a medium latency response (Diener *et al.*, 1984a; see Schieppati & Nardone *et al.*, 1999; Fig. 2.11(*d*)). The early response can be attributed to the short-latency spinal stretch reflex, because (i) its latency is consistent with transmission through the monosynaptic Ia pathway (see Chapter 7, pp. 293–4); (ii) increasing the velocity of platform displacement increases its amplitude (Diener *et al.*, 1984a), as would be expected with muscle spindle primary endings; (iii) it is markedly reduced by an ischaemic block of group I afferents (Bussel *et al.*, 1980), and (iv) it is not dependent on cutaneous and muscle afferents from the foot (Diener *et al.*, 1984b). The loss of large-diameter muscle spindle afferents in normal subjects after ischaemic blockade applied above the knee (Mauritz & Dietz, 1980) or in patients with Charcot–Marie–Tooth type 1A disease (Nardone *et al.*, 2000) is not detrimental to the control of body sway during upright stance. It has therefore been suggested that the M1 response is not indispensable for appropriate equilibrium control during stance. Short-latency

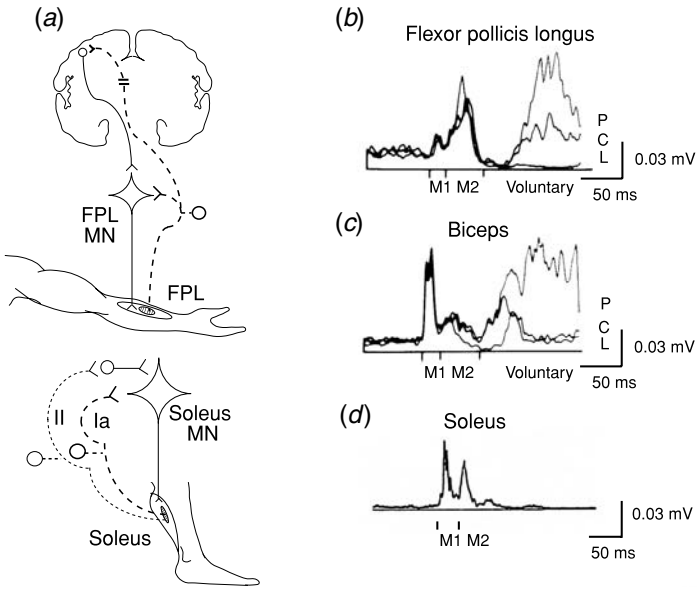


Fig. 2.11. Different pathways for the long-latency stretch response in hand and leg muscles. (*a*) Sketch of the pathways of long-latency Ia stretch responses in the flexor pollicis longus (FPL, a Ia-mediated transcortical response, the relays of the afferent pathway are not represented) and in the soleus (a group II-mediated spinal reflex). (*b*), (*c*) Rectified and averaged on-going EMG ($n = 16$) of the flexor pollicis longus (*b*) and the biceps brachii (*c*) in response to stretch. The subject was instructed to maintain a constant effort (C), to pull/press hard on perceiving the stimulus (P), or to let go (L). All three sets of trials are superimposed. The latency of the monosynaptic Ia spinal (M1), the long-latency automatic (M2) and the voluntary components (Voluntary) are indicated. (*d*) Rectified and averaged ($n = 15$) EMG of the soleus in response to stretch induced by toe-up platform rotation. Modified from Marsden, Rothwell & Day (1983) (*b*), (*c*), and Schieppati & Nardone (1999) (*d*), with permission.

Ia-mediated responses might have a role when subjects have to correct rapid perturbations to stance (Dietz, Mauritz & Dichgans, 1980), although these responses can also destabilise the posture (cf. Diener *et al.*, 1984a; Chapter 11, pp. 540–1). Unless the perturbation is very fast (300° s^{-1}, Nakazawa *et al.*, 2003), there is no short-latency spinal stretch reflex in the tibialis anterior to passive ankle plantar flexion during stance.

Spinal and transcortical stretch reflexes

Although transcortical reflexes fall outside the theme of a book centred on spinal circuitry, it is impossible not to mention them briefly because: (i) the origin of long-latency stretch reflexes, spinal vs. transcortical, has long been a matter of dispute, (ii) the history of this dispute enlightens how human neurophysiology progresses by successive steps, and (iii) the final conclusion is that some responses are spinal and others transcortical. The following section is based on comprehensive reviews by Marsden, Rothwell & Day (1983) and by Matthews (1991).

History of the long-latency reflexes in humans

Initial findings

Hammond (1956, 1960) showed that, when the human elbow is suddenly and forcibly extended, the voluntary EMG activity in biceps brachii contains a small burst at spinal monosynaptic latency followed by a larger response with a latency too long for the classical monosynaptic spinal reflex, but too short for the reaction to be 'voluntary'.

Hammond's interpretation of his late recordings is now known to be incorrect (cf. below), even though his original traces contain true long-latency automatic responses (i.e. responses independent of will). The study of Marsden, Merton & Morton (1972) was the first to document unequivocally large long-latency automatic responses to stretch, following weak and inconstant responses at monosynaptic Ia spinal latency in the voluntarily activated flexor pollicis longus (Fig. 2.11(*b*)). Hammond had originally suggested that the extra delay of the second response might be produced by either a longer pathway in the central nervous system or by a longer conduction time in the peripheral afferent pathway (see the sketches in Fig. 2.11(*a*), showing the pathways for the hand and leg, respectively).

Evidence continued to accumulate in favour of the transcortical hypothesis

Thus, it was shown that: (i) in the monkey, pyramidal tract neurones can respond very rapidly to a peripheral disturbance (Evarts, 1973), (ii) there is ample time for afferent information carried by the fastest (Ia) afferents from the stretched muscles of the thumb to reach motor cortex, and to produce the cortico-motoneuronal volleys responsible for the long-latency responses recorded in the flexor pollicis longus (Marsden, Merton & Morton, 1972), and (iii) lesions of the dorsal columns caused the M2 response to disappear (Marsden *et al.*, 1977).

Counter-arguments

An alternative mechanism for the M2 response was proposed on the basis of recordings from Ia afferent fibres in humans (Hagbarth *et al.*, 1981). The response to muscle stretch often consisted of repetitive bursts of spindle firing reminiscent of the bursting EMG pattern. An alternative possibility that the long-latency response to stretch was due to slow afferents was examined using vibration which excites rapidly conducting Ia afferents more than slowly conducting group II afferents (cf. Chapter 7, p. 289). Because of the failure of vibration to elicit a long-latency response, Matthews (1984) suggested that the long-latency response might be mediated by slower conducting group II afferents.

Denouement

To confirm his slow afferent hypothesis, Matthews (1989) used cooling of the arm, with the rationale that this would slow a reflex mediated by slowly conducting group II afferents disproportionately more than a long-loop response mediated by Ia afferents (cf. Chapter 7, pp. 297–9, for experimental details on the technique of cooling). Contrary to his original hypothesis, the experiments provided evidence that the afferent limb of the long-latency stretch response of hand muscles does depend on Ia afferents. Further support for the existence of a transcortical Ia loop emerged from studies on patients with Klippel–Feil syndrome, with mirror movements because corticospinal axons branch abnormally to supply homologous motoneurones bilaterally. In these patients, stretch of one hand muscle evoked typical long-latency stretch responses bilaterally, whereas the M1 response was restricted to the stretched muscle (Matthews, Farmer & Ingram, 1990).

Origin of long-latency stretch reflexes in different muscles

Lower limb

Long-latency responses have been recorded regularly in calf muscles after a sudden disturbance of the ankle joint and, somewhat unfortunately, were termed the 'functional stretch reflex' by Melvill-Jones & Watt (1971a,b). The response occurs only when subjects actively oppose the disturbance, and has a variable but long latency of $\geq$120 ms. It thus resembles more the voluntary contraction, which follows the stretch reflex in the upper limb (see below). However, medium-latency stretch responses can be recorded regularly in foot and leg muscles (Fig. 2.11(*d*)), where they are probably due to a spinal pathway fed by slow group II afferents (see Schieppati & Nardone, 1999; Chapter 7, pp. 297–9). Thus, interestingly, the two hypotheses proposed by Hammond (1960) to account for M2 responses are likely to be valid: a long-loop (transcortical) pathway fed by rapid Ia afferents

in hand muscles, but a spinal pathway fed by slow afferents (group II) in foot and leg muscles. However, there is evidence that a transcortical pathway fed by Ia afferents may contribute to stretch reflexes in the tibialis anterior (Petersen *et al.*, 1998), and group II pathways probably contribute to the M2 response in wrist muscles (Cody *et al.*, 1986).

Upper limb

The responses to stretch in the voluntarily activated flexor pollicis longus and biceps are compared in Fig. 2.11(*b*), (*c*) (Marsden, Rothwell & Day, 1983). The early excitation at spinal monosynaptic latency (M1) is small in the flexor pollicis longus but large in the biceps. A later response can also be seen in the biceps, but is much smaller than the equivalent component in the flexor pollicis longus. Its latency is compatible with a transcortical response, but it cannot be excluded that spinal group II pathways also contribute to M2 responses in proximal upper limb muscles.

Interaction with voluntary intent

In Hammond's experiments the late response to stretch depended on the subject's intention: it was well-developed when the subject was instructed to resist the stretch, but small when instructed to 'let go'. This dependence on voluntary control introduced doubts about the reflex nature of the long-latency response, and further experiments showed that it was not automatic. Thus, Fig. 2.11(*b*), (*c*) compares the responses in the flexor pollicis longus and biceps when the subject was instructed to maintain a constant effort (C), to pull/press hard on perceiving the stimulus (P), or to let go (L). The M1 and M2 stretch responses are not influenced by intent and are truly automatic. In contrast, the following activity ('Voluntary' in Fig. 2.11(*b*), (*c*)) is enhanced when the subject resists the stretch and suppressed when the subject lets go. This activity is still subject to will, even though it occurs without thought, and represents the voluntary reaction to a known proprioceptive stimulus: such reactions can occur with a remarkably short latency (Marsden, Rothwell & Day, 1983).

Functional significance

Investigations performed in the human hand have demonstrated that long-latency stretch reflexes play a role in positional servo-assistance. However, although the reflex may compensate fully for small disturbances that are only just perceived, the compensation for larger disturbances is less satisfactory. When prediction of the external conditions is reasonably accurate, mechanisms involving the long-latency stretch reflex machinery could automatically tune the motor program to match the actual loading conditions on the limb. When these mechanisms fail, conscious intervention by the subject becomes necessary. 'Such a control system trades off automaticity against flexibility in the face of a largely unpredictable world' (Marsden, Rothwell & Day, 1983).

Heteronymous monosynaptic Ia excitation

In contrast with the abundant literature dealing with the role of the homonymous monosynaptic reflex, there are scarce data demonstrating a functional role for heteronymous Ia connections. However, there are differences in the organisation of these connections in the hindlimb of the cat and baboon and in the human lower limb (see p. 83, and Table 2.1), and this suggests that the human connections have evolved to provide the particular reflex assistance required for bipedal stance and gait. In this respect, Hongo *et al.* (1984) stated that the wide range of Ia projection strength (homonymous and heteronymous) in the baboon probably represents a purposeful adaptation: 'adequate control of movements may require a very exact balance between direct α-excitation and indirect γ-route excitation via spindle afferents, which ultimately depends on the amount of Ia-excitation that can be evoked in motoneurones via the existing connections. If so, it is not surprising that the projection strength is not the same in different motor nuclei and between different animal species.' The possible functional role of the particular organisation of Ia connections observed in human subjects is discussed below.

Lower limb

Weakness of the connections between some close synergists acting at the same joint

In the cat heteronymous monosynaptic Ia facilitation is strong between close synergists operating at the same joint, e.g. between the different ankle extensors, or between medial and lateral hamstrings (Eccles, Eccles & Lundberg, 1957).

Ankle extensors

In humans heteronymous Ia connections from soleus to gastrocnemius medialis or from gastrocnemius medialis to gastrocnemius lateralis are weak. They are absent from gastrocnemius medialis to soleus, something that might have been predicted given the near-absence of Ia excitation from gastrocnemius medialis to soleus in the baboon (Hongo *et al.*, 1984). The reason for the absence may be related to the role of the gastrocnemius-soleus during plantigrade gait. As discussed on p. 89, reflex contraction of gastrocnemius-soleus does not contribute greatly to propulsion during the late stance of human walking, but it resists and thereby slows the passive ankle dorsiflexion produced by extrinsic mechanisms, such as kinetic and gravitational forces. This calf muscle resistance needs to be overcome if the body is to be brought forward, and, together with other mechanisms, weak Ia connections between the different heads of triceps surae would be expedient. Conversely, Ia connections between ankle muscles that are not synergistic in flexion-extension movements (soleus and peroneus brevis, tibialis anterior and gastrocnemius medialis) might help stabilise the ankle during the stance phase of locomotion (see Chapter 11, p. 546).

Hamstrings

Connections between lateral and medial hamstrings are weaker in the baboon than in the cat, and weaker still in humans. Hongo *et al.* (1984) argued that weak connections between hamstrings might be an advantage in lateral limb movements. Such movements occur particularly during unipedal stance, and this would therefore be of greater value for baboons than cats, and for humans than baboons.

Widespread transjoint connections and walking

Transjoint heteronymous Ia connections are almost the rule in the human lower limb (cf. Table 2.1). Some may appear weak (e.g. those from the intrinsic plantar muscles), but their strength is underestimated (as pointed out on p. 78) and, in any case, they would be sufficient to modulate the excitability of already depolarised motoneurones. It has been suggested that the particular pattern of heteronymous monosynaptic Ia connections observed in the cat and baboon has evolved to assist locomotion in each species (Engberg & Lundberg, 1969; Hongo *et al.*, 1984). Similarly, it has been proposed that the more widespread pattern of Ia connections found in the human lower limb might have evolved to provide the more elaborate reflex assistance required for bipedal stance and gait, in which the equilibrium is much less stable than in quadrupeds (Pierrot-Deseilligny *et al.*, 1981; Meunier, Pierrot-Deseilligny & Simonetta, 1993). Any role of heteronymous Ia connections during human walking must also take into account that the pattern of activation of muscles is more complex than in the cat, with activity of extensors that is not in phase and a pattern which, as a whole, is not one of reciprocal activation of flexors and extensors (see Capaday, 2002; Chapter 11, p. 544; Fig. 11.3).

Running, hopping and landing

During the stance phase of these tasks, all extensors (intrinsic plantar muscles, triceps surae, quadriceps, and hamstrings [hip extensors]) are co-contracted and undergo a lengthening contraction. This will evoke a strong Ia discharge from the contracting muscles (see Chapter 3, p. 137). As a result, the short-latency Ia stretch reflex of the gastrocnemius-soleus contributes to the pushing off of the foot. There is also a short-latency stretch response in the quadriceps during running and landing (see pp. 87–9). It is probable that Ia connections linking the

different extensors (from intrinsic plantar muscles to all proximal muscles; from gastrocnemius-soleus to hamstrings; from gastrocnemius-soleus to quadriceps and vice versa) help control the contribution of these different muscles to load compensation. Thus, during standing, stretch of quadriceps elicits an overt excitation of soleus α motoneurones at monosynaptic latency (Capaday, 2002).

Projections onto antagonists operating at another joint

These projections do not occur in the cat or baboon hindlimb, but are quite common in the human lower limb (cf. p. 83). Functionally, this may be explained in different terms.

(i) Versatile synergisms are required to accomplish the various tasks in the repertoire of the human lower limb, tasks that are more variable than in the cat hindlimb. Thus, for example, there is a co-contraction of all extensors in running, hopping and landing (see above), of gastrocnemius-soleus and intrinsic plantar muscles with hamstrings when leaning forward, and of quadriceps and tibialis anterior when leaning backward.

(ii) When stumbling over an obstacle in the swing phase of walking, monosynaptic responses occur simultaneously in flexors and extensors (Schillings *et al.*, 1999). Collision of the limb with the obstacle will create a sudden jar that is transmitted through the limb and causes widespread muscle spindle activation (see Lance & de Gail, 1965). However, it is likely that heteronymous monosynaptic Ia connections also contribute to the diffusion of the reflex responses. The resulting co-activation of antagonists and the lack of obvious kinaesiologic consequences following the responses suggest that the diffuse reflex activity is used to stiffen the limb.

Suppression of unwanted Ia connections

An invariant diffuse pre-wired pattern of monosynaptic connections in the human lower limb could be functionally inconvenient, because the activation of Ia afferents from one contracting muscle might then result in the automatic activation of unwanted muscle(s) linked in Ia synergism. Through focused corticospinal drive, two mechanisms allow the selection of the heteronymous Ia connections appropriate for a given task: increased presynaptic inhibition of Ia afferents directed to unwanted motoneurones (Chapter 8, pp. 359–60), and recurrent inhibition of unwanted motoneurones (Chapter 4, pp. 183–4). It has been consistently observed that there are suppressive mechanisms, such as these, opposing the unintended contractions that would result from heteronymous Ia discharges during voluntary or postural contractions. This finding suggests that heteronymous Ia discharges do have a functional role, because their pathways are suppressed in tasks for which they are not required.

Upper limb

Proximal-to-distal projections

Proximal-to-distal projections from elbow to wrist muscles are presumed to assist locomotion in the cat (Fritz *et al.*, 1989). Accordingly they are absent in the human upper limb.

Ia projections from intrinsic hand muscles

Those projections supplied by the median and ulnar nerves are much more widely distributed than in the cat. They have been found on motoneurones of all tested proximal muscles operating at finger, wrist and elbow levels. They reach both flexors and extensors and cross the radio-ulnar plane. This diffuse distribution and the finding that the connections are stronger on muscles operating at the wrist than on long flexors and extensors of the fingers suggest that these projections might be used to stabilise the wrist and the elbow in order to provide a firm support to hand muscles during grasping and manipulatory movements (Marchand-Pauvert, Nicolas & Pierrot-Deseilligny, 2000). The strength of these connections could then simply reflect the greater requirement for such movements in humans.

Studies in patients and clinical implications

Methodology

H reflex

When testing the H reflex in patients, there is a number of advantages to performing studies during voluntary contractions (see p. 69). It is then possible: (i) to record the reflex in virtually all accessible limb muscles; (ii) to reduce the latency variability; (iii) to increase stimulus repetition rates up to 3 Hz to minimise the duration of the test, and (iv) to focus the reflex response on the active motoneurone pool so that specific reflex arcs (and specific segmental levels) can be investigated.

Modulation of the on-going EMG by a heteronymous volley

This modulation (see p. 73) may be a useful way to access a motoneurone pool, using afferent inputs that do not traverse the same nerve or nerve root as homonymous afferents, particularly in patients with lateralised disturbances in whom the uninvolved side would serve as a control.

Peripheral neuropathies, mononeuropathies and proximal nerve lesions

Reflex attenuation

A decrease in the amplitude and an increase in the latency of the H reflex have been observed in various radiculopathies (C6, C7, L4, S1) (e.g. Schimsheimer, Ongerboer de Visser & Kemp, 1985; Sabbahi & Khalil, 1988; Verhagen *et al.*, 1988), plexus and nerve lesions (e.g. Ongerboer de Visser, Schimsheimer & Hart, 1984), and polyneuropathies (e.g. Schimsheimer *et al.*, 1987). Reflex depression is usually due to an afferent abnormality and will occur when there is either loss of conducting afferents or dispersion of the afferent volley (because of uneven slowing of conduction in the afferent fibres). When the lesion is in the afferent limb of the arc, reflex slowing may only be mild (~1–2 ms). Indeed, it is critical that the afferent volley remains sufficiently synchronised to discharge the motoneurone pool: there is a limit to the slowing and dispersion that can occur in an afferent abnormality before the reflex is abolished.

Location

Reflex function can be assessed for most clinically relevant spinal segments, including those likely to be compromised by, e.g. disc prolapse: biceps brachii (C5–C6), ECR (C6), FCR (C6–C7), abductor pollicis brevis (C8–T1), quadriceps (L2–L4), tibialis anterior (L4–L5) and soleus (S1). They also may provide a tool to distinguish between isolated peripheral nerve lesions and lesions involving roots or plexus.

Advantage of reflex studies over somatosensory evoked potentials (SSEPs)

Because the relationship between the size of a nerve volley and the size of the cortical SSEP produced by that nerve volley is not linear, sparing of only 10–20% of the sensory fibres innervating the test region will result in a SSEP that is within normal limits for latency and amplitude (see Gandevia & Burke, 1984). This is a disadvantage when trying to define a subtle lesion that is producing few clinical changes, if any. On the other hand, the H reflex depends on a synchronised afferent volley and on the resulting excitation being sufficient to discharge motoneurones in the pool. Any pathology that prevents conduction in some afferent axons or increases the dispersion of the afferent volley could increase reflex latency or abolish the reflex discharge.

Comparison with F wave studies

Routine reflex and F wave studies do not provide information on the conduction velocity of the same motor axons: F wave studies may not explore

conduction in slowly conducting efferents, the very efferents preferentially accessed in reflex studies (see Chapter 1, p. 4). A major limitation of F wave studies is that, in practice, they cannot be performed on proximal muscles, because F waves may not be identifiable when their latency is so short that they merge with the end of the M wave. On the other hand, reflex studies can be performed on any limb muscle provided that access can be obtained to the parent nerve (for the H reflex) or the appropriate tendon (for the tendon jerk).

Spasticity

H reflex

There is abundant literature showing that the ratio H_{max}/M_{max} is, on average, increased in soleus in spastic patients (see Chapter 12, p. 562). However, it is not, or hardly so, in the FCR in hemiplegics (Aymard *et al.*, 2000). The mechanisms contributing to the increase in the H_{max}/M_{max} ratio of soleus and the inhibitory mechanisms helping limit the size of the FCR reflex are discussed in detail in Chapter 12.

Reflex irradiation

Reflex irradiation in spastic patients is associated with the transmission through skeletal structures of a vibration wave set up by percussion of bone or tendon, so that spindles are activated in muscles throughout the limb (Lance & de Gail, 1965). However, the widespread heteronymous Ia connections present in the lower limb contribute to reflex irradiation and could even be a more important mechanism.

Post-activation depression

Post-activation depression at the Ia afferent-motoneurone synapse is reduced in spastic patients, and this might be an important spinal mechanism underlying spasticity (see pp. 99–100).

Post-activation depression at the Ia afferent-motoneurone synapse

Previous activation of Ia fibres mediating the afferent volley of the H reflex produces a dramatic reflex depression at short ISIs (1–2 s), referred to as 'post-activation depression' or 'homosynaptic depression' (Crone & Nielsen, 1989). This raises particular methodological problems when using the H reflex (see Chapter 1, pp. 13–14). In addition, a reduction in post-activation depression at the synapse of the Ia afferent on the motoneurone seems to be one of the mechanisms underlying spasticity. The definitive work on this phenomenon was undertaken by Hultborn, Nielsen and colleagues and the following section is largely based on a comprehensive review by Hultborn & Nielsen (1998).

Background from animal experiments

It has long been known that the size of the monosynaptic reflex in the cat decreases during repetitive stimulation (Eccles & Rall, 1951), and a frequency-related depression of the reflex has been described at stimulus intervals as long as 10–20 s (Lloyd & Wilson, 1957). In a variety of preparations, including the Ia-motoneurone synapse in the cat spinal cord, there is early facilitation of relatively short duration, superimposed on a depression of much longer duration (several seconds) when more than one impulse is conducted (see Curtis & Eccles, 1960; Mendell, 1984; Hultborn *et al.*, 1996). Statistical analysis of the quantal release at the Ia-motoneurone synapse suggests that the early facilitation and the subsequent depression are both due to changes in the probability of transmitter release at the synapse (Kuno, 1964; Hirst, Redman & Wong, 1981). For the Ia-motoneurone synapse, it has been demonstrated that facilitation and depression dominate at different frequencies (Lüscher, Ruenzel & Henneman, 1983), and depend on the particular Ia-motoneurone connection (facilitation being dominant for high-threshold 'fast' motoneurones and depression for low-threshold 'slow' ones, Honig, Collins & Mendell, 1983).

Functional significance

Ia afferents may have a background discharge and commonly discharge in relatively long bursts during natural movements. The overall synaptic efficacy at a given Ia-motoneurone synapse depends on the 'adapted' state of synaptic transmission created by the background Ia firing. If there is a pause in the discharge, the EPSP due to the first spike in a subsequent train of afferent impulses will be unaffected by these facilitation/depression processes. During the train, however, the post-activation depression would help hold the synaptic efficacy of the Ia fibre at a relatively low level during voluntary movements. This is likely to be important functionally (see Hultborn & Nielsen, 1998), because it would favour a low gain for the stretch reflex, and thus help prevent oscillations and clonus from developing (see Matthews, 1972). Differences in post-activation depression of the synaptic actions of the collaterals of the same group II afferents have been found in the cat in dorsal horn and intermediate zone interneurones, suggesting that post-activation depression could depend on the different target neurones of these collaterals (Hammar, Slawinska & Jankowska, 2002). Differences in the susceptibility of different terminals of the same Ia afferent could allow rapid adaptation of the monosynaptic Ia input to motoneurones but a constant input to other spinal targets (such as lumbar propriospinal neurones, see Lamy *et al.*, 2005) and to supraspinal centres.

Methodology

Under normal conditions synapses are activated by trains of impulses of varying frequency and pattern, but the rules of the activity dependency are best investigated under stereotyped conditions in which the response in the post-synaptic cell to stimulation of the presynaptic fibre covers a range of intervals following a conditioning stimulus. In practice, two methods may be used to assess post-activation depression at the Ia fibre-motoneurone synapse in humans. They are illustrated in Fig. 2.12.

Post-activation depression following passive stretch of the test muscle

Passive dorsiflexion of the foot produces a considerable reduction of the soleus H reflex at ISIs up to 2 s, and the reflex only returns to its control value at ISIs >10 s (cf. Hultborn *et al.*, 1996; Fig. 2.12(*b*), ●). This depression is due to activity in large-diameter afferent fibres with receptors located in the leg muscles: an ischaemic block just below the knee joint abolished the depression, but a similar block just proximal to the ankle joint was ineffective. The same passive dorsiflexion did not modify the amount of heteronymous Ia facilitation of the soleus H reflex produced by femoral nerve stimulation (Fig. 2.12(*b*), ❍). This indicates that the depression: (i) is confined to the Ia pathway activated by the passive stretch, and (ii) is not due to presynaptic inhibition with primary afferent depolarisation (PAD) of Ia terminals directed to soleus motoneurones (because this should have reduced the femoral-induced heteronymous facilitation of the H reflex by a similar extent; Chapter 8, pp. 345–6, see also Wood, Gregory & Proske, 1996). With passive wrist extension, there was similar depression of the FCR H reflex 2 s after the end of the stretch, (Fig. 2.12(*i*), (*j*)). However, passive wrist extension did not modify the FCR MEP (Fig. 2.12(*g*), (*h*)), indicating that the post-activation depression was not due to post-synaptic inhibition of the tested motoneurones. These results have been confirmed in experiments in the decerebrate cat in which there was depression of the EPSP originating from the previously activated Ia afferents without depression of Ia EPSPs from other (heteronymous) nerves (Hultborn *et al.*, 1996).

Post-activation depression occurring when the stimulus rate is increased

Depression at rest

It has long been known that stimulus rate has a depressive effect on the size of the test reflex (Magladery & McDougal, 1950; Fig. 2.12(*c*)). This depression can be attributed to the previous activation of Ia afferents because it is also observed after a conditioning stimulus that is

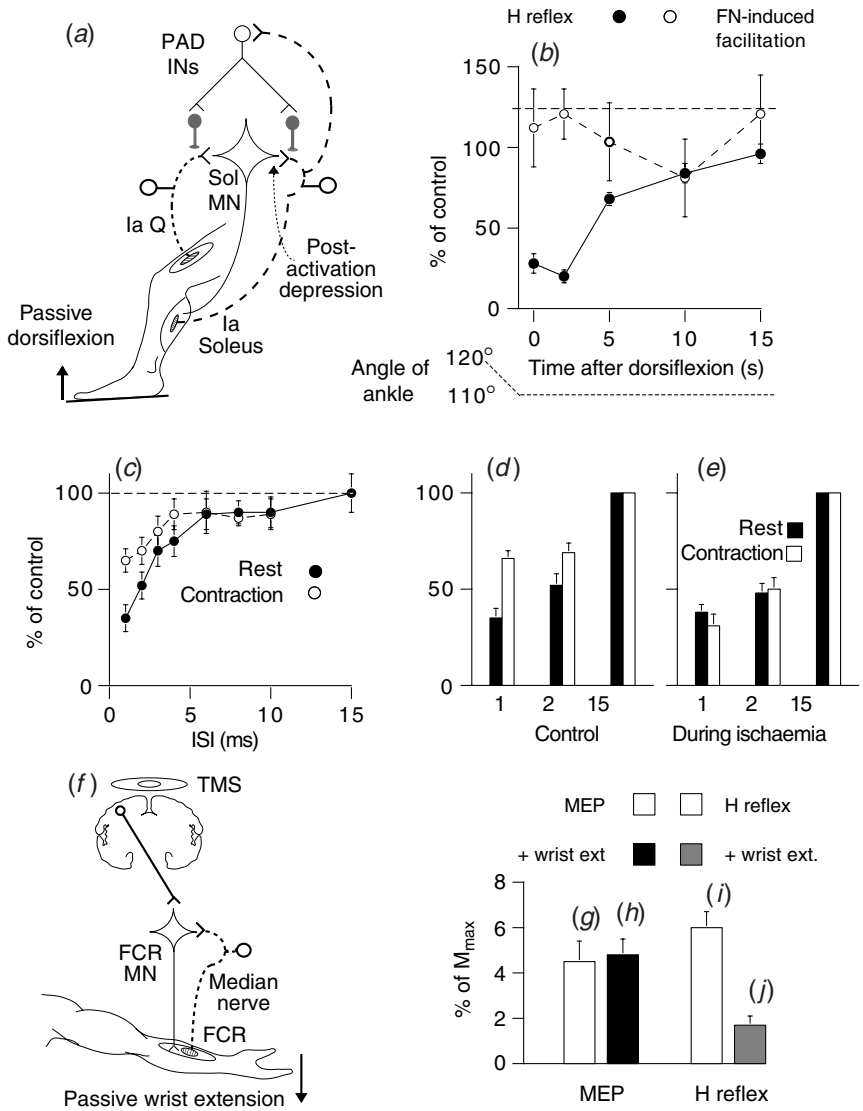


Fig. 2.12. Evidence for post-activation depression in normal subjects. (*a*) Sketch of the pathway for post-activation depression at the Ia-motoneurone (MN) synapse of soleus (Sol), and of heteronymous Ia facilitation from quadriceps (Q) to Sol. The pathway of presynaptic inhibition of Ia terminals is also represented (PAD INs). (*b*) The size of the Sol H reflex (●) and the amount of femoral-induced facilitation (1 × MT, – 5.4 ms ISI, ❍) of the Sol H reflex, both expressed as a percentage of their control value, are plotted against the time after the end of a passive dorsiflexion (dotted line at the bottom of the panel, 10° in 600 ms, too slow and too small to evoke any EMG activity). (*c*) The size of the soleus H reflex (as a percentage of its value when elicited at an interstimulus interval [ISI] of 15 s) is plotted against the ISI between two consecutive stimuli at rest (●) and during Sol voluntary contraction (❍). (*d*), (*e*) The size of the Sol H reflex at ISIs of 1, 2 and 15 s (as a percentage of its value at the 15-s ISI) at rest (■) and during voluntary contraction (□) before (*d*) and 25 minutes after ischaemia by cuff around the upper part of the leg (*e*). (*f*) Sketch of the pathways explored in (*g*)–(*j*). (*g*)–(*j*) The size of the MEP ((*g*), (*h*)) and of the H reflex ((*i*), (*j*)) of the flexor carpi radialis (FCR) are compared before (□, (*g*) and (*i*)) and 2 s after passive wrist extension (filled columns, (*h*) and (*j*)). Modified from Hultborn & Nielsen (1998), with permission.

subthreshold for the H reflex or tendon jerk (Táboríková & Sax, 1969; Katz *et al.*, 1977; Crone & Nielsen, 1989).

Depression during voluntary contraction

During voluntary contraction of the tested muscle the depression is attenuated (Rothwell, Day & Marsden, 1986; Burke, Adams & Skuse, 1989; Hultborn & Nielsen, 1998; Fig. 2.12*c*). The most parsimonious explanation for this is that the enhanced Ia firing during voluntary contraction (see Chapter 3, pp. 133–5) causes a background level of post-activation depression, and this can only be enhanced slightly by the additional depression caused by a preceding H reflex. This interpretation is supported by the finding that the difference between the amount of post-activation depression observed at rest and during contraction (Fig. 2.12(*d*), ■, □) disappears when the activity of Ia afferents is blocked by ischaemia (Hultborn & Nielsen, 1998; Fig. 2.12(*e*)). That the H reflex is still facilitated during contraction indicates that other mechanisms outweigh the reduction caused by the background post-activation depression. These mechanisms include increased motoneurone excitability and, for the H reflex, decreased inhibitory mechanisms gating the test volley. Driving spindle afferents by vibration of the muscle tendon does not similarly abolish post-activation depression of the H reflex (Van Boxtel, 1986) but this could be due to the additional presynaptic inhibition of Ia terminals produced by vibration (see Chapter 8, p. 341).

Reflexes elicited in small motoneurones

Reflexes elicited in small motoneurones are more sensitive to post-activation depression, in agreement with animal data (see above). As a result, the decline of the reflex response when increasing the stimulus rate is greater for soleus H reflexes of small than of large size (Floeter & Kohn, 1997). This difference in susceptibility to homosynaptic depression may serve to concentrate the damping effect upon those motoneurones that are the most likely to be activated by small stretches or perturbations, without disabling the stretch responses of higher-threshold motoneurones. The weaker sensitivity to post-activation depression of reflexes elicited in high-threshold motoneurones could also account for the lesser susceptibility of FCR H reflexes to high stimulus rates (Rossi-Durand *et al.*, 1999).

Post-activation depression in spastic patients

Decreased post-activation depression in spastic patients

The depression produced by passive dorsiflexion is much less pronounced in spastic patients with spinal cord lesion(s), whether due to trauma or multiple sclerosis, than in healthy subjects (Fig. 2.13(*a*); Nielsen & Hultborn, 1993; Nielsen, Petersen & Crone, 1995; Hultborn & Nielsen, 1998). Similarly, the amount of post-activation depression of the FCR and soleus H reflexes, assessed as the size of the H reflex elicited every 2 s and expressed as a percentage of its value when elicited every 8 s, is significantly reduced on the affected side of hemiplegic patients. In contrast, the depression is similar on their unaffected side and in normal subjects (Fig. 2.13(*b*), (*c*); Aymard *et al.*, 2000).

Post-activation depression and pathophysiology of spasticity

The reduction of post-activation depression would enhance the synaptic efficacy of trains of Ia impulses and could contribute to the stretch reflex exaggeration that characterises spasticity. As emphasised by Hultborn and Nielsen (1998), the decreased depression seen in patients with a lesion of the central nervous system does not necessarily imply that post-activation depression is under direct control by descending pathways. Several lines of evidence suggest that adaptive changes in the

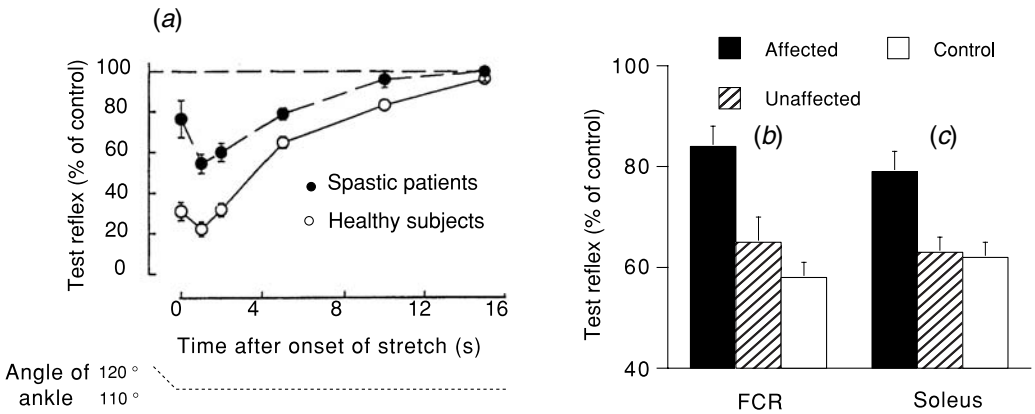


Fig. 2.13. Reduction of post-activation depression in spastic patients. (*a*) The mean value (± SEM) of the soleus H reflex (expressed as a percentage of its control value) plotted against the time after the onset of passive dorsiflexion of the foot (illustrated by the dotted line at the bottom of the panel, 10° in 600 ms, too slow and too small to evoke any EMG activity) in 30 healthy subjects (●) and 17 spastic patients with multiple sclerosis or spinal cord injury (○). (*b*), (*c*) The mean value (+ SEM) of the FCR (*b*) and soleus (*c*) H reflex elicited every 2 s, and expressed as a percentage of its value when elicited every 8 s, is compared in 16 normal subjects (□) and on the affected (■) and unaffected (dashed columns) of hemiplegic patients ($n = 16$ in (*b*), and 10 in (*c*)). Modified from Hultborn & Nielsen (1998) (*a*), and Aymard *et al.* (2000) ((*b*), (*c*)), with permission.

efficacy of the Ia-motoneurone synapse develop following the changes in activity of motoneurones and Ia fibres resulting from the impairment of the motor command. (i) The fact that spasticity progresses during weeks or months after the causal lesion (whether a spinal lesion or stroke) fits this hypothesis, because such adaptive changes develop over time. (ii) In this respect, a longitudinal study of one patient with spinal cord injury found that the reduction of post-activation depression developed with the transition from flaccid to spastic paralysis, even though reduced post-activation depression preceded clinically observable spasticity (Schindler-Ivens & Shield, 2000). (iii) Contrary to several other electrophysiological changes explored (see Chapter 12, pp. 577–9), post-activation depression is unchanged on the unaffected side of patients with hemiplegia (Fig. 2.12(*b*), (*c*), dashed columns). (iv) The synaptic efficacy of primary afferents can be up- or down-regulated by disuse or use of synapses, respectively (Gallago *et al.*, 1979).

Conclusions

Role of monosynaptic Ia excitation in natural motor tasks

The short-latency spinal stretch reflex

This reflex has been extensively investigated in ankle extensors, where it contributes to rapid automatic load compensation in various motor tasks such as running, hopping, landing, walking and standing by helping the stabilisation of the supporting limb. Available data concerning the functional role of the stretch reflex in other muscles are more sparse, and it would be important to investigate the role of the short-latency spinal stretch reflexes for muscles operating at knee and hip level in natural tasks. In the upper limb, the well-developed homonymous monosynaptic Ia excitation of muscles operating at the wrist and elbow suggests that these connections could be used to compensate rapidly and automatically for errors in the programmed movement, but

so far experiments have focused on the role of the long-latency stretch reflex rather than the spinal reflex pathway.

Heteronymous monosynaptic Ia connections

In the cat and the baboon hindlimb these connections link motoneurones of muscles acting synergistically at the same joint but, in the human lower limb, these connections are more widespread and transjoint connections are almost the rule. The more widespread distribution of Ia connections found in the human lower limb could have evolved to provide the more elaborate reflex assistance required for bipedal stance and gait, in which the equilibrium is less stable than in quadrupeds. In the upper limb, there is also a different organisation, with absence of the proximal-to-distal projections used in feline locomotion, but with strong projections from intrinsic hand muscles to muscles acting at the wrist and elbow, projections which serve to stabilise the limb for manipulatory tasks.

Changes in monosynaptic Ia excitation in patients

Reflex attenuation

A decrease in the amplitude (and an increase in the latency) of the H reflex ocurs in various radiculopathies, plexus and nerve lesions, and in polyneuropathies, and will occur when there is loss of conducting afferents and/or dispersion of the afferent volley.

Spasticity

In spasticity the H_{max}/M_{max} ratio is increased in soleus, but is largely unchanged in FCR. Post-activation depression following previous activation of Ia fibres is reduced in spastic patients. This reduction could be a consequence of altered use due to motor impairment, and may be an important spinal mechanism underlying spasticity.

Résumé

Importance of studies of Ia connections

Several reasons account for the continuing interest in studies of monosynaptic Ia excitation of motoneurones.

(i) One objective of the study of reflexes is to trace the effects of a given input. The monosynaptic excitation of Ia afferents occurs without an interneurone, and therefore constitutes the simplest example of reflex function.

(ii) It is a challenging problem to understand how different feedback systems have adapted to evolutionary demands for changed patterns of movement, and here again investigations of the distribution of monosynaptic Ia connections provides the easiest way to approach evolutionary changes.

(iii) They are technically the easiest to study because Ia effects are the first to appear in motoneurones after peripheral stimulation and do so with the lowest threshold.

(iv) γ-innervation modulates the sensitivity of spindle endings and the resulting Ia discharges, and it is likely that this modulation helps maintain movement (see Chapter 3).

(v) Reduction of post-activation depression at the Ia-motoneurone synapse could be one of the main spinal mechanisms underlying spasticity.

As discussed below, there is little doubt that the monosynaptic Ia pathway contributes to the spinal stretch reflex, but whether it is the sole input driving the reflex discharge is debatable. With this caveat, the following focuses on the Ia contribution.

Background from animal experiments

Ia afferents originate from the primary endings of muscle spindles, and are sensitive to muscle stretch and high-frequency vibration. They have excitatory monosynaptic projections to homonymous motoneurones, and this constitutes the excitatory pathway underlying the tendon jerk and the

short-latency spinal stretch reflex. Projections are stronger on motoneurones innervating slow-twitch units than on those of fast-twitch units. Heteronymous projections are weaker than homonymous projections, and exist to motoneurones of close synergists operating at the same joint. Transjoint connections are more developed in the forelimb than in the hindlimb of the cat.

Methodology

Homonymous monosynaptic Ia excitation

Evidence for a two-neurone arc in the human soleus

Stimulation of the posterior tibial nerve produces a synchronised response in the soleus muscle, and this has become known as the Hoffmann reflex or H reflex. Recordings of the action potentials from both dorsal and ventral roots intrathecally have demonstrated that the first motoneurones discharging in the soleus H reflex may do so at a latency consistent with a monosynaptic pathway. Besides the monosynaptic latency, several arguments indicate that the pathway is fed by Ia afferents: low electrical threshold, similar excitation elicited by a tap on the Achilles tendon, facilitation by a homonymous volley to the inferior branch of the soleus nerve, and simultaneous blockade by ischaemia of the homonymous facilitation and of the Achilles tendon jerk.

Routine diagnostic studies

In routine studies there is a number of advantages of studying the H reflex during voluntary contraction, because it is then possible to record the reflex in virtually all accessible limb muscles, to reduce the latency variability, to increase the stimulus rate, and to direct the reflex response to the active motoneurone pool.

PSTH method

Stimulation of the parent nerve evokes an early peak in PSTHs with the characteristics of homonymous monosynaptic Ia excitation in all limb muscles tested (same latency as the H reflex after allowance for the trigger delay of the unit, low threshold, elicitation by tendon taps).

Critique

By analogy with the soleus H reflex, the H reflex and the early peak in the PSTHs of single units in other muscles are probably evoked by Ia afferents with a monosynaptic linkage. However, so far, unequivocal evidence for a 'two-neurone-arc' in humans has been presented only for the soleus H reflex.

Heteronymous monosynaptic Ia excitation

Heteronymous facilitation of the H reflex

H reflex studies do not allow reliable assessment of the central delay of the resulting facilitation.

PSTHs of single motor units

The principle is to compare the latencies of the early facilitation evoked in the same unit by stimulation of homonymous and heteronymous nerves. The difference between the two latencies must reflect the differences in the afferent conduction times and in the central (synaptic) delay of the Ia effects of the homonymous and heteronymous volleys. If, like homonymous excitation, heteronymous excitation is mediated through a monosynaptic pathway, the difference in latencies between heteronymous and homonymous peaks should be explained by the difference in afferent conduction times. Afferent conduction times for the Ia homonymous and heteronymous volleys can be estimated from the distance from stimulation sites to the arrival of the afferent volleys at the spinal cord, as measured on the skin, and the conduction velocity in Ia afferents. The validity of the calculation depends on the reliability of these estimates.

Bidirectional connections

To eliminate uncertainties in estimates of peripheral conduction times, studies have been performed on

Ia connections linking a pair of motor units in two different muscles (e.g. soleus and peroneus brevis). In this case, the homonymous volley for one member of the pair is the heteronymous volley for the other, and vice versa. The absolute value of the difference in afferent conduction times is the same for the two members of the pair. Such studies provide cogent evidence for heteronymous monosynaptic connections, independent of estimates of peripheral afferent conduction times.

Facilitation of the on-going EMG

Some heteronymous monosynaptic Ia connections described in PSTH experiments are sufficiently strong to be demonstrable in averages of unrectified on-going voluntary EMG activity.

Ia afferent origin

Besides the monosynaptic connection, several features argue that the heteronymous pathway is fed by Ia afferents: low electrical threshold, similar excitation elicited by a tendon tap, increase in the threshold of the excitation by long-lasting vibration applied to the tendon of the 'conditioning' muscle, a manoeuvre that raises the threshold of Ia afferents, and inability of cutaneous stimulation to reproduce the early peak of excitation.

The difference between the stimulus intensity required for the full recruitment of Ia afferents in cat and human experiments ($2 \times$ Ia threshold and $8 \times$ Ia threshold, respectively) is due to the fact that, in human experiments, the afferents are stimulated through surface electrodes at a distance from the nerve. This factor is important because: (i) the 'true monosynaptic latency' can only be disclosed at intensities much greater than $1 \times$ MT; and (ii) if some Ia afferents are only activated by such strong stimuli, the potential Ia reflex contribution may have been underestimated in previous human studies performed with stimulus intensities $\leq 1 \times$ MT.

Organisation and pattern of connections

Homonymous monosynaptic Ia excitation

In virtually all limb muscles, stimulation of the parent nerve can elicit an H reflex and a peak of monosynaptic Ia excitation in PSTHs of single motor units during voluntary contractions. At rest, H reflexes can be recorded from the soleus, quadriceps and FCR in healthy subjects. The ease with which the H reflex can be elicited at rest and the size of the peak of excitation elicited by stimulation subthreshold for the compound H reflex are closely related. The efficacy of the monosynaptic Ia input in activating motoneurones depends on its preferential distribution to early recruited (small) motoneurones in most muscles (Henneman's size principle), and inhibitory mechanisms limiting the efficacy of the Ia volley (e.g. presynaptic inhibition of Ia terminals; contamination of monosynaptic EPSPs by oligosynaptic IPSPs).

Heteronymous monosynaptic Ia excitation

Lower limb

In the human lower limb, in striking contrast with data for the cat hindlimb, connections between some close synergists operating at the same joint (e.g. the different heads of triceps surae) are weak or absent. This pattern is consistent with weaker connections in the baboon than the cat. Conversely, transjoint connections are rare in the cat and baboon hindlimb, but are almost the rule in the human lower limb. These transjoint connections can be strong, e.g. gastrocnemius medialis to biceps femoris. They often link a muscle or group of muscles to a pair of antagonistic muscles operating at another joint, e.g. quadriceps onto all tested muscles acting at the ankle.

Upper limb

The upper limb lacks the proximal-to-distal transjoint connections used in feline locomotion, while distal-to-proximal connections, in particular from

intrinsic hand muscles, are stronger and more widespread than in the cat.

Maturation of Ia connections during development

It has been reported that, in the normal newborn baby, a tendon tap may elicit short-latency heteronymous excitatory responses in antagonistic muscle pairs in the upper and lower limbs (e.g. biceps and triceps brachii) at monosynaptic latencies. However, it would be prudent to retain reservations about these conclusions (see p. 86). This 'reciprocal excitation' disappears during the first years of life.

Motor tasks and physiological implications

Muscle stretch elicits a reflex response from the corresponding motoneurone pool, and this has at least two separate components: the classical short-latency spinal reflex (M1), the latency of which is compatible with monosynaptic Ia excitation, and a medium-latency component (M2) of more complex origin.

The short-latency spinal stretch reflex during natural motor tasks

The spinal stretch reflex utilises the simplest reflex pathway and interacts with pre-programmed and other reflex mechanisms to compensate for disturbances during natural motor tasks. There is considerable literature about the contribution of the short-latency stretch reflex of triceps surae to various natural movements, but few data for other muscles.

Running, hopping and landing

During the stance phase of running and hopping and after the impact of landing, the short-latency spinal stretch reflex of the triceps surae is superimposed on pre-programmed activity and contributes to the muscle contraction responsible for the pushing off of the foot. There is probably also a concomitant short-latency stretch response in the quadriceps.

Walking

The spinal stretch reflex can produce a mechanically effective contraction and provides a pathway through which rapid automatic load compensation to an unexpected disturbance can be generated. Short-latency stretch reflexes in triceps surae, triggered by unexpected ankle joint displacement, contribute significant stabilisation of the supporting limb during walking. Heteronymous Ia connections between ankle muscles that are not synergistic in flexion–extension movements probably contribute further to the stability of the ankle.

Perturbations of upright stance

Perturbations of the upright stance in subjects standing on a rotating platform produce an early spinal stretch reflex response (M1), which is prominent in soleus. After loss of large-diameter muscle spindle afferents, M1 is absent but posture is quite stable, suggesting that M1 is not essential for equilibrium control during quiet stance.

Spinal and transcortical stretch reflexes

The medium-latency (M2) response to stretch following the early spinal (M1) response has a different origin in various muscles: in the flexor pollicis longus (and intrinsic muscles of the hand) the long latency is due to a transcortical pathway fed by Ia afferents, whereas in foot and leg muscles the stretch response is mediated through a spinal pathway fed by slowly conducting group II afferents. Both transcortical and spinal group II pathways could contribute to the M2 response in proximal upper limb muscles, such as the biceps brachii.

Heteronymous monosynaptic Ia excitation

There are little experimental data on the functional role of heteronymous Ia connections. However, the

different organisation of these connections in the cat and baboon hindlimb and the human lower limb suggests that the connections are functionally important, having adapted to provide the particular reflex assistance required in each species.

Weak connections between ankle extensors

The weakness of the connections between ankle extensors in human subjects may be related to the role of triceps surae in walking: it resists and brakes the passive ankle dorsiflexion produced by extrinsic forces (kinetic force and gravity), but must be overcome by these forces if the body is to be brought forward. It would then be undesirable to have excessive activity from the triceps surae stretch reflex, and weak Ia connections between the different heads of the muscle would help ensure this.

Transjoint connections

Widespread transjoint connections in the lower limb have probably evolved to provide the more elaborate reflex assistance required in bipedal stance and gait, in which equilibrium is much less stable than in quadrupedal stance and gait. Some of these connections are weak, but their strength has been underestimated in experimental studies and, in any case, this would not prevent them from modulating the excitability of motoneurones that are already depolarised. During the stance phase of running, hopping and landing, all extensors undergo a lengthening contraction that evokes a strong Ia discharge, and it is probable that the extensive Ia connections linking muscles across joints modulate the role played by the different muscles in load compensation.

Projections onto antagonists operating at another joint

These projections are desirable functionally because of the versatile synergisms required to accomplish the various tasks of the human lower limb (e.g. co-contraction of quadriceps and gastrocnemius-soleus in running and hopping, but of quadriceps and tibialis anterior when leaning backward). On the other hand, diffuse Ia connections could become functionally inconvenient, because the activation of Ia afferents from a contracting muscle might result in the automatic unwanted activation of muscles linked by Ia synergism. Suppression of unwanted heteronymous Ia discharges can be achieved through focused corticospinal control of presynaptic inhibition of Ia terminals and of recurrent inhibition. The need for this control suggests that the heteronymous Ia discharge does play a functional role, because it must be suppressed in tasks for which it is not required.

Upper limb

The diffuse distribution of the Ia projections from intrinsic hand muscles and the finding that they are stronger on muscles operating at the wrist than on long flexors and extensors of the fingers suggest that these projections might be used to stabilise the wrist to provide a firm support to hand muscles during manipulatory movements.

Studies in patients and clinical implications

In practice, assessing Ia connectivity involves measurements of the H reflex. There are a number of advantages of doing so during voluntary contractions (see above). Modulation of the on-going EMG by a heteronymous volley may allow access to a motoneurone pool by afferent inputs that do not traverse the same nerve or nerve root as homonymous afferents.

Peripheral neuropathies, mononeuropathies and nerve lesions

These may be accompanied by a decrease in the amplitude and an increase in the latency of the H reflex. Reflex depression usually results from an afferent abnormality and will occur when there is either a loss of conducting afferents or dispersion of

the afferent volley. Tests of reflex function provide a tool to distinguish between isolated peripheral nerve lesions and lesions involving roots or plexus.

Spasticity

The ratio H_{max}/M_{max} is, on average, increased in soleus but not, or hardly so, in FCR in hemiplegics.

Post-activation depression at the Ia-motoneurone synapse

Background from animal experiments

It has long been known that the size of the monosynaptic reflex decreases when it is repeatedly elicited. This results from a decrease in transmitter release due the repetitive activation of the Ia-motoneurone synapse. The results from a variety of preparations indicate the presence of an early facilitation of relatively short duration superimposed on a depression of much longer duration. Post-activation depression helps to maintain the synaptic efficacy of the Ia-motoneurone synapse at a relatively low level during voluntary movements.

Methodology

Passive stretch

Passive stretch of the tested muscle depresses the H reflex, a phenomenon confined to the Ia pathway activated by the passive stretch. There is experimental evidence that this depression is not due to presynaptic inhibition of Ia terminals with primary afferent depolarisation or to post-synaptic inhibition of the motoneurones.

Increasing the stimulus rate

This produces a reflex depression that is prominent at relatively high stimulus rates (>0.3 Hz), lessens when the stimulus rate is decreased, and disappears at stimulus rates below 0.1 Hz. During a voluntary contraction of the test muscle, the reflex depression is markedly attenuated, probably because the enhanced Ia firing during voluntary contraction causes a background level of post-activation depression, which can be increased further by only a small amount.

Post-activation depression in spastic patients

Whether measured as the depression induced by passive stretch of the test muscle or by high stimulus rate, post-activation depression is significantly decreased in spastic patients due to spinal cord injury and multiple sclerosis, and on the affected side of patients with hemiplegia. This reduction is probably a consequence of the disuse due to motor impairment, and may be an important spinal mechanism underlying spasticity.

REFERENCES

Ashby, P. & Labelle, K. (1977). Effects of extensor and flexor group I afferent volleys on the excitability of individual soleus motoneurones in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 910–19.

Ashby, P. & Zilm, D. (1982). Characteristics of postsynaptic potentials produced in single human motoneurones by homonymous group I volleys. *Experimental Brain Research*, **47**, 41–8.

Ashby, P., Hilton-Brown, P. & Stålberg, E. (1986). Afferent projections to human tibialis anterior motor units active at various levels of muscle contraction. *Acta Physiologica Scandinavica*, **127**, 523–32.

Awiszus, F. & Feistner, H. (1993). The relationship between estimates of Ia-EPSP amplitude and conduction velocity in human soleus motoneurons. *Experimental Brain Research*, **95**, 365–70.

Aymard, C., Katz, R., Lafitte, C. *et al.* (2000). Presynaptic inhibition and homosynaptic depression: a comparison between lower and upper limbs in normal subjects and patients with hemiplegia. *Brain*, **123**, 1688–702.

Baldissera, F., Hultborn, H. & Illert, M. (1981). Integration in spinal neuronal systems. In *Handbook of Physiology*, section I, *The Nervous System*, vol. II, *Motor Control*, ed. V. B. Brooks, pp. 508–95. Bethesda, USA: American Physiological Society.

Bayoumi, A. & Ashby, P. (1989). Projections of group Ia afferents to motoneurons of thigh muscles in man. *Experimental Brain Research*, **76**, 223–8.

Beevor, C. E. (1904). *The Croonian Lectures on Muscular Movements and their Representation in the Central Nervous System*. London: Adlard.

Berger, W., Dietz, V. & Quintern, J. (1984). Corrective reactions to stumbling in man: neuronal coordination of bilateral leg muscle activity during gait. *Journal of Physiology (London)*, **405**, 1–37.

Bergmans, J., Delwaide, P. J. & Gadea-Ciria, M. (1978). Short-latency effects of low-threshold muscular afferent fibers on different motoneuronal pools of the lower limb in man. *Experimental Neurology*, **60**, 380–5.

Birnbaum, A. & Ashby, P. (1982). Postsynaptic potentials in individual soleus motoneurons in man produced by Achilles tendon taps and electrical stimulation of tibial nerve. *Electroencephalography and Clinical Neurophysiology*, **54**, 469–71.

Bouaziz, Z., Bouaziz, M. & Hugon, M. (1975). Modulation of soleus electromyogram by electrical stimulation of medial gastrocnemius nerve in man. *Electromyography*, **15**, 31–42.

Brock, L. G., Eccles, J. C. & Rall, W. (1951). Experimental investigations on the afferent fibres in muscle nerves. *Proceedings of the Royal Society B*, **138**, 453–75.

Buller, N. P., Garnett, R. & Stephens, J. A. (1980). The reflex responses of single motor unit in human hand muscles following afferent stimulation. *Journal of Physiology (London)*, **303**, 337–49.

Burke, D., Hagbarth, K.-E., Löfstedt, L. & Wallin, B. G. (1976). The responses of human muscle spindle endings to vibration of non-contracting muscles. *Journal of Physiology (London)*, **261**, 673–93.

Burke, D., Gandevia, S. C. & McKeon, B. (1983). The afferent volleys responsible for spinal proprioceptive reflexes in man. *Journal of Physiology (London)*, **339**, 535–52.

(1984). Monosynaptic and oligosynaptic contributions to human ankle jerk and H-reflex. *Journal of Neurophysiology*, **52**, 435–48.

Burke, D., Adams, R. W. & Skuse, N. F. (1989). The effect of voluntary contraction on the H reflex of various muscles. *Brain*, **112**, 417–33.

Burke, R. E. (1981). Motor units: anatomy, physiology and functional organization. In *Handbook of Physiology*, section I, *The Nervous System*, vol. II, *Motor Control*, Part 1, ed. V. B. Brooks, pp. 345–422. Bethesda, MD: American Physiological Society.

Bussel, B., Katz, R., Pierrot-Deseilligny, E., Bergego, C. & Hayat, A. (1980). Vestibular and proprioceptive influences on the postural reactions to a sudden body displacement in man. In *Spinal and Supraspinal Mechanisms of Voluntary Motor Control and Locomotion*, ed. J.E. Desmedt, vol. 8, pp. 310–22. Basel: Karger.

Capaday, C. (2002). The special nature of human walking and its neural control. *Trends in Neurosciences*, **25**, 370–6.

Cavallari, P. & Katz, R. (1989). Pattern of projections of group I afferents from forearm muscles to motoneurones supplying biceps and triceps muscles in man. *Experimental Brain Research*, **78**, 465–78.

Cavallari, P., Katz, R. & Pénicaud, A. (1992). Pattern of projections of group I afferents from elbow muscles to motoneurones supplying wrist muscles in man. *Experimental Brain Research*, **91**, 311–19.

Chalmers, G. R. & Bawa, P. (1997). Synaptic connections from large afferents of wrist flexor and extensor muscles to synergistic motoneurones in man. *Experimental Brain Research*, **116**, 351–8.

Christensen, L. A. D., Andersen, J. B., Sinkjaer, T. & Nielsen, J. (2001). Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking. *Journal of Physiology (London)*, **531**, 545–57.

Clough, J. F. M., Kernell, D. & Phillips, C. G. (1968). The distribution of monosynaptic excitation from the pyramidal tract and from primary spindle afferents to motoneurones of the baboon's hand and forearm. *Journal of Physiology (London)*, **198**, 145–66.

Cody, F. W. J., MacDermott, P. B., Matthews, P. B. C. & Richardson, H. C. (1986). Observations on the genesis of the stretch reflex in Parkinson's disease. *Brain*, **109**, 229–49.

Coppin, C. M. C., Jack, J. J. B. & MacLennan, C. R. (1970). A method for the selective electrical stimulation of tendon organ afferent fibres from the cat soleus muscle. *Journal of Physiology (London)*, **210**, 18–20*P*.

Créange, A., Faist, M., Katz, R. & Pénicaud, A. (1992). Distribution of heteronymous Ia facilitation and recurrent inhibition in the human deltoid motor nucleus. *Experimental Brain Research*, **90**, 620–4.

Crone, C. & Nielsen, J. (1989). Methodological implications of the post-activation depression of the soleus H-reflex in man. *Experimental Brain Research*, **78**, 28–32.

Curtis, D. R. & Eccles, J. C. (1960). Synaptic action during and after repetitive stimulation. *Journal of Physiology (London)*, **150**, 374–98.

Diener, H. C., Dichgans, J., Bootz, F. & Bacher, M. (1984a). Early stabilization of human posture after a sudden disturbance: influence of rate and amplitude of displacement. *Experimental Brain Research*, **56**, 126–34.

Diener, H. C., Dichgans, J., Guschlbauer, B. & Mau, H. (1984b). The significance of proprioception on postural stabilization as assessed by ischaemia. *Brain Research*, **296**, 103–9.

Dietz, V. (1981). Contribution of spinal stretch reflexes to the activity of leg muscles in running. In *Muscle Receptors and Movement*, ed. A. Taylor & A. Prochazka, pp. 339–46. London: MacMillan.

Dietz, V., Schmidtbleicher, D. & Noth, J. (1979). Neuronal mechanisms of human locomotion. *Journal of Neurophysiology*, **42**, 1212–22.

Dietz, V., Mauritz, K. H. & Dichgans, J. (1980). Body oscillations in balancing due to segmental stretch reflex activity. *Experimental Brain Research*, **40**, 89–95.

Dietz, V., Noth, J. & Schmidtbleicher, D. (1981). Interaction between pre-activity and stretch reflex in human triceps brachii during landing from forward falls. *Journal of Physiology (London)*, **311**, 113–25.

Duncan, A. & McDonagh, M. J. N. (2000). Stretch reflex distinguished from pre-programmed muscle activations following landing impacts in man. *Journal of Physiology (London)*, **526**, 456–68.

Dyhre-Poulsen, P., Simonsen, E. B. & Voigt, M. (1991). Dynamic control of muscle stiffness and H reflex modulation during hopping and jumping in man. *Journal of Physiology (London)*, **437**, 287–304.

Eccles, J. C., Eccles, R. M. & Lundberg, A. (1957). The convergence of monosynaptic excitatory afferents onto many different species of alpha motoneurones. *Journal of Physiology (London)*, **137**, 22–50.

Eccles, J. C. & Rall, W. (1951). Effects induced in a monosynaptic reflex path by its activation. *Journal of Neurophysiology*, **14**, 353–76.

Eccles, R. M. & Lundberg, A. (1958). Integrative pattern of Ia synaptic actions of motoneurones of hip and knee muscles. *Journal of Physiology (London)*, **144**, 271–98.

Eccles, R. M., Shealy, C. N. & Willis, W. D. (1963). Patterns of innervation of kitten motoneurones. *Journal of Physiology (London)*, **165**, 395–402.

Edgerton, V. R., Smith, J. L. & Simpson, D. R. (1975). Muscle fibre type populations of human leg muscles. *Histochemical Journal*, **7**, 259–66.

Edgley, S., Jankowska, E. & McCrea, D. (1986). The heteronymous monosynaptic actions of triceps surae group Ia afferents on hip and knee extensor motoneurones in the cat. *Experimental Brain Research*, **61**, 443–6.

Engberg, I. & Lundberg, A. (1969). An electromyographic analysis of muscular activity in the hindlimb of the cat during unrestrained locomotion. *Acta Physiologica Scandinavica*, **75**, 105–22.

Ertekin, C., Mungan, B. & Uludag, B. (1996). Sacral cord conduction time of the soleus H-reflex. *Journal of Clinical Neurophysiology*, **13**, 77–83.

Evarts, E. V. (1973). Motor cortex reflexes associated with learned movement. *Science*, **179**, 501–3.

Ferris, D. P., Aagaard, P., Simonsen, E. B., Farley, C. T. & Dyhre-Poulsen, P. (2001). Soleus H-reflex gain in humans walking and running under simulated reduced gravity. *Journal of Physiology (London)*, **530**, 167–80.

Fetz, E. E. & Gustafsson, B. (1983). Relation between shapes of post-synaptic potentials and changes in firing probability of cat motoneurones. *Journal of Physiology (London)*, **341**, 387–410.

Fetz, E. E., Jankowska, E., Johannisson, T. & Lipski, J. (1979). Autogenetic inhibition of motoneurones by impulses in group Ia muscle spindle afferents. *Journal of Physiology (London)*, **293**, 173–95.

Floeter, M. K. & Kohn, A. F. (1997). H-reflexes of different sizes exhibit differential sensitivity to low frequency depression. *Electroencephalography and Clinical Neurophysiology*, **105**, 470–5.

Forster, M. (1879). *Textbook of Physiology* (cited by Liddell, E. G. T. 1960, in *The Discovery of Reflexe*s, p. 98 and 101, Oxford: Clarendon Press).

Fournier, E., Meunier, S., Pierrot-Deseilligny, E. & Shindo, M. (1986). Evidence for interneuronally mediated Ia excitatory effects to human quadriceps motoneurones. *Journal of Physiology (London)*, **377**, 143–69.

Fritz, N., Illert, M., De la Motte, S., Reeh, P. & Saggau, P. (1989). Pattern of monosynaptic Ia connections in the cat forelimb. *Journal of Physiology (London)*, **419**, 321–51.

Fukushima, Y., Yamashita, N. & Shimada, Y. (1982). Facilitation of H reflex by homonymous Ia afferent fibres in man. *Journal of Neurophysiology*, **48**, 1079–88.

Funase, K., Higashi, T., Sakakibara, A., Imanaka, K., Nishihira, Y. & Miles, T. S. (2001). Patterns of muscle activation in human hopping. *European Journal of Applied Physiology*, **84**, 503–9.

Gallago, R., Kuno, M., Nunez, R. & Snider, W. D. (1979). Disuse enhances synaptic efficacy in spinal motoneurones. *Journal of Physiology (London)*, **321**, 191–205.

Gandevia, S. C. & Burke, D. (1984). Saturation in human somatosensory pathways. *Experimental Brain Research*, **54**, 582–5.

Gracies, J. M., Meunier, S., Pierrot-Deseilligny, E. & Simonetta, M. (1991). Pattern of propriospinal-like excitation to different species of human upper limb motoneurones. *Journal of Physiology (London)*, **434**, 151–67.

Gracies, J. M., Pierrot-Deseilligny, E. & Robain, G. (1994). Evidence for further recruitment of group I fibres with high stimulus intensities when using surface electrodes in man. *Electroencephalography and Clinical Neurophysiology*, **93**, 353–7.

Greenwood, R. & Hopkins, A. (1976). Landing from an unexpected fall and a voluntary step. *Brain*, **99**, 375–86.

Grey, M. J., Ladouceur, M., Andersen, J. B., Nielsen, J. B. & Sinkjaer, T. (2001). Group II muscle afferents probably contribute to the medium latency soleus stretch reflex during walking in humans. *Journal of Physiology (London)*, **534**, 925–33.

Hagbarth, K.-E., Hägglund, J. V., Wallin, E. U. & Young, R. R. (1981). Grouped spindle and electromyographic responses to abrupt wrist extension movement in man. *Journal of Physiology (London)*, **312**, 81–96.

Hammar, I., Slawinska, U. & Jankowska, E. (2002). A comparison of postactivation depression of synaptic actions evoked by different afferents and at different locations in the feline spinal cord. *Experimental Brain Research*, **145**, 126–9.

Hammond, P. H. (1956). The influence of prior instruction to the subject on an apparently neuromuscular response. *Journal of Physiology (London)*, **132**, 17–18*P*.

Hammond, P. H. (1960). An experimental study of servo action in human muscular control. *Proceedings IIIrd International Conference on Medical Electronics*, pp. 190–9. London: Institution of Electrical Engineers.

Heckman, C. J., Condon, M. S., Hutton, R. S. & Enoka, R. M. (1984). Can Ib axons be selectively activated by electrical stimuli in human subjects? *Experimental Neurology*, **86**, 576–82.

Henneman, E. & Mendell, L. M. (1981). Functional organization of motoneurone pool and its inputs. In *Handbook of Physiology*, Section I, *The Nervous System*, vol. II, *Motor Control*, Part 1, ed. V. B. Brooks, pp. 423–507. Bethesda, MD, USA: American Physiological Society.

Hirst, G. D. S., Redman, S. J. & Wong, K. (1981). Post-tetanic potentiation and facilitation of synaptic potentials evoked in cat spinal motoneurones. *Journal of Physiology (London)*, **321**, 97–109.

Hongo, T., Lundberg, A., Phillips, C. G. & Thompson, R. F. (1984). The pattern of monosynaptic Ia-connections to hindlimb motor nuclei in the baboon: a comparison with the cat. *Proceedings of the Royal Society B*, **221**, 261–89.

Honig, M. G., Collins, W. F. & Mendell, L. M. (1983). α-motoneuron EPSPs exhibit different frequency sensitivities to single Ia-afferent fiber stimulation. *Journal of Neurophysiology*, **49**, 886–901.

Hultborn, H. (2001). State-dependent modulation of sensory feedback. *Journal of Physiology (London)*, **533**, 5–13.

Hultborn, H. & Nielsen, J. B. (1998). Modulation of transmitter release from Ia afferents by their preceding activity – a 'postactivation depression'. In *Presynaptic Inhibition and Neural Control*, ed. P. Rudomin, R. Romo & L. Mendell, pp. 178–91. New York: Oxford University Press.

Hultborn, H., Meunier, S., Morin, C. & Pierrot-Deseilligny, E. (1987). Assessing changes in presynaptic inhibition of Ia fibres: a study in man and the cat. *Journal of Physiology (London)*, **389**, 729–56.

Hultborn, H., Illert, M., Nielsen, J., Paul, A., Ballegaard, M. & Wiese, H. (1996). On the mechanism of the post-activation depression of the H-reflex in human subjects. *Experimental Brain Research*, **108**, 450–62.

Illert, M. (1996). Monosynaptic Ia pathways and motor behaviour of the cat distal forelimb. *Acta Neurobiologiae Experimentalis*, **56**, 423–33.

Inglis, J. T., Meunier, S., Leeper, J. B., Burke, D. & Gandevia, S. C. (1997). Weak short-latency spinal projections to the long flexor of the human thumb. *Experimental Brain Research*, **115**, 165–8.

Jankowska, E. & McCrea, D. (1983). Shared reflex pathways from Ib tendon organ afferents and Ia muscle spindle afferents in the cat. *Journal of Physiology (London)*, **338**, 99–111.

Jolly, W. A. (1911). On the time relations of the knee-jerk and simple reflexes. *Quarterly Journal of Experimental Physiology*, **4**, 67–87.

Katz, R., Mazzocchio, R., Pénicaud, A. & Rossi, A. (1993). Distribution of recurrent inhibition in the human upper limb. *Acta Physiologica Scandinavica*, **149**, 189–98.

Katz, R., Morin, C., Pierrot-Deseilligny, E. & Hibino, R. (1977). Conditioning of H-reflex by a preceding subthreshold tendon reflex stimulus. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 575–80.

Katz, R., Pénicaud, A. & Rossi, A. (1991). Reciprocal Ia inhibition between elbow flexors and extensors in the human. *Journal of Physiology (London)*, **437**, 269–86.

Kearney, R. E., Lortie, M. & Stein, R. B. (1999). Modulation of stretch reflexes during imposed walking movements of the human ankle. *Journal of Neurophysiology*, **81**, 2893–902.

Kuno, M. (1964). Mechanism of facilitation and depression of the excitatory synaptic potential in spinal motoneurones. *Journal of Physiology (London)*, **175**, 100–12.

Lamy, J. C., Wargon, I., Baret, M. *et al.* (2005). Post-activation depression in various spinal pathways in humans. *Experimental Brain Research*, submitted.

Lance, J. W. & De Gail, P. (1965). Spread of phasic muscle reflexes in normal and spastic subjects. *Journal of Neurology, Neurosurgery and Psychiatry*, **28**, 328–34.

Lee, R. G. & Tatton, W. G. (1975). Motor responses to sudden limb displacements in primates with specific CNS lesions and in human patients with motor system disorders. *Canadian Journal of Neurological Sciences*, **2**, 285–93.

Liddell, E. G. T. & Sherrington, C. S. (1924). Reflexes in response to stretch (myotatic reflexes). *Proceedings of the Royal Society, London B*, **96**, 212–42.

Lloyd, D. P. C. (1943a). Neuron patterns controlling transmission of ipsilateral hind limb reflexes in cat. *Journal of Neurophysiology*, **6**, 293–315.

(1943b). Conduction and synaptic transmission of the reflex response to stretch in spinal cats. *Journal of Neurophysiology*, **6**, 317–26.

(1946). Integrative pattern of excitation and inhibition in two-neuron reflex arcs. *Journal of Neurophysiology*, **9**, 439–44.

Lloyd, D. P. C. & Wilson, V. G. (1957). Reflex depression in rythmically activated monosynaptic reflex pathways. *Journal of General Physiology*, **40**, 409–26.

Lundberg, A. & Winsbury, G. (1960). Selective adequate activation of large afferents from muscle spindles and Golgi tendon organs. *Acta Physiologica Scandinavica*, **49**, 155–64.

Lüscher, R. R., Ruenzel, P. & Henneman, E. (1983). Effects of impulse frequency, PTP, and temperature on responses elicited in large populations of motoneurons by impulses in single Ia-fibers. *Journal of Neurophysiology*, **50**, 1045–58.

McClelland, V. M., Miller, S. & Eyre, J. A. (2001). Short latency heteronymous excitatory and inhibitory reflexes between antagonist and heteronymous muscles of the human shoulder and upper limb. *Brain Research*, **899**, 82–93.

Macefield, G., Gandevia, S. C. & Burke, D. (1989). Conduction velocities of muscle and cutaneous afferents in the upper and lower limbs of human subjects. *Brain*, **112**, 1519–32.

Magladery, J. W. & McDougal, D. B. (1950). Electrophysiological studies of nerve and reflex activity in normal man. I. Identification of certain reflexes in the electromyogram and the conduction velocity of peripheral nerve fibres. *Bulletin of Johns Hopkins Hospital*, **86**, 265–90.

Magladery, J. W., McDougal, D. B. & Stoll, J. (1950). Electrophysiological studies of nerve and reflex activity in normal man. II. The effects of peripheral ischemia. *Bulletin of Johns Hopkins Hospital*, **86**, 291–312.

Magladery, J. W., Porter, W. E., Park, A. M. & Teasdall, R. D. (1951). Electrophysiological studies of nerve and reflex activity in normal man. IV. Two-neurone reflex and identification of certain action potentials from spinal roots and cord. *Bulletin of Johns Hopkins Hospital*, **88**, 499–519.

Malmgren, K. & Pierrot-Deseilligny, E. (1988). Evidence for non-monosynaptic Ia excitation of wrist flexor motoneurones, possibly via propriospinal neurones. *Journal of Physiology (London)*, **405**, 747–64.

Mao, C. C., Ashby, P., Wang, M. & McCrea, D. (1984). Synaptic connections from large muscle afferents to the motoneurones of various leg muscles in man. *Experimental Brain Research*, **56**, 341–50.

Marchand-Pauvert, V. & Nielsen, J. B. (2002). Modulation of non-monosynaptic excitation from ankle dorsiflexor afferents to quadriceps motoneurones during human gait. *Journal of Physiology (London)*, **538**, 647–57.

Marchand-Pauvert, V., Mazevet, D., Nielsen, J., Petersen, N. & Pierrot-Deseilligny, E. (2000a). Distribution of non-monosynaptic excitation to early and late recruited units in human forearm muscles. *Experimental Brain Research* **134**, 274–8.

Marchand-Pauvert, V., Nicolas, G. & Pierrot-Deseilligny, E. (2000b). Monosynaptic Ia projections from intrinsic hand muscles to forearm motoneurones in humans. *Journal of Physiology (London)*, **525**, 241–52.

Marque, P., Nicolas, G., Marchand-Pauvert, V., Gautier, J., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (2001). Group I projections from intrinsic foot muscles to motoneurones of leg and thigh muscles in humans. *Journal of Physiology (London)*, **536**, 313–27.

Marsden, C. D., Merton, P. A. & Morton, H. B. (1972). Servo action in human voluntary movement. *Nature*, **238**, 140–3.

Marsden, C. D., Merton, P. A., Morton, H. B. & Adam, J. (1977). The effect of posterior column lesions on servo responses from the human long thumb flexor. *Brain*, **100**, 185–200.

Marsden, C. D., Rothwell, J. C. & Day, B. L. (1983). Long-latency automatic responses to muscle stretch in man: origin and function. In *Motor Control Mechanisms in Health and Disease*, ed. J. E. Desmedt, pp. 509–39. New York: Raven Press.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and Their Central Action*. 630 pp. London: Arnold.

(1984). Evidence from use of vibration that the human long-latency stretch reflex depends upon spindle secondary afferents. *Journal of Physiology (London)*, **348**, 383–415.

(1989). Long-latency stretch reflexes of two intrinsic muscles of the human hand analysed by cooling the arm. *Journal of Physiology (London)*, **419**, 519–38.

(1991). The human stretch and the motor cortex. *Trends in Neurosciences*, **14**, 87–91.

Matthews, P. B. C., Farmer, S. F. & Ingram, D. A. (1990). On the localization of the stretch reflex of intrinsic hand muscles in a patient with mirror movements. *Journal of Physiology (London)*, **428**, 561–77.

Mauritz, K. H. & Dietz, V. (1980). Characteristics of postural instability induced by ischaemic blocking of leg afferents. *Experimental Brain Research*, **38**, 117–19.

Mazevet, D. & Pierrot-Deseilligny, E. (1994). Pattern of descending excitation of presumed propriospinal neurones at the onset of voluntary movement in man. *Acta Physiologica Scandinavica*, **150**, 27–38.

Mazzocchio, R., Rothwell, J. C. & Rossi, A. (1995). Distribution of Ia effects onto human hand muscle motoneurones as revealed using an H reflex technique. *Journal of Physiology (London)*, **489**, 263–73.

Melvill Jones, G. & Watt, D. G. D. (1971a). Observations on the control of stepping and hopping movements in man. *Journal of Physiology (London)*, **219**, 709–27.

(1971b). Muscular control of landing from unexpected falls in man. *Journal of Physiology (London)*, **219**, 729–37.

Mendell, L. M. (1984). Modifiability of spinal synapses. *Physiological Reviews*, **64**, 260–324.

Meunier, S. & Pierrot-Deseilligny, E. (1989). Gating of the afferent volley of the monosynaptic stretch reflex during movement in man. *Journal of Physiology (London)*, **419**, 753–63.

Meunier, S., Pénicaud, A., Pierrot-Deseilligny, E. & Rossi, A. (1990). Monosynaptic Ia excitation and recurrent inhibition from quadriceps to ankle flexors and extensors in man. *Journal of Physiology (London)*, **423**, 661–75.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta, M. (1993). Pattern of monosynaptic heteronymous Ia connections in the human lower limb. *Experimental Brain Research*, **96**, 533–44.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1994). Pattern of heteronymous recurrent inhibition in the human lower limb. *Experimental Brain Research*, **102**, 149–59.

Meunier, S., Mogyoros, I., Kiernan, M. & Burke, D. (1996). Effects of femoral nerve stimulation on the electromyogram and reflex excitability of tibialis anterior and soleus. *Muscle and Nerve*, **19**, 1110–15.

Miller, T. A., Mogyoros, I. & Burke, D. (1995). Homonymous and heteronymous monosynaptic reflexes in biceps brachii. *Muscle and Nerve*, **18**, 585–92.

Myklebust, B. M. & Gottlieb, G. L. (1993). Reciprocal excitation and reflex irradiation of short-latency reflexes in the healthy neonate. *Child Development*, **64**, 1036–45.

Nakazawa, K., Kawashima, N., Obata, H., Yamanaka, K., Nozaki, D. & Akai, M. (2003). Facilitation of both stretch reflex and corticospinal pathways of the tibialis anterior muscle during standing in humans. *Neuroscience Letters*, **338**, 53–6.

Nardone, A., Tarantola, J., Miscio, G., Pisano, F., Schenone, A. & Schieppati, M. (2000). Loss of large-diameter spindle afferent fibres is not detrimental to the control of body sway during upright stance: evidence from neuropathy. *Experimental Brain Research*, **135**, 155–62.

Nielsen, J. B. & Hultborn, H. (1993). Regulated properties of motoneurons and primary afferents: new aspects on possible spinal mechanisms underlying spasticity. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 177–92. Heidelberg, Berlin: Springer Verlag.

Nielsen, J., Petersen, N. & Crone, C. (1995). Changes in transmission across synapses of Ia afferents in spastic patients. *Brain*, **118**, 995–1004.

Ongerboer de Visser, B. W., Schimsheimer, R. J. & Hart, A. A. M. (1984). The H-reflex of the flexor carpi radialis muscle: a study in control and radiation-induced brachial plexus lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 1098–101.

O'Sullivan, M. C., Eyre, J. A. & Miller, S. (1991). Radiation of phasic stretch reflex in biceps brachii to muscles of the arm in man and its restriction during development. *Journal of Physiology (London)*, **439**, 529–43.

O'Sullivan, M. C., Miller, S., Ramesh, V. *et al.* (1998). Abnormal development of biceps brachii phasic stretch reflex and persistence of short latency heteronymous excitatory responses to triceps brachii in spastic cerebral palsy. *Brain*, **121**, 2381–95.

Petersen, N., Morita, H., Christensen, L., Sinkjaer, T. & Nielsen, J. (1998). Evidence that a transcortical pathway contributes to stretch reflexes in the tibialis anterior in man. *Journal of Physiology (London)*, **512**, 267–76.

Pierrot-Deseilligny, E., Morin, C., Bergego, C. & Tankov, N. (1981). Pattern of group I fibre projections from ankle flexor and extensor muscles in man. *Experimental Brain Research*, **42**, 337–50.

Rossi-Durand, C., Jones, K. E., Adams, S. & Bawa, P. (1999). Comparison of the depression of H-reflexes following previous activation in upper and lower limb muscles in human subjects. *Experimental Brain Research*, **126**, 117–27.

Rothwell, J. C., Day, B. L. & Marsden, C. D. (1986). Habituation and conditioning of the human long latency stretch reflex. *Experimental Brain Research*, **63**, 197–204.

Sabbahi, M. A. & Khalil, M. (1988). Segmental H-reflex studies in upper and lower limbs of patients with radiculopathy. *Archives of Physical Medicine and Rehabilitation*, **71**, 223–7.

Saito, K. (1979). Development of spinal reflexes in the rat fetus studied in vitro. *Journal of Physiology (London)*, **294**, 581–94.

Santello, M. & McDonagh, M. J. N. (1998). The control of timing and amplitude of EMG activity in landing movements in humans. *Experimental Physiology*, **83**, 857–74.

Schieppati, M. & Nardone, A. (1999). Group II spindle afferent fibers in humans: their possible role in the reflex control of stance. In *Progress in Brain Research*, ed. M. D. Binder, vol. 123, pp. 461–72. Amsterdam: Elsevier Science.

Schillings, A. M., Van Wezel, B. M. H., Mulder, T. H. & Duysens, J. (1999). Widespread short-latency stretch reflexes and their modulation during stumbling over obstacles. *Brain Research*, **816**, 480–6.

Schimsheimer, R. J., Ongerboer de Visser, B. W. & Kemp, B. (1985). The flexor carpi radialis H-reflex in lesions of the sixth and seventh cervical nerve roots. *Journal of Neurology, Neurosurgery and Psychiatry*, **48**, 445–9.

Schimsheimer, R. J., Ongerboer de Visser, B. W., Kemp, B. & Bour, L. J. (1987). The flexor carpi radialis H-reflex in polyneuropathy: relations to conduction velocities of the median nerve and the soleus H reflex latency. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 447–52.

Schindler-Ivens, S. & Shields, R. (2000). Low frequency depression of H-reflexes in humans with acute and chronic spinal-cord injury. *Experimental Brain Research*, **133**, 233–40.

Schmied, A., Morin, D., Vedel, J. P. & Pagni, S. (1997). The 'size principle' and synaptic effectiveness of muscle afferent projections to human extensor carpi radialis motoneurones during wrist extension. *Experimental Brain Research*, **113**, 214–29.

Semmler, J. G. & Türker, K. S. (1994). Compound group I excitatory input is differentially distributed to motoneurones of the human tibialis anterior. *Neuroscience Letters*, **178**, 206–10.

Severin, F. V. (1970). The role of the gamma motor system in the activation of the extensor alpha motor neurones during controlled locomotion. *Biophysics*, **15**, 1138–44.

Sherrington, C. (1910). Flexion–reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *Journal of Physiology (London)*, **40**, 28–121.

Sinkjaer, T., Andersen, J. B. & Larsen, B. (1996). Soleus stretch reflex modulation during gait in man. *Journal of Neurophysiology*, **76**, 1112–20.

Stein, R. B., Misiaszek, J. E. & Pearson, K. G. (2000). Functional role of muscle reflexes for force generation in the decerebrate walking cat. *Journal of Physiology (London)*, **525**, 781–91.

Táboríková, H. & Sax, D. S. (1969). Conditioning H reflex by preceding subthreshold H reflex stimulus. *Brain*, **92**, 203–12.

Trontelj, J. V. (1973). A study of the H-reflex by single fibre EMG. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 951–9.

Van Boxtel, A. (1986). Differential effects of low-frequency depression, vibration-induced inhibition, and post-tetanic potentiation on H-reflexes and tendon jerks in the human soleus muscle. *Journal of Neurophysiology*, **55**, 551–68.

Verhagen, W. I. M., Schrooten, G. J. M., Schiphof, P. R. & Van Ammers, V. (1988). The H-reflex of the medial vastus muscle: a study in controls and patients with radiculopathy. *Electromyography and Clinical Neurophysiology*, **28**, 421–5.

Voigt, M., Bojsen-Moller, F., Simonsen, E. B. & Dyhre-Poulsen, P. (1995). The influence of tendon Youngs modulus, dimensions and instantaneous moment arms on the efficiency of human movement. *Journal of Biomechanics*, **28**, 281–91.

Voigt, M. Dyhre-Poulsen, P. & Simonsen, E. B. (1998). Modulation of short latency stretch reflexes during human hopping. *Acta Physiologica Scandinavica*, **163**, 181–94.

Wood, S. A., Gregory, J. E. & Proske, U. (1996). The influence of muscle spindle discharge on the human H reflex and the monosynaptic reflex in the cat. *Journal of Physiology (London)*, **497**, 279–90.

Yang, J. F., Stein, R. B. & James, K. B. (1991). Contribution of peripheral afferents to the activation of the soleus muscle during walking in humans. *Experimental Brain Research*, **87**, 679–87.

Zehr, E. P. & Stein, R. B. (1999). What function do reflexes have during human locomotion? *Progress in Neurobiology*, **58**, 185–205.

Zhu, Y., Starr, A., Su, S. H., Woodward, K. G. & Haldeman, S. (1992). The H-reflex to magnetic stimulation of lower-limb nerves. *Archives of Neurology*, **49**, 66–71.

3

Muscle spindles and fusimotor drive: microneurography and other techniques

The muscle spindle has intrigued physiologists since it was first described anatomically more than 100 years ago. Its *in-parallel* response during twitch contractions of muscle was defined in 1933 by B. H. C. Matthews. The fascination has been heightened by the fact that the muscle spindle is a sensory organ that receives a motor innervation, an unusual but not unique property. The attention paid to the muscle spindle in the control of movement has often been at the expense of the Golgi tendon organ (cf. Chapter 6), intramuscular free nerve endings and, in particular, cutaneous mechanoreceptors (cf. Chapter 9), all of which play important roles in modulating motor output and (probably) in generating appropriate movement or contraction-related sensations. The attention paid to the muscle spindle/fusimotor system may be disproportionate for its role in the control of normal and pathological movement. However, despite this attention, its role is still the subject of debate, possibly because no unitary hypothesis satisfactorily explains the findings in all animal species. Human muscle spindles are innervated, as in the cat, by γ and β motoneurones, the former exclusively motor to the 'intrafusal' muscle fibres within the muscle spindle, the latter motor to both the contractile ('extrafusal') muscle as well as the spindle. The term 'fusimotor' (i.e. motor to the fusiform structure) was coined by Hunt and Paintal (1958) to refer to the γ efferent innervation of the muscle spindle, and 'skeleto-fusimotor' by Emonet-Dénand, Jami & Laporte (1975) for β innervation. The latter may be more important in small muscles where the spindle is more likely to be close to the motor point.

Background from animal experiments

Data from animal experiments are reviewed in detail elsewhere (e.g. Matthews, 1972, 1981; Hulliger, 1984; see the book edited by Taylor, Gladden & Durbaba, 1995), and the following is restricted to background data relevant to controversies concerning muscle spindle behaviour and fusimotor function in human subjects.

Initial investigations

During an ischaemic block of large (α) motor axons innervating muscle, it proved possible to stimulate small γ motor axons selectively to produce a contraction of intrafusal muscle fibres without contraction of extrafusal muscle fibres (Leksell, 1945). Selective fusimotor stimulation (whether during ischaemic block of α motor axons or following dissection and isolation of single γ axons) increases the discharge of spindle afferents (Kuffler, Hunt & Quillian, 1951), and peripheral afferent inputs may alter spindle discharge reflexly by altering the discharge of γ motoneurones (e.g. Hunt, 1951; Hunt & Paintal, 1958; Grillner, 1969). A conceptual leap occurred with the landmark studies of P. B. C. Matthews in the 1960s demonstrating that the static and dynamic sensitivity of muscle spindle primary endings can be controlled independently by two kinds of γ efferents, static (γ_s) and dynamic (γ_d), respectively (see Matthews, 1972).

From follow-up length servo to servo assistance

That the activation of γ motoneurones could lead to muscle spindle activation and, thereby, to excitation of α motoneurones led Merton (1951, 1953) to postulate that some movements might be controlled as in a follow-up length servo. The hypothesis that the central command first activated γ motoneurones and that this then led to α motoneurone recruitment dominated the literature for many years. This hypothesis was invalidated as a mechanism for driving movement, but retained in modified form, in which movements receive 'servo assistance' from spindle inputs (see Matthews, 1972). There are different supraspinal projections onto α and γ motoneurones, but there are also striking parallels, and Granit (1955) therefore suggested that voluntary movement involved an α-γ linkage (or co-activation), a suggestion that received some support from human studies using microneurography (e.g. Hagbarth & Vallbo, 1968; Vallbo, 1971, 1974; Vallbo *et al.*, 1979), but has been roundly criticised (Prochazka & Hulliger, 1983).

Current views of spindle structure and function

Intrafusal fibres

Muscle spindles contain modified muscle fibres (intrafusal fibres) with nuclei collected into a central bulbous region ('nuclear bag' fibres, usually 1–2/spindle in the cat) or arranged serially along the central region of the fibre ('nuclear chain' fibres, usually 3–5/spindle) (see Fig. 3.1). There are two types of bag fibre, the bag_1 and the bag_2 fibre with morphological and functional differences. The dynamic bag_1 fibre receives terminals from only the primary ending and is innervated by dynamic fusimotor (γ_d) axons, which can increase the dynamic sensitivity of the ending. The bag_2 fibre has terminals of both primary and secondary endings and is innervated by static fusimotor (γ_s) axons, which increase the static sensitivity of the primary and secondary endings.

There are two types of sensory endings

The primary ending spirals around the central region of the bag and chain fibres and gives rise to a single large group Ia afferent (i.e. there is only one primary ending and one group Ia afferent per spindle). Secondary endings are more distal, on either side of the central region, mainly on chain fibres but also on one of the bag fibres (the static bag_2 fibre), and give rise to several group II afferent axons/spindle (i.e. there may be several secondary endings and several group II afferents per spindle). Primary endings are sensitive to both the static and dynamic components of muscle stretch and also to high-frequency vibration, while secondary endings are similarly sensitive to the static component of stretch, but are much less sensitive to the dynamic component of stretch and less sensitive to vibration (see Matthews, 1972). The properties of the bag_2 fibre (not the bag_1 fibre) largely determine both the background firing rate of the group Ia afferent and the dynamic response to stretch of passive spindles (Gioux, Petit & Proske, 1991; Scott, 1991; Proske, 1997). The chain fibres are largely responsible for the static response to stretch of both the primary and secondary endings.

γ innervation

Fusimotor (γ) efferents cause the peripheral regions of intrafusal muscle fibres to contract and increase the stiffness of the intrafusal fibre, thereby exciting spindle endings and increasing their sensitivity to stretch. There are two types of fusimotor efferents: static fusimotor (γ_s) axons, which increase the static sensitivity of the primary and secondary endings by causing contraction in bag_2 and chain fibres; dynamic fusimotor (γ_d) axons, which can increase the dynamic sensitivity of the primary ending by causing contraction in bag_1 fibres (see Matthews, 1972; Fig. 3.1). The β (skeleto-fusimotor) innervation is considered below (p. 117). Note that the dynamic response of primary endings in passive spindles arises from the bag_2 fibre, but the increase in the dynamic response due to γ_d action comes from the bag_1 fibre.

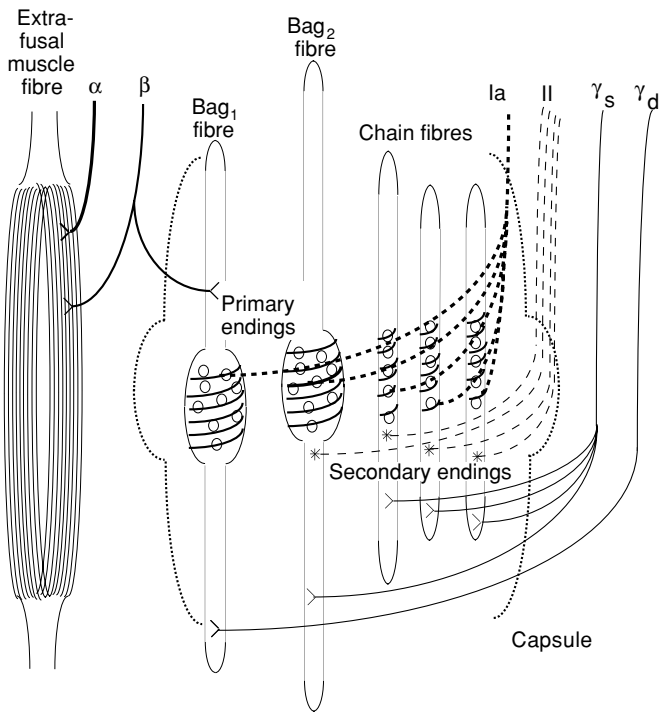


Fig. 3.1. Sketch of the muscle spindle and its afferent and efferent innervation. The capsule of the spindle (dotted line) contains intra-fusal muscle fibres – the so-called nuclear bag (bag_1 and bag_2) and chain fibres. The primary ending spirals around the central region of the bag and chain fibres and gives rise to a single large group Ia afferent. Secondary endings are more distal (asterisks), on either side of the central region (although shown on only one side, for simplicity), mainly on chain fibres but also on the static bag_2 fibre, and give rise to several group II afferent axons. Chain fibres and static bag_2 fibres receive efferent innervation from static fusimotor (γ_s) neurones, while dynamic bag_1 fibres receive efferent innervation from dynamic fusimotor (γ_d) neurones. β (skeleto-fusimotor) efferents innervate both intra- and extra-fusal muscle fibres. Only the β innervation of bag_1 fibres is represented, but some bag_2 fibres also receive β innervation. The main innervation of extra-fusal muscle fibres comes from large (α) efferents.

Differences in spindles

In the cat, there are differences in spindle morphology in different muscles

Complex spindles involving more than one spindle or a spindle/tendon organ combination, and spindles in tandem with two or more spindles end to end, are common in neck muscle. There are also differences in conduction velocity of the afferent axons innervating muscle spindles in different muscles, slower, for example, for spindles in jaw muscles than for spindles in the hindlimb (where most studies have focussed). These morphological differences within a single species seem to be greater than the morphological differences between species.

Morphological differences between feline and human spindles

The differences are summarised by Prochazka & Hulliger (1983) and Gandevia & Burke (2004). Some may be of some functional relevance.

(i) The size of the muscle spindle varies with the muscle in which it is located, often some 7–10 mm (but only 1–3 mm in the lumbrical muscles). However, overall, the human spindle is slightly longer

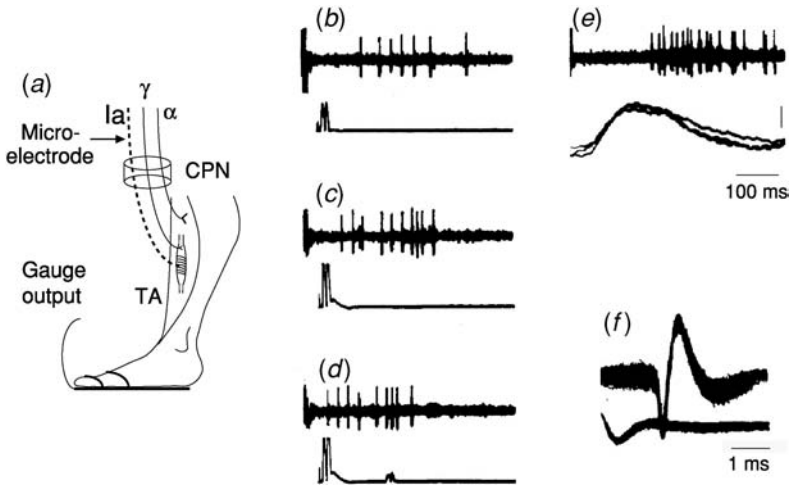


Fig. 3.2. Ambiguous responses of a spindle afferent during graded twitch-induced contractions of tibialis anterior. (*a*) Sketch of the experimental paradigm: recording with a microelectrode in the common peroneal nerve (CPN) from a tibialis anterior (TA) muscle spindle ending (a presumed primary ending). (*b*)–(*d*) Single sweeps showing the responses during graded twitch contractions produced by intrafascicular stimulation. *Upper traces*, neural activity from the afferent; *lower traces*, rectified EMG, with the amplification for (*b*) twice that for (*c*) and (*d*). (*b*) Liminal twitch involving three motor units. (*c*) Moderately strong but submaximal twitch. (*d*) Near-maximal twitch. (*e*) Superimposed responses to three maximal twitch contractions produced by stimulation at the motor point using EMG electrodes. *Upper trace*, afferent potentials; *lower trace*, twitch force, calibration: 1 Nm. (*f*) Superimpositions of all afferent potentials recorded during intrafascicular stimulation. The potentials (*upper trace*) are displayed without filtering, after passage through a digital delay line. The oscilloscope sweep was triggered by the potential, filtered as in (*b*)–(*e*) (*lower trace*). From Burke, Aniss & Gandevia (1987), with permission.

than the feline spindle. The spindle is always shorter than the muscle fibres with which it is associated, but muscle fibres are longer in human muscles.

(ii) There seem to be more fascial connections between human spindles and nearby muscle fibres, and sometimes muscle fibres insert into the spindle capsule. This would produce a greater tendency for human spindles to be stimulated when nearby muscle fibres contract (Burke, Aniss & Gandevia, 1987). The muscle afferent in Fig. 3.2 was classified as of spindle origin using maximal twitch contractions produced by strong stimuli to the peroneal nerve (panel (*e*)). However, weaker twitch contractions in Fig. 3.2(*b*), (*c*) and (*d*) reveal an in-series coupling with some motor units, such that the spindle afferent discharges during the rising phase of the contraction when a truly 'in-parallel' receptor would be unloaded (to appreciate the timing, see the twitch contraction in panel (*e*)).

(iii) The human spindle contains more intrafusal fibres (1–4 bag fibres and up to 14 chain fibres) than in the cat, and

(iv) the fusimotor innervation may be less selective in primates (and human subjects) than in the cat.

(v) There is evidence suggesting that the primary ending of the human spindle is distributed more around bag fibres than chain fibres.

(vi) The unmyelinated afferent terminal is longer than in the cat, perhaps allowing greater sensitivity to metabolites that have accumulated in the intracapsular space around the spindle.

(vii) The afferent and efferent axons appear to be of similar size in the two species, but the conduction velocities of human axons, afferent at least, appear to be much lower than in the cat. This implies that the 'Hursh constant' (the relationship between conduction velocity and diameter for large myelinated axons) is lower in humans than the cat.

Spindle density

The facial muscles and the digastric lack identifiable muscle spindles or spindle-like structures. The number of spindles in other muscles varies from <50 for intrinsic muscles of the hand to >1000 for quadriceps femoris. However, spindle density seems to be greatest for the muscles of the neck (where they may have a complex morphology, particularly in deep paraspinal muscles, see above) and the intrinsic muscles of the hand.

β (skeleto-fusimotor) neurones

These neurones innervate both intra- and extra-fusal muscle fibres (Bessou, Emonet-Dénand & Laporte, 1965) and, in the cat hindlimb, perhaps 30% spindles receive such innervation. Their activity would obligatorily result in a coupling of spindle excitation and muscle contraction. However, this is unlikely to account for the consistent finding that voluntary effort results in parallel activation of muscle and muscle spindle endings because (i) during pressure block experiments to the point of paralysis (presumably blocking large α axons before small γ axons), voluntary effort can still activate spindle endings (Burke, Hagbarth & Skuse, 1979); (ii) specific search for a coupling of spindle discharge to EMG activity using spike-triggered averaging has been unrewarding in one study (Gandevia, Burke & McKeon, 1986a) though not in a subsequent study (Kakuda, Miwa & Nagaoka, 1998); and (iii) there have been anecdotal reports of changes in spindle discharge that could be produced in relaxed muscles without the appearance of detectable EMG (Gandevia *et al.*, 1986b, 1994; Aniss *et al.*, 1990a; Ribot-Ciscar *et al.*, 1991). There is anatomical evidence of β innervation of human spindles and suggestive evidence that this may be physiologically significant: corticospinal volleys and voluntary effort seem capable of activating β efferents (Rothwell, Gandevia & Burke, 1990; Kakuda & Nagaoka, 1998, respectively), as also may volleys in low-threshold cutaneous afferents (Aniss, Gandevia & Burke, 1988). In general, β efferents innervate the dynamic bag_1 fibre (cf. Fig. 3.1) and their action is therefore to increase the dynamic sensitivity of the primary ending. However, there are also static β efferents (not represented in Fig. 3.1), which are of slightly larger size than the dynamic β efferent and, when present, they innervate the long chain fibre, so altering the static behaviour of the primary ending.

Methodology

Discredited techniques

Comparisons of tendon jerk and H reflex as measures of fusimotor drive

Underlying principle

Based on the fact that the H reflex bypasses the muscle spindle while the tendon jerk does not, many authors have, following Paillard (1955), implicitly accepted that comparisons of the H reflex and tendon jerk can be used to provide a reliable measure of fusimotor activity. As a result of such comparisons, and of the uncritical use of local anaesthetic nerve blocks, it became accepted that (i) there is a significant level of background fusimotor drive in the relaxed state, particularly in dynamic γ motor axons; (ii) this background fusimotor drive sensitises spindle endings to percussion in the relaxed state; and (iii) without this background fusimotor drive there would be no tendon jerk. These views have been the subject of critical reappraisal, as have many of the conclusions about motor control mechanisms in health and disease that were based on them (Burke, 1983; e.g. see Fig. 3.11). Each of the above statements is probably erroneous: there is now substantial experimental evidence to support the view that valid conclusions about fusimotor function cannot be drawn from such comparisons (e.g. Burke, McKeon & Skuse, 1981a,b; Burke, Gandevia & McKeon, 1983, 1984; Morita *et al.*, 1998).

Differences in the afferent volleys of the two reflexes

Tendon jerk

Because of the properties of the tendon, tendon percussion presents an oscillatory stimulus to the

muscle spindle, and sensitive primary endings discharge multiple times to a single percussion, responding to the damped oscillating disturbance that reaches the ending. The afferent volley for the soleus tendon jerk reaches the popliteal fossa some 4–5 ms after percussion on the Achilles tendon, reaches a peak some 5–10 ms later and lasts some 30–40 ms (Burke, Gandevia & McKeon, 1983). Due to the extreme sensitivity of primary spindle endings, it is not necessary to percuss the appropriate tendon directly: percussion on a bony protuberance will result in a vibration wave that travels along the bone exciting muscle spindles in nearby muscles and, in subjects with brisk tendon jerks, may produce tendon jerks in multiple muscles throughout the limb – the phenomenon of 'reflex irradiation', best seen in patients with spasticity (Lance & de Gail, 1965). The muscle spindle is not the only receptor responsive to tendon percussion, even when the mechanical stimulus is delivered carefully only to the appropriate muscle: sensitive muscle and cutaneous receptors throughout the limb, even those in antagonists, may be excited and the extent of this will be dependent only on effective transmission of the mechanical stimulus (Burke, Gandevia & McKeon, 1983; Ribot-Ciscar, Vedel & Roll, 1989).

H reflex

On the other hand, a 1-ms current pulse will excite axons only once, producing a more synchronised afferent volley, but one that involves group Ib as well as group Ia afferents. In addition, the stimulated nerve usually innervates many muscles: e.g. the posterior tibial nerve innervates calf muscles other than triceps surae and the intrinsic muscles of the foot, the afferents of which (both Ia and Ib) have heteronymous projections to soleus motoneurones (see Table 2.1; Chapter 10, p. 497).

Presynaptic inhibition of Ia terminals

This is more effective on the afferent volley of the H reflex than on that eliciting the tendon jerk (Morita *et al.*, 1998; Chapter 8, pp. 354–5).

Differences at the motoneurone pool level

The dispersed afferent volley produced by tendon percussion results in a long-lasting compound EPSP, the rising phase of which may be some 5–10 ms, much longer than the 1–2 ms rising phase of the EPSP produced by a single electrical stimulus to the tibial nerve (Burke, Gandevia & McKeon, 1984). There is thus greater opportunity for oligosynaptic inputs to affect the motoneurone discharge with the tendon jerk than the H reflex. Notwithstanding, the rising phase of the electrically evoked EPSP is briefer than might be expected given the opportunity for dispersion of the volley created by the long conduction pathway (much longer than in the cat), the slower conduction velocities of group Ia afferents (maximally ~60–70 m s^{-1} in the lower limb, i.e. much lower than in the cat hindlimb) and the likely range of Ia conduction velocities (~60–70 m s^{-1} down to ~48 m s^{-1}; see Chapter 7, pp. 302–3). It has been suggested that group Ib afferents curtail the electrically evoked EPSP and that the H reflex can be altered by altering transmission across the Ib inhibitory interneurone, a situation not equally applicable to the tendon jerk (Burke, Gandevia & McKeon, 1984). There is now direct experimental support for this suggestion (Marchand-Pauvert *et al.*, 2002; Chapter 1, pp. 14–15).

Conclusions

The tendon jerk and the H reflex are both dependent on the monosynaptic excitation from homonymous Ia afferents, but they differ in so many other respects that comparison of them as a measure of fusimotor function is invalid.

Nerve blocks

Underlying principle

In the cat, Matthews & Rushworth (1957a,b) demonstrated that it is possible to block γ efferents using local anaesthetic applied directly to the nerve because they are smaller than α efferents. Rushworth (1960) then showed that injections of

dilute procaine into the motor point reduced both spasticity and rigidity, an effect attributed, not unreasonably, to γ efferent blockade (however, see below).

Situation in human subjects

The situation in human subjects is quite different from the controlled experimental circumstances possible in the cat. Given the larger size of human nerves, diffusion of the local anaesthetic through perineural and fascicular tissues will result in non-selective effects because of involvement of closer rather than smaller axons, and this will also be so when the injection is into the motor point. The anaesthetic will not differentiate between afferents and efferents and, theoretically at least, reflex depression could result from loss of small afferent inputs rather than loss of fusimotor function. Loss of the tendon jerk but preservation of near-normal strength does not constitute an adequate control for the integrity of α motor axons because considerable denervation is required before the triceps surae muscles become weak to clinical testing. Finally, microneurographic studies have shown that, in general, the sequence of cutaneous afferent blockade by local anaesthetics is from small afferents to large afferents, *but* they have also demonstrated that the blocks are extremely difficult to control and their sequence not exactly the same in different experiments (Torebjörk & Hallin, 1973; Mackenzie *et al.*, 1975). It is likely that greater involvement of γ efferents occurs during the recovery from a complete local anaesthetic block than during its induction, but this remains to be proven. Pressure blocks seem to produce a more reliable sequence of axon block, large before small, possibly because their temporal development can be controlled, at least in part, by adjusting pressure.

Conclusion

Local anaesthetic nerve blocks cannot be used to produce *selective* de-efferentation of muscle spindles.

Acceptable techniques

Microneurography

Microelectrode

The first definitive reports of microneurography were published by Vallbo & Hagbarth (1968) on cutaneous afferents and Hagbarth & Vallbo (1968) on muscle afferents. The technique is illustrated in the sketch in Fig. 3.3(*a*), and a recording from a presumed secondary spindle afferent innervating the fourth dorsal interosseous muscle of the hand is shown in Fig. 3.3(*b*). The basic technique has not changed greatly since then, and adequate descriptions are available (e.g. Hagbarth, 1979; Vallbo *et al.*, 1979; Burke, 1981; Gandevia & Burke, 1992). The traditional microelectrode is a monopolar tungsten electrode with a shaft diameter of ∼200 μm, insulated to the tip, with an optimal impedance *in situ* of ∼100–150 kΩ for single unit recordings and perhaps ∼50 kΩ for multi-unit recordings. Some authorities prefer concentric needle electrodes with or without a bevelled tip, but the electrode has a wider shaft and, in practice, there is probably little advantage over the traditional electrode.

Basic methodology

The microelectrode is inserted manually through the skin into the peripheral nerve trunk and then guided into an appropriate nerve fascicle. In most laboratories this is facilitated by delivering weak electrical stimuli through the electrode to produce radiating cutaneous paraesthesiae (when trying to home in on a fascicle innervating skin) or a twitch contraction of the innervated muscle (when focussing on a fascicle innervating muscle). When the tip is within the fascicle, gentle stroking of the skin or tapping on the appropriate muscle tendon will activate mechanoreceptors in skin or muscle, respectively, and auditory feedback is then used to make further small adjustments of the electrode to bring the desired neural activity into focus. The electrode is left floating free, secured by tissue resistance at the recording end

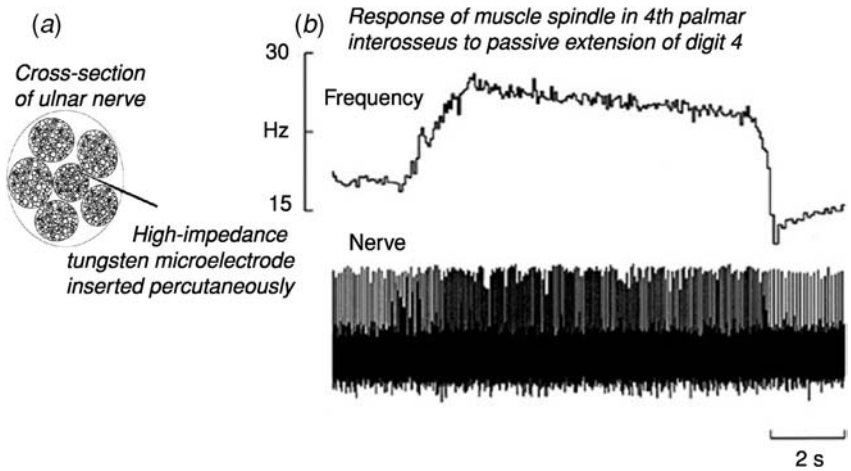


Fig. 3.3. Unitary recording from a human muscle spindle. (*a*) Sketch of the technique for the recording in (*b*): the tungsten microelectrode was inserted percutaneously into a motor fascicle of the ulnar nerve at the wrist. The microelectrode was introduced manually. When *in situ*, it was supported without rigid fixation at one end by its connecting lead and at the other by the skin and subcutaneous tissue. Its position was adjusted within the nerve until the tip penetrated the desired nerve fascicle. Minor adjustments were made to bring the desired neural activity into focus. Note that the microelectrode has a shaft diameter of ~200 μm and that the largest axons have a diameter of ~20 μm. The target muscle was identified by the responses to intraneural electrical stimulation and the responses to passive and active movements of the digits. (*b*) A recording from the afferent of a spontaneously active presumed secondary spindle ending in the fourth dorsal interosseous. *Lower trace*: action potentials; *upper trace*: instantaneous frequency of the afferent's discharge. The ending increased its discharge during extension and passive abduction (not shown) at the fourth metacarpophalangeal joint, the responses to stretch and shortening being essentially static. From Burke, Gandevia & Macefield (2003), with permission.

and by a coiled insulated copper wire to the preamplifier at the other. This is preferable to external fixation because movement by the subject cannot be avoided, and external fixation then leads to electrode dislodgement. Even so, the stability of the recording can be jeopardised by minor movements, particular those that displace skin at the recording site.

Identification

If a recording is obtained from a single axon it is necessary to identify the axon as an afferent and then to characterise its response to various stimuli in order to clarify its origin (e.g. from a primary or secondary ending or a Golgi tendon organ). This can be time-consuming, and often recordings from partially or completely identified afferents are lost before experimental manipulations can be studied. Criteria to differentiate muscle spindle afferents from Golgi tendon organ afferents include the classical response to a twitch contraction of the receptor-bearing muscle (unloading with spindles: Figs. 3.2(*e*), 3.4(*b*) and 3.5(*c*); activation with tendon organs: Fig. 3.6(*e*)). This is now incorporated into the usual identification processes. The twitch contractions can be produced by stimuli delivered through the recording microelectrode, transiently switching off the recording to do so (McKeon & Burke, 1980; Burke, Aniss & Gandevia, 1987) or by using external stimuli to the nerve trunk (e.g. Edin & Vallbo, 1987). However, responses to twitch contractions are sometimes ambiguous, possibly because of the above-mentioned fascial interconnections between nearby motor units and the spindle (see Burke, Aniss &

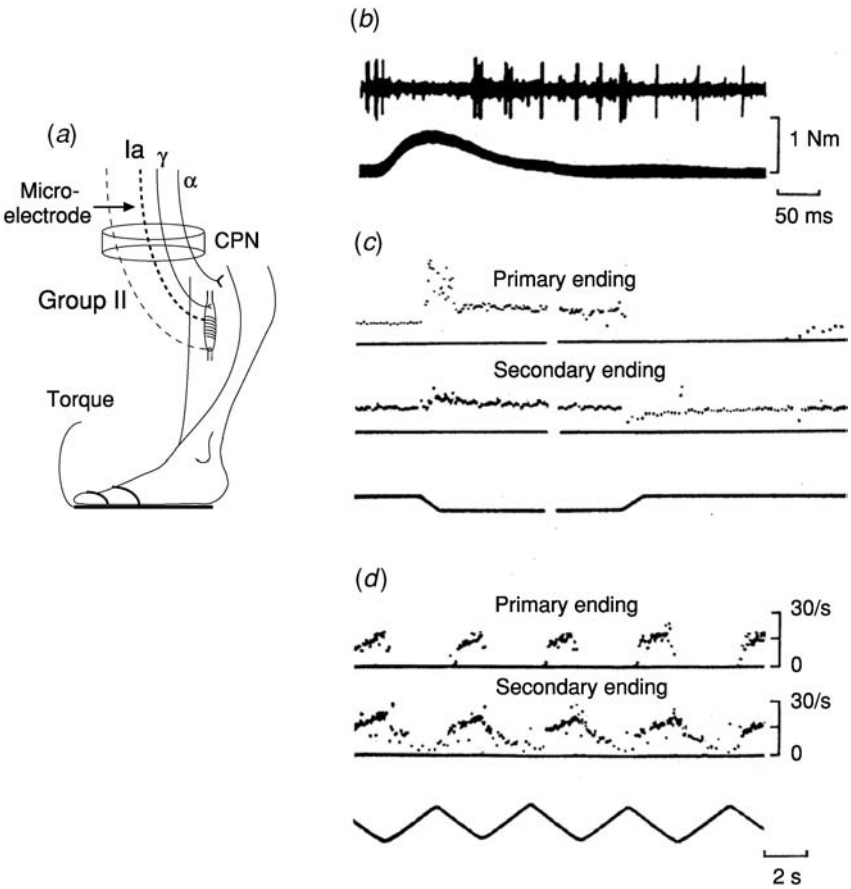


Fig. 3.4. Identification of spindle endings in tibialis anterior. (*a*) Sketch of the experimental paradigm: recording with a microelectrode in the common peroneal nerve (CPN) from a muscle spindle primary ending and a muscle spindle secondary ending in tibialis anterior (TA). (*b*) Twitch test for the primary ending showing afferent potentials in the original neurogram (upper trace) and the torque produced by the twitch contraction of the receptor-bearing muscle (lower trace). Five superimposed sweeps. Note that an early discharge occurs before torque starts to rise (associated with the α volley, cf. Hunt & Kuffler, 1951). Spindle discharge pauses as torque rises. (*c*) 'Instantaneous' frequency plots of spindle responses to ramp stretch and shortening of 3–4° at 7.5°/s for a primary ending (*upper trace*) and a secondary ending (*middle trace*). In both (*c*) and (*d*) the movement of the ankle joint is shown in the lower trace, but for simplicity, the goniometer record for the primary ending has been omitted. A downward deflexion represents stretch of the receptor-bearing muscle. In (*d*) the imposed movements for the two endings were very similar, but not quite identical in amplitude, so that occasionally the discharge of the primary ending appears slightly out of phase. From Burke *et al.* (1976a), with permission.

Gandevia, 1987; Fig. 3.2(*c*), (*d*); p. 116). Additional criteria include the presence or absence of background activity, the regularity of any background discharge, behaviour during voluntary contractions and on abrupt relaxation, and the responses to stretch and vibration (e.g. Edin & Vallbo, 1990a,b,c). These criteria also help distinguish group Ia afferents and primary endings from group II afferents and secondary endings. Figure 3.4 summarises some of these features. Both primary and secondary

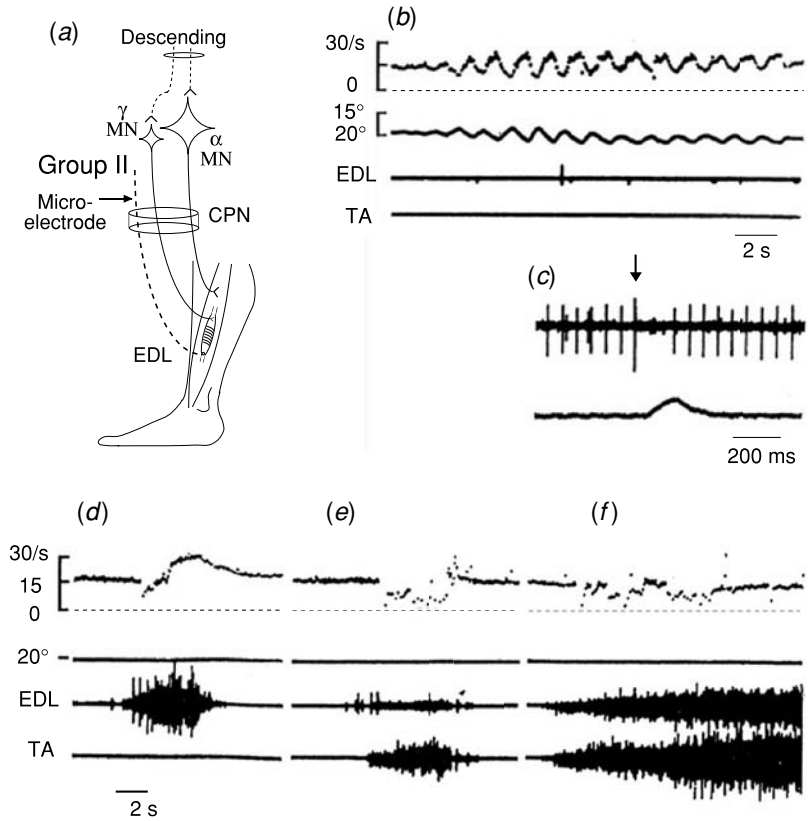


Fig. 3.5. The effects of isometric voluntary contractions on background discharge rate of a secondary ending in extensor digitorum longus. (*a*) Sketch of the experimental paradigm: during voluntary contraction of the extensor digitorum longus (EDL), there is descending activation of both α and γ motoneurones (MNs) innervating EDL. Recording with a microelectrode in the common peroneal nerve (CPN) from an EDL muscle spindle secondary ending. (*b*) Response of the ending to imposed joint movement. (*c*) An electrically induced twitch delivered at the arrow produces a twitch contraction, recorded by the myograph (lower trace), and a typical pause in spindle discharge, seen in the original neurogram (upper trace). In (*b*), (*d*), (*e*) and (*f*), traces are from top to bottom: instantaneous frequency; joint angle (downward deflection represents stretch of the receptor-bearing muscle); EMG of EDL; EMG of tibialis anterior (TA). The regularity of the background discharge in (*d*)–(*f*) and the close parallelism between imposed joint movement and discharge rate in (*b*) suggest that the ending was a secondary ending. In (*d*) contraction of the receptor-bearing muscle (EDL) accelerates the spindle (after a brief unloading). In (*e*) contraction of predominantly TA (a synergist) decreases discharge rate. In (*f*) contraction of both muscles, the opposing effects largely cancelling out. Note that in (*d*) spindle discharge remains enhanced after EDL EMG has subsided, probably due to the thixotropic properties of intrafusal fibres. Modified from Burke *et al.* (1976b), with permission.

endings should be unloaded by a maximal twitch contraction of the receptor-bearing muscle and activated on the falling phase of the twitch (panel (*b*), see also Fig. 3.2(*e*)). However, the primary ending (upper traces) has a more prominent dynamic response to stretch (indicated by a downward movement of the joint angle in the lower trace in Fig. 3.4(*c*), (*d*)) than the secondary ending (middle traces). Figure 3.5(*b*) illustrates an essentially static response to stretch for another presumed secondary ending.

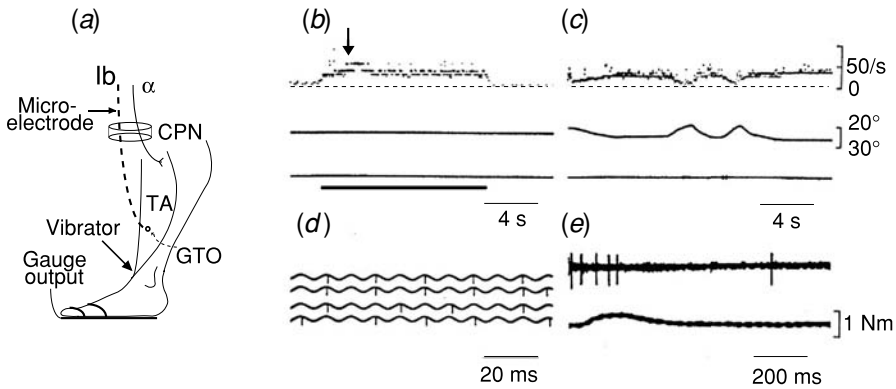


Fig. 3.6. Effects of tendon vibration at 110 Hz on a Golgi tendon organ in tibialis anterior. (*a*) Sketch of the experimental paradigm: recording with a microelectrode in the common peroneal nerve (CPN) from a Golgi tendon organ (GTO) in tibialis anterior (TA). (*b*) Responses to vibration at constant muscle length, and (*c*), during alternating passive movements. Upper traces: frequency plots. Middle traces: ankle position. Lower traces: EMG of tibialis anterior. Note the EMG silence throughout the traces. Vibration indicated by bar in (*b*), but is constant throughout the sweep in (*c*). (*d*) Individual vibration cycles taken from the position indicated by the arrow in (*b*) with the spikes superimposed on the vibration wave to demonstrate phase-locking and subharmonic activation of the GTO. Note that these responses to vibration were recorded for a non-contracting muscle (see flat EMG traces in (*b*) and (*c*). (*e*) Electrical twitch test. Three superimposed sweeps, showing discharge of the ending (upper trace) during the rising phase of torque (lower trace). Contrast (*e*) with the spindle behaviour during twitch tests in Figs. 3.2(*e*), 3.4(*b*), 3.5(*c*) and 3.7(*d*). Modified from Burke *et al.* (1976a), with permission.

Sampling bias

There is a bias in microneurographic recordings towards axons that are large and have a background discharge. The former is because the action potential must be discriminated from noise, and action potential amplitude is a function of the square of axonal diameter. The latter is because, if you cannot hear action potentials, you may not know that you have a suitable recording site. Accordingly, most studies have been dominated by recordings from group Ia afferents, and it is possible that the sample of group Ib afferents studied to date are from the more mechanically responsive end of the spectrum of tendon organs. This might explain the sensitivity to vibration of the three tendon organs in the study of Burke *et al.* (1976a), as illustrated in Fig. 3.6(*b*)–(*d*). These results do not necessarily imply that human tendon organs as a group are more stretch-sensitive than in the cat. More group Ib afferents might be isolated if searching was undertaken during a background voluntary contraction rather than at rest. Nevertheless, Fig. 3.6 indicates that at least some tendon organs are vibration-sensitive. This ending responded appropriately in a twitch test (*e*) but was sensitive to vibration at rest (as verified by the quiescent EMG in panels (*b*) and (*c*)), discharging at subharmonics of the vibration frequency (*d*).

Uncertainties of the technique

Muscle spindle endings are extremely sensitive to minute perturbations, but small disturbances to the spindle's environment within the muscle may not be apparent to inspection. EMG electrodes and force and length transducers must be used if one wishes to have reasonable certainty that the receptor-bearing muscle is truly relaxed. However, the very same recordings may not be appropriate if one wishes to know whether only the receptor-bearing muscle is active (in which case intramuscular needles or wires should be used to record EMG). No one EMG set-up can guarantee the recording from every motor unit

in a muscle, no length transducer can detect motor unit activity that does not produce movement, and no force transducer will keep a limb absolutely isometric. Hence, it is impossible to generate data with the same degree of precision as in animal experiments. This disadvantage is offset by the ability to study volitional processes in co-operative human subjects, capable of generating or changing motor drives on request. Nevertheless, the uncertainties must be kept in mind when assessing the validity of evidence for, e.g. selective activation of γ motoneurones during different manoeuvres, a controversial topic discussed further below (pp. 131–3).

Studies that exploit the thixotropic properties of intrafusal fibres

Underlying principle

Thixotropy refers to the change in passive stiffness of muscle, analogous to the behaviour of certain gels which can become fluid when stirred or shaken, only to set into a gel again when allowed to stand. Both extrafusal and intrafusal muscle fibres can manifest thixotropic behaviour. This behaviour is important because intrafusal thixotropy can dramatically alter the discharge of primary and secondary spindle endings. For example, the thixotropic properties of intrafusal fibres underlie (i) the 'initial burst' from a primary ending in response to abrupt ramp stretch, a response that has been termed an acceleration-like response (Brown, Goodwin & Matthews, 1969; Edin & Vallbo, 1990a), (ii) the after-effects of fusimotor activation on spindle discharge (Brown, Goodwin & Matthews, 1969), and (iii) stretch sensitisation of spindle endings (Edin & Vallbo, 1988; Edin, 1991). The effects of changes in the thixotropic properties of muscle spindles on spindle discharge have been studied extensively by Proske and colleagues in the cat and in human subjects (Proske, Morgan & Gregory, 1993). They depend upon the formation, break down and re-formation of actin-myosin bonds in the intrafusal fibres, with consequent changes in stiffness of the fibres and an alteration in the stretch placed on spindle endings. Prolonged stretch or fusimotor activity will cause bonds to form at the prevailing muscle length. Thus, if a muscle is held in a stretched position and then abruptly shortened, intrafusal fibres will develop slack, and this will lead to a reduced spindle discharge. The 'slack' can be removed by activating fusimotor neurones to the spindle and, if the muscle is then slowly stretched back to the original length, spindle discharge and responsiveness will be greater than originally even though the fusimotor activity may have long ceased. The type of fusimotor axon stimulated will determine which intrafusal fibre is activated, and this will determine how spindle responsiveness changes.

Thixotropy in human investigations

In human subjects, the γ activity associated with a voluntary contraction can induce long-lasting enhancements in spindle discharge, changes that persist long after the contraction (Fig. 3.7(*c*); see also Fig. 3.5(*d*)). The discharge of the spindle primary ending in Fig. 3.7(*c*) continues long after the cessation of EMG and the return of contraction force to the control level. The discharge of the secondary ending in Fig. 3.5(*d*) declines slowly and remains elevated for some seconds after EMG has disappeared. The latter ending is illustrated because many of the thixotropic after-effects of fusimotor activity in the literature involve primary endings rather than secondary endings (Brown, Goodwin & Matthews, 1969; Matthews, 1972; Edin & Vallbo, 1988, 1990a). In both instances, the after-discharge is not evidence of continuing γ drive but of a long-lasting change in stiffness of intrafusal fibres that contracted under γ drive during the voluntary contraction (Jahnke, Proske & Struppler, 1989; Ribot-Ciscar *et al.*, 1991; Wilson, Gandevia & Burke, 1995). As actin–myosin bonds break down and re-form at the prevailing muscle length, the discharge slowly declines. In other words, the enhanced spindle discharge is a lasting memory of past γ efferent activity, not evidence of the current level of fusimotor drive, and the enhanced discharge can be abolished by stretch sufficient to break the persistent actin-myosin bonds. Proske and

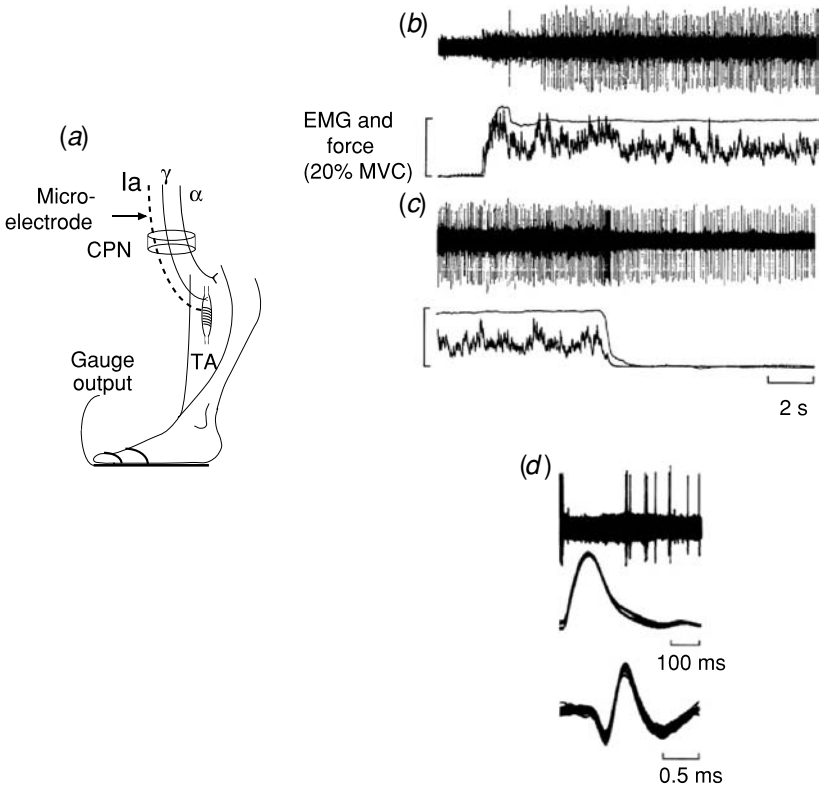


Fig. 3.7. Muscle spindle primary ending in tibialis anterior during and after a voluntary contraction illustrating the effects of thixotropy on spindle discharge. (*a*) Sketch of the experimental paradigm: recording with a microelectrode in the common peroneal nerve (CPN) from a muscle spindle primary ending in tibialis anterior (TA). (*b*) and (*c*) show the start and end of a 1 min submaximal contraction of ankle dorsiflexors at ~20 % maximal voluntary force (MVC). 30 s have been omitted between (*b*) and (*c*). The traces are from top to bottom raw neurogram, force, and integrated EMG of tibialis anterior. The spindle was initially silent, maintained a discharge at ~12 Hz throughout the 60-s contraction. There was a high-frequency burst of impulses on relaxation of the contraction, and the discharge continued at ~8 Hz in the absence of EMG following the contraction. This persistent discharge probably results from intrafusal thixotropy. (*d*) Upper two panels show the twitch test for the unit (three traces superimposed). The lowest panel shows superimposed action potentials from the unit on a faster time base. Modified from Macefield *et al.* (1991), with permission.

colleagues have exploited this behaviour to study fusimotor action in human subjects indirectly, have documented appropriate changes in spinal reflexes, and have used the behaviour to confirm the role of muscle afferents in kinaesthesia (Proske, Morgan & Gregory, 1993; Wood, Gregory & Proske, 1996; Gregory *et al.*, 1998; Wise, Gregory & Proske, 1998). For example, tendon jerks recorded at the same test muscle length can be enhanced or depressed following a voluntary contraction, if the contraction is performed at a muscle length that is shorter or longer, respectively, than the test muscle length.

Perspectives

Potentially, this approach could be used to document fusimotor function during contractions that are too strong for microneurography or in patients unsuitable for microneurography, and there is one such recent report on patients spastic following

stroke (Wilson *et al.*, 1999b). A complicating factor is that extrafusal muscle fibres also display thixotropic behaviour. This serves as a warning that careful controls are required even with this experimental paradigm. A further lesson is that the thixotropic properties of intrafusal muscle can distort spindle discharge and must be considered when interpreting unexpected changes in spindle discharge, reflex behaviour or perception, especially when they occur after a muscle contraction. The history of what the spindle was subjected to can influence how it responds to a new stimulus.

Critique of the tests to study muscle spindle afferent discharge and fusimotor drive

Microneurography

Necessity for careful controls

Microneurography is less indirect than other techniques, but it is possible to make valid conclusions about fusimotor activity from recordings of muscle spindle discharge only if all disturbances to the spindle are rigidly controlled. This is possible in feline experiments but is rarely so in human subjects, in whom spindle endings have been noted to respond to mechanical stimuli that are not immediately obvious, such as respiration and the arterial pulse (Hagbarth *et al.*, 1975a; McKeon & Burke, 1981) or the mechanical twitch produced by single motor units (McKeon & Burke, 1983). It is absolutely essential that all possible perturbations to the highly sensitive spindle ending be controlled, whether they be external or internal.

Uncertainties about identification

The identification of an axonal recording as afferent rather than efferent (or vice versa) and then the subclassification of the afferent (or efferent) must be beyond dispute, particularly when the conclusions are based on only a couple of 'positive' findings from a larger sample. For example, it has been suggested that some of the findings on α/γ co-activation from human studies can be attributed to incorrect identification of Ib afferents as Ia (Prochazka & Hulliger, 1983).

Sensitivity to displacements

Even small movements of the skin at the recording site can disturb the microelectrode and disrupt the recording. As a result the movement repertoire that can be studied with this technique is quite limited. The need to apply restraints to prevent, or transducers to measure perturbations that could be transmitted to the endings creates artificial conditions, and it is conceivable that this could alter the explored fusimotor 'set'.

The technique is traumatic

It involves insertion of a needle electrode into the nerve trunk and, while the risks are very small indeed, some oedema is inevitable and there are theoretical risks of infection or of intraneural bleeding from a small vessel.

The technique is technically demanding

It is not unusual to spend a couple of hours searching in vain for a specific afferent type, having been unable to hold promising recordings for sufficiently long to gain meaningful data.

Thixotropy

Studies of intrafusal thixotropy can allow stronger contractions to be assessed and can be of value in patients for assessing fusimotor activity. While reflex studies using thixotropy to change behaviour do not involve comparing dissimilar reflexes (as with the discredited comparison of mechanically and electrically evoked reflexes), the technique is much more indirect than microneurography, and it is important to exclude other possible causes of variable reflex function.

Organisation and pattern of connections

Background fusimotor drive

Static fusimotor drive

There is now considerable evidence that human spindle endings behave as if passive receptors without active fusimotor drive in the relaxed state. The evidence is more cogent for static fusimotor (γ_s) drive (see Vallbo *et al.*, 1979; Burke, 1981; Gandevia & Burke, 1992) than for dynamic fusimotor (γ_d) drive. In relaxed muscle, human primary spindle endings maintain much lower firing rates and their responses to stretch are smaller than those of passive spindle endings in the cat (Vallbo, 1974; Vallbo *et al.*, 1979; Burke, Skuse & Stuart, 1979; Prochazka & Hulliger, 1983; Gandevia & Burke, 1992). The regularity of discharge is similar to that of de-efferented feline endings (Burke, Skuse & Stuart, 1979; Nordh, Hulliger & Vallbo, 1983), and there is no evidence of a negative serial correlation between successive interspike intervals (i.e. that long interspike intervals tend to be followed by short ones, something that is a feature of γ_s drive (Matthews & Stein, 1969) and appears during a voluntary contraction). In addition, de-efferenting spindles by blocking the nerve completely with local anaesthetic or by pressure does not alter muscle spindle discharge or the responses to muscle stretch, tendon vibration or tendon percussion (Burke *et al.*, 1976b; Burke, Hagbarth & Skuse, 1979; Burke, McKeon & Skuse, 1981b). Thus, when the spindle primary ending in Fig. 3.8(*b*), (*c*) was de-efferented by a complete block of the peroneal nerve proximal to the recording site, there was no detectable effect on the ending's background discharge rate or on its responses to stretch (downward movement of the angle trace) and shortening (upward movement), as can be confirmed by comparing the discharge frequencies in (*b*) and (*c*). These findings do not prove that there is no background activity in γ motoneurones, but they suggest a very low level of activity, at least in γ_s motoneurones, insufficient to affect the background spindle discharge or the response to stretch materially.

Dynamic fusimotor drive

There is a difficulty in comparing dynamic responses in relaxed muscles with those when the state of the muscle changes due to, e.g. a background contraction, because the muscle and tendon stiffen and this could dampen or enhance the stimulus actually reaching the receptors in the muscle. The responses to muscle stretch or to tendon percussion do not change in relaxed muscle when subjects perform reinforcement manoeuvres, are provided with alerting stimuli or anticipate the need to contract the test muscle, provided that the receptor-bearing muscle remains relaxed (Hagbarth *et al.*, 1975a; Burke *et al.*, 1980; Burke, McKeon & Skuse, 1981a; Gandevia & Burke, 1985; see, however, Ribot-Ciscar, Rossi-Durand & Roll, 2000). This argues against significant γ_d drive to resting muscles, in agreement with the nerve block studies discussed above. Nevertheless, there is some evidence to suggest that there may be some background γ_d activity (Aniss *et al.*, 1990a; Gandevia *et al.*, 1994), and this would be consistent with some views on the mechanisms of reflex reinforcement (Ribot, Roll & Vedel, 1986; Ribot-Ciscar *et al.*, 2000; see, however, the critique below: pp. 131–3).

Effects of cutaneous afferents on fusimotor neurones

There is extensive literature on the reflex effects of cutaneous afferents on γ motoneurones in different feline preparations, dating back to Hunt (1951) and Hunt & Paintal (1958), and there are now detailed studies in locomoting animals (see the book edited by Taylor, Gladden & Durbaba, 1995).

Lower limb

Evidence for reflex activation of γ motoneurones by inputs from cutaneous mechanoreceptors has been sought without success in lower limb muscles of reclining human subjects, who were at rest or

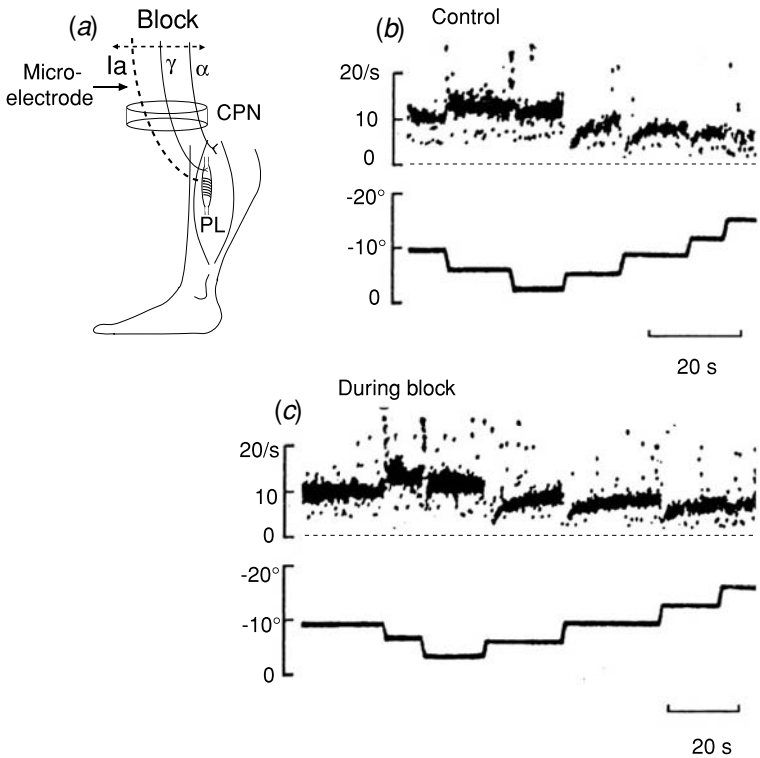


Fig. 3.8. The effect of de-efferentation on the responses to stretch and shortening of a primary ending in the relaxed peroneus longus muscle. (*a*) Sketch of the experimental paradigm: recording with a microelectrode in the common peroneal nerve (CPN) from a muscle spindle primary ending in peroneus longus (PL). De-efferentation was achieved by complete nerve block with lignocaine proximal to recording site (horizontal double-headed dashed line in (*a*)). In (*b*) and (*c*) upper trace: 'instantaneous' frequency plot; lower trace: joint position. A downward deflexion indicates stretch of the receptor-bearing muscle. Responses of the ending are identical before (*b*) and during (*c*) the nerve block. Modified from Burke *et al.* (1976b), with permission.

performing isometric voluntary contractions. However, when subjects were performing an appropriate task (active standing), muscle spindle endings could be activated by the same volleys without producing EMG activity. The tibialis anterior spindle ending in Fig. 3.9(*b*) had no background discharge when the subject was standing without support and with eyes closed, and was therefore activated by steady pressure applied to the tendon. The absence of vision and external support ensured that the subject was maximally dependent on proprioceptive cues for stability. A train of five non-painful stimuli to the ipsilateral sural nerve activated the spindle ending (PSTH in the second trace), but produced no EMG in the silent tibialis anterior. The stimuli produced a reflex response in soleus (fourth trace) and a forward body sway (fifth and six traces) but this would have unloaded the spindle ending, and cannot explain the spindle activation. Findings such as this suggest that fusimotor reflexes are task-dependent, only active when subjects are performing an appropriate motor task (Aniss *et al.*, 1990a; Burke & Gandevia, 1992), when their role may lie more in setting the background operating level of fusimotor drive than in the moment-to-moment control of movement (see p. 138).

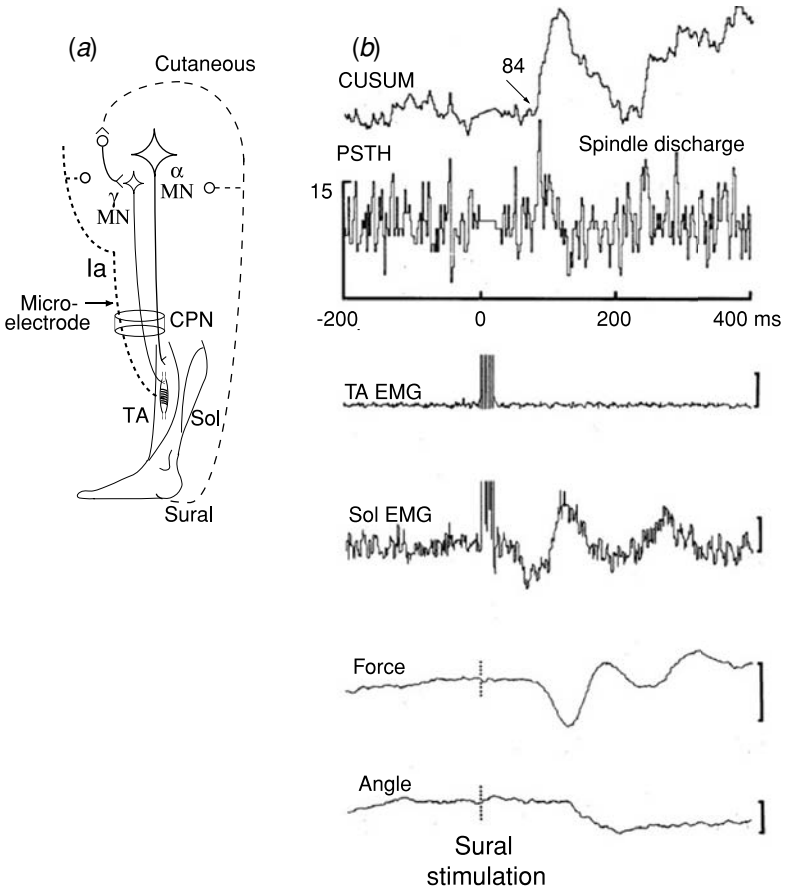


Fig. 3.9. Poststimulus increase in discharge of a muscle spindle ending in tibialis anterior after non-painful trains of stimuli to the sural nerve during unsupported standing with eyes shut. (*a*) Sketch of the presumed pathways: cutaneous afferents in the sural nerve reflexly excite γ motoneurones in tibialis anterior (TA). Recording with a microelectrode in the common peroneal nerve (CPN) from a TA muscle spindle ending. (*b*) The ending was silent at rest but was given a background discharge of 9.5 Hz by applying steady pressure to the tendon of TA (not illustrated). Traces are, from above, CUSUM of the PSTH with the onset of the increase in discharge indicated by the arrow at the 84 ms latency; PSTH of spindle discharge; stimulus-triggered averages of rectified surface EMG of TA, of rectified surface EMG of soleus, of force and of ankle-joint angle. The histogram is based on 500 successive trials. Count ratio between the CUSUM and the histogram is ×5. Vertical bars represent 10 μV for EMG traces, 2N for force, and 0.25° for the ankle-joint angle. Pre-trigger EMG level for soleus was 21 μV. In this figure, stretch of pretibial flexors (i.e. backward body sway) is shown as an upward deflection in force and angle traces. Modified from Aniss *et al.* (1990a), with permission.

Relaxed forearm extensor muscles

In these muscles cutaneous afferents can change the muscle spindle response to tendon percussion, though this has been demonstrated for only four afferents – for two, the discharge increased and for two, it decreased (Gandevia *et al.*, 1994). It is likely that, in the upper limb, such reflexes may be active even at rest. More importantly, the decreased response to percussion of two spindle endings suggests that there must have been some background fusimotor drive to the resting muscles, in

this case γ_d activity. Contrary to the hypothesis that, because of temporal and spatial facilitation, natural cutaneous volleys would have more powerful effects on γ motoneurones than artificially synchronised electrically evoked volleys, natural activity of cutaneous afferents evoked by skin stroking or taps failed to affect spindle discharge in these studies.

Corticospinal volleys

Motor cortex stimulation using single transcranial magnetic or electrical stimuli can alter the discharge of muscle spindle endings, presumably through effects on γ and probably β motoneurones (Rothwell, Gandevia & Burke, 1990). However, it does not do so at a lower threshold than that required to produce the MEP, and these findings suggest that an effective γ discharge cannot be generated by corticospinal volleys without discharging α motoneurones and producing EMG activity in the test muscle.

Effects of muscle vibration on human muscle spindles

Muscle vibration has been employed extensively in human subjects to produce reflex effects or to distort proprioceptive sensations. It has been used to produce reflex contractions (the tonic vibration reflex, TVR), to suppress the H reflex or tendon jerk, and to alter the excitability of group Ia afferents. For these reasons the specificity of vibration for primary spindle endings needs to be addressed. There are many fallacious or over-interpreted reports in the literature based on the assumption that transverse tendon vibration in intact human subjects can be a selective stimulus for primary spindle endings, driving them to respond 1:1 with the vibration frequency. When applied transversely to a muscle tendon of an intact subject, vibration is commonly *not* selective for muscle spindle receptors and, in intact human subjects, it may not excite only the primary spindle ending.

Relaxed muscles

Primary endings

The dominant input produced by vibration of a tendon will be from primary spindle endings in the vibrated muscle. The majority of human primary endings will respond vigorously to vibration and may discharge 1:1, i.e. at the frequency of vibration (120 Hz in Fig. 3.10(*b*)), particularly during muscle stretch. However, the discharge is often at subharmonics of the vibration frequency, particularly if the amplitude of tendon vibration is kept small in order to make it as selective as possible. A frequency of ~80 Hz seems the optimal frequency for most vibration-induced perceptual and motor effects (see Roll & Vedel, 1982; Roll, Vedel & Ribot, 1989), whether the vibration is applied using an eccentrically weighted motor or as high-frequency tendon taps (using, e.g. a Brüel and Kjaer shaker).

Secondary endings

Human secondary endings may respond to vibration (Burke *et al.*, 1976a), virtually always discharging at relatively low rates at subharmonics of the vibration frequency, rarely if ever reaching 1:1, even during muscle stretch (Fig. 3.10(*d*)). Again, this depends on the amplitude of vibration (Roll & Vedel, 1982; Roll, Vedel & Ribot, 1989). With low-amplitude vibration it should be possible to avoid activating secondary endings, but the lower the amplitude the less secure the driving of primary endings.

Tendon organs

Some tendon organs can respond to tendon vibration in relaxed muscles and many do so during voluntary contractions. Indeed, all three tendon organs in the study of Burke *et al.* (1976a) responded to vibration when the muscles were relaxed (Fig. 3.6(*b*), (*c*)). That all did so may be the result of a sampling bias of microneurography towards stretch-responsive receptors (see p. 123). Further studies isolating Ib afferents during a voluntary contraction might produce a more representative sample,

possibly less responsive to vibration. Nevertheless, the data in Figs. 3.6(*b*), (*c*) and 3.10(*d*) indicate that mechanoreceptors other than the primary spindle ending may be activated by tendon vibration.

Cutaneous mechanoreceptors

Most cutaneous mechanoreceptors respond to vibration (e.g. Ribot-Ciscar, Vedel & Roll, 1989), and it is probable that Ruffini endings in joints do so as well.

Like any mechanical stimulus, vibration of a tendon will spread widely through bone, exciting receptors in skin, muscles (see Chapter 8, p. 344), fascia and joints remote from the site of vibration. This phenomenon has been invoked to explain 'reflex irradiation' in spastic patients (see Lance & De Gail, 1965; Chapter 2, pp. 86, 96).

Contracting muscles

In contracting muscles, fusimotor drive can enhance the spindle response to vibration (Burke *et al.*, 1976b), but contractions may unload spindle endings and thereby decrease the spindle discharge for three reasons. First, the application of the vibrator to the tendon is not exactly the same as in the relaxed state, secondly, the spread of the vibration wave to the muscle belly is altered when the muscle contracts and the tendon stiffens, and thirdly, the contraction may not be associated with a sufficient increase in γ drive to offset these effects. Indeed, if the contraction is a reflex contraction to the vibration (tonic vibration reflex, TVR), unloading is the rule, in human subjects (Burke *et al.*, 1976b) and in the cat (Clark, Matthews & Muir, 1981). These problems are even greater if overt movement occurs at the joint, because movement can displace the vibrator and because the responses of different endings are not modulated identically by the change in length. For example, the response of primary endings is maximal during the stretching phase of passive oscillating movements (Fig. 3.10(*b*)), while that of secondary endings is more statically related to muscle length (Fig. 3.10(*c*); Burke *et al.*, 1976a). Because the response of the primary ending switches off during shortening, while that of the secondary decreases through subharmonics (Fig. 3.10(*b*), (*d*)), there could, paradoxically, be a greater vibration-induced discharge from secondary endings during slow passive muscle shortening. Responses during voluntary movements will not be accurately predictable, particularly if the vibrator is not servo-controlled so that there is a constant force of application to the moving tendon (Cordo *et al.*, 1993). The final discharge pattern will be determined by: (i) the stability of the vibrator, (ii) the sensitivity of the endings to vibration, (iii) the potency of any fusimotor drive directed to the endings (see pp. 133–5), and (iv) whether the movement is eccentric or concentric, slow or rapid, performed against a load or not.

Motor tasks and physiological implications

Reflex reinforcement by remote muscle contraction: the Jendrassik manoeuvre

Remote contractions may be of limited functional significance, but the mechanisms responsible for the widespread reflex enhancement accompanying such contractions have long been a matter of dispute, and the manoeuvre is important in the clinical examination. It was previously thought that performance of the Jendrassik manoeuvre potentiated tendon jerks in uninvolved non-contracting muscles due to widespread activation of dynamic γ motoneurones. Similarly, the reflex potentiation accompanying other alerting stimuli, such as a warning cue, has been attributed to the same mechanism. However, attractive as it may be, this hypothesis is seriously flawed for a number of reasons.

(i) It is based on the belief that the H reflex is not potentiated to the same extent by the reinforcement manoeuvre. In fact, this is not so: tendon jerks and H reflexes of similar size undergo similar potentiation (e.g. Landau & Clare, 1964; Bussel, Morin & Pierrot-Deseilligny, 1978; Zehr & Stein, 1999).

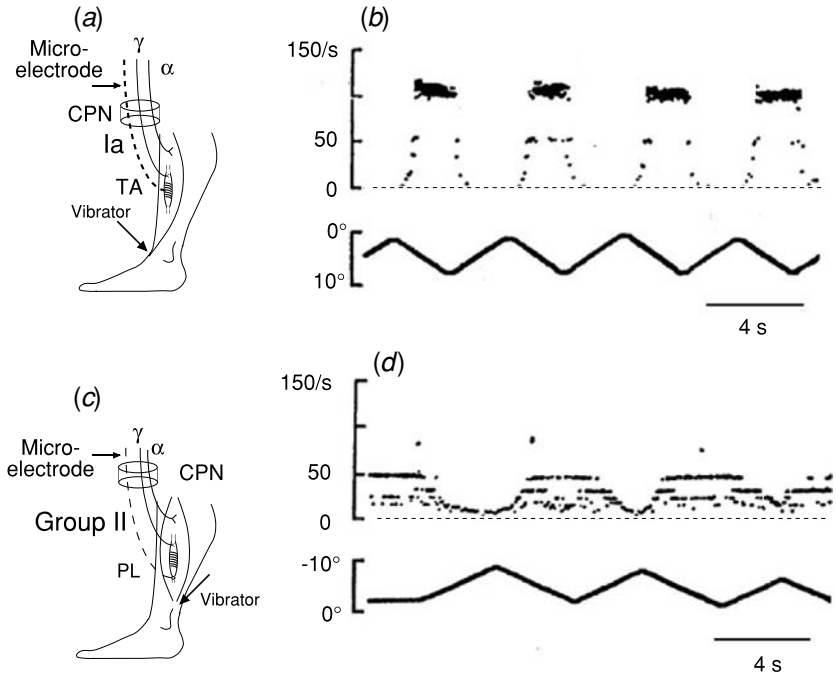


Fig. 3.10. The effects of alternating passive movements on the spindle response to vibration. (*a*), (*c*) Sketches of the experimental paradigm: recording with a microelectrode in the common peroneal nerve (CPN) from a muscle spindle primary ending in tibialis anterior (TA) and from a muscle spindle secondary ending in peroneus longus (PL). (*b*), (*d*) Upper trace: 'instantaneous' frequency plot from the recorded afferent (the dashed horizontal line indicates the absence of discharge of the unit); lower trace: goniometer, stretch is indicated by a downward movement of the goniometer trace (the lower trace in each panel). (*b*) Vibration of the primary ending in TA at 120 Hz produces a 1:1 response during the stretch phases of the passive movement and silence during the shortening phases. (*d*) Vibration of a secondary ending in PL at 100 Hz. The response increases more gradually through subharmonics during the stretching phase to 1:2. With shortening, the response gradually decreases again through subharmonics. Modified from Burke *et al.* (1976a), with permission.

(ii) It is based on the belief that the increased excitability of the motoneurone pool depends on a muscle spindle input from the test muscle. However, the H reflex is still potentiated when the Ia input from the test muscle is blocked by ischaemia (Bussel, Morin & Pierrot-Deseilligny, 1978).

(iii) It ignores the fact that increased background activity in Ia afferents would produce post-activation depression of transmission from those afferents (see Chapter 2, pp. 96–9).

(iv) It assumes that increased dynamic γ drive would be sufficient to potentiate the spindle response to percussion and that this would be sufficient to enhance the discharge of the motoneurone pool, assumptions that have been questioned (see Morgan, Prochazka & Proske, 1984; Wood *et al.*, 1994).

(v) A γ role for reflex reinforcement cannot be demonstrated in studies that have controlled for post-activation depression and the thixotropic properties of muscle spindles (Gregory, Wood & Proske, 2001).

(vi) Many (but not all) recordings from spindle afferents using microneurography have failed to demonstrate that the Jendrassik manoeuvre produces (i) an increased background discharge of muscle spindles; (ii) an increase in their response to stretch; (iii) a change in α–γ balance (see Hagbarth

et al., 1975a; Burke, 1981; Burke, Gandevia & Macefield, 2003; however, see also Burg *et al.*, 1973, 1974; Ribot, Roll & Vedel, 1986; Ribot-Ciscar, Rossi-Durand & Roll, 2000). If a γ mechanism was responsible for the reflex reinforcement, one would expect the effects on spindle activity to be large, not small, not restricted to a few afferents, and one would expect all studies to have no difficulty demonstrating this same finding.

Some studies have demonstrated that there are central changes in the gain of the tendon jerk, changes which, together with the sensitivity of the H reflex (see above), indicate that the reflex enhancement involves central processes (e.g. Burke, McKeon & Skuse, 1981b). This is illustrated in Fig. 3.11 with data from a single subject. Panel (*b*) plots the size of the muscle afferent volley from soleus against the intensity of tendon percussion. The round symbols represent data when the subject was at rest and the triangles when the subject performed the Jendrassik manoeuvre. There is no difference in the relationships. However, the manoeuvres were effective reinforcing manoeuvres because a tendon jerk occurred (filled symbols) with weaker percussion and a lesser afferent volley. Panel (*c*) plots, for the same data, the size of the reflex response against the intensity of the afferent volley. When performing the Jendrassik manoeuvre (triangles), the reflex response was obtained at lower threshold than at rest (circles) and was larger for any given size of afferent volley.

The question then arises about which spinal circuits contribute to the reflex enhancement. Decreased presynaptic inhibition of Ia terminals has been suggested (Zehr & Stein, 1999), but, if anything, presynaptic inhibition of Ia terminals to soleus motoneurones is slightly increased at the onset of a brisk ECR contraction (Meunier & Morin, 1989; Chapter 8, p. 362). Teeth clenching has been reported to enhance the H reflexes of both soleus and tibialis anterior (as might be expected for a reinforcement manoeuvre) but also to decrease peroneal-induced reciprocal Ia inhibition of the soleus H reflex (Takada *et al.*, 2000; Chapter 5, p. 227). However, reciprocal Ia inhibition is only one of a number of circuits that could be involved in the reflex potentiation due to a remote muscle contraction.

Effects of voluntary effort on fusimotor drive to the contracting muscle

Increased spindle discharge during contraction

Evidence for activation of γ motoneurones

When movement is prevented so that contractions are quasi-isometric, there is, during a deliberate voluntary contraction, an increase in the discharge of active endings (Fig. 3.5(*d*)), activation of previously silent spindle endings (Fig. 3.7(*b*)), and an increase in overall muscle spindle discharge (Hagbarth & Vallbo, 1968; Vallbo, 1971, 1974; Vallbo *et al.*, 1979; Edin & Vallbo, 1990b). As mentioned above (p. 117), pressure block experiments suggest that this increase in spindle discharge is mediated, at least in part, by the activation of γ motoneurones (Burke, Hagbarth & Skuse, 1979). The unloading reflex provides evidence that muscle afferent feedback (presumably mainly of spindle origin) contributes to the maintenance of α motor firing during a tonic isometric contraction. When a muscle is pulling against a fixed resistance that suddenly gives way, a silent period appears in the EMG of the contracting muscle at a latency appropriate for the withdrawal of Ia afferent support to the active motoneurones (see Hagbarth, 1967). Thus, overall the fusimotor-driven inflow from primary and secondary endings during a voluntary contraction has an autogenetic excitatory effect at spinal level.

Spindle acceleration after the onset of EMG

With brisk phasic contractions, the increase in spindle discharge follows the appearance of EMG in the contracting muscle by up to 50 ms (Vallbo, 1971), evidence that is inconsistent with the follow-up length servo hypothesis (Merton, 1951, 1953; see Matthews, 1972). Attempts to produce consistent spindle activation in advance of EMG by, e.g. providing a warning cue, by using biofeedback training or in learning paradigms, have been unsuccessful (Burke, McKeon, Skuse & Westerman, 1980; Gandevia & Burke, 1985; Al-Falahe & Vallbo, 1988;

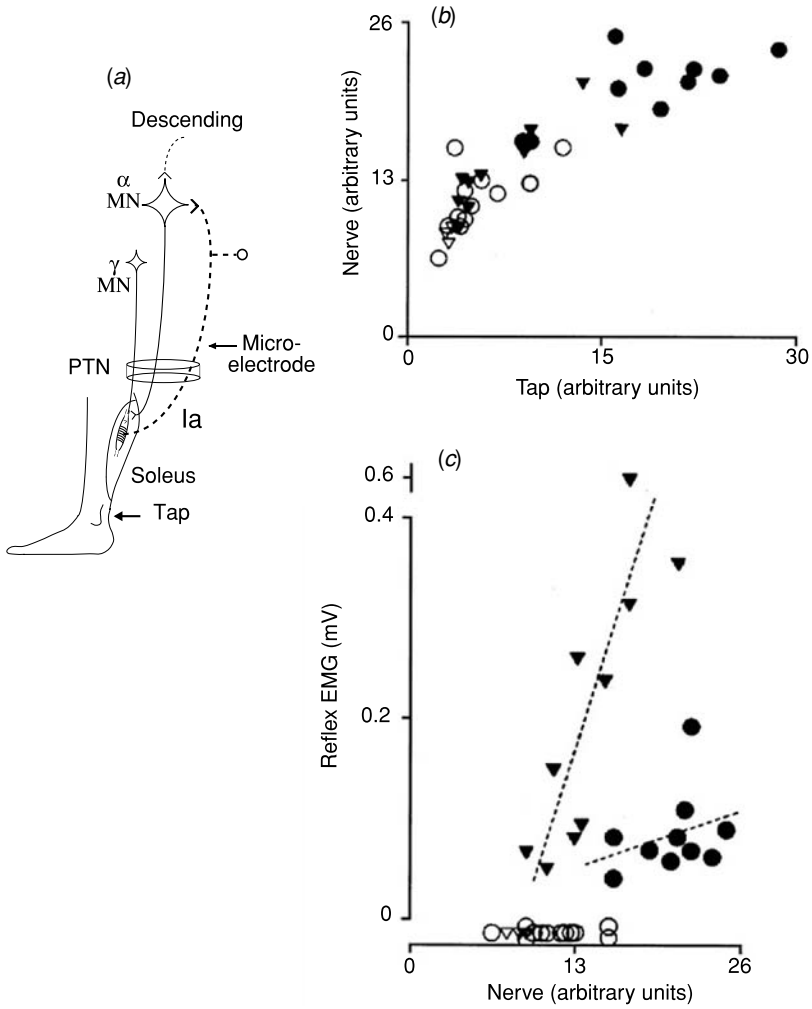


Fig. 3.11. Effects of the Jendrassik manoeuvre on muscle afferent discharge and the size of the tendon jerk. (*a*) Sketch of the presumed pathways. During the Jendrassik manoeuvre, there is a descending excitatory influence that enhances reflex transmission to α motoneurones (MN), but not (or minimally) to γ MNs. (*b*) Relationship between intensity of tendon percussion (in arbitrary units) and amplitude of the rectified and smoothed neural afferent responses to percussion (also in arbitrary units) for one subject. (Circles = sequences when the subject was relaxed; triangles = those for which the subject performed reinforcement manoeuvres; filled symbols = tendon taps that produced a tendon jerk; open symbols = no reflex response.) (*c*) Relationship between amplitude of the rectified and smoothed afferent volley and peak-to-peak amplitude of the resulting reflex EMG bursts for the data in (*b*). Taps that failed to produce a tendon jerk are shown as open symbols alongside the appropriate afferent volley size. Dashed lines are linear regression lines for the taps that produced reflex EMG. The data obtained during reinforcement manoeuvres (filled triangles) differ significantly ($P < 0.01$) from those obtained during relaxation (filled circles). From Burke, McKeon & Skuse (1981b), with permission.

Al-Falahe, Nagaoka & Vallbo, 1990a,b; Vallbo & Al-Falahe, 1990).

Spindle activation

The degree of spindle activation increases with the degree of effort (Vallbo, 1974) and occurs only or predominantly for spindles in the contracting muscle. Spindles in nearby inactive synergists may be unloaded (Vallbo, 1973, 1974; Burke *et al.*, 1976b; Fig. 3.5(*e*)). Unloading, as in Fig. 3.5(*e*), would not be expected if reinforcement manoeuvres produced widespread activation of γ motoneurones sufficient to enhance the muscle spindle discharge from inactive muscles (see above). The discharge of muscle spindle endings in the contracting muscle declines during long-lasting contractions by about one-third over 60 s, even when the presence of increasing EMG activity indicates some fatigue (Fig. 3.7(*b*), (*c*); Macefield *et al.*, 1991). This indicates that the fusimotor system has a limited role in compensating for muscle fatigue, contrary to early suggestions (e.g. Merton, 1951, 1953).

Concentric and eccentric contractions

The efficacy of γ drive in activating spindle endings during a voluntary contraction depends on whether the contraction produces changes in length, that shorten or stretch the spindle (Burke, Hagbarth & Löfstedt, 1978a,b). Shortening (in a 'concentric' contraction) will unload spindle endings, and an increase in spindle discharge will then occur only in slow contractions or when the contracting muscle is working against a load so that greater effort is required to perform the same movement. During unloaded phasic shortening contractions, it is likely that muscle spindle endings in the contracting muscle will be silenced, and any perceptual or reflex cues will come from other receptors, particularly spindles in the antagonist (see Ribot-Ciscar & Roll, 1998). Spindle endings in the contracting muscle may discharge, but this occurs after the appearance of the first EMG potentials and before the limb has actually commenced moving. When a contracting muscle is shortening against a load, the discharge pattern becomes less modulated by the change in muscle length, and spindle endings may behave less like length-transducing receptors and more like tension-transducing organs (Burke, Hagbarth & Löfstedt, 1978b). During an 'eccentric' contraction, the spindle discharge is much higher than when the relaxed muscle is subjected to passive stretch of similar amplitude and velocity because the fusimotor effects are potentiated by stretch. More complex responses are seen with two-dimensional limb movements. Again, these responses come essentially from the stretched antagonistic muscles, and they correlate with the direction of vibration-induced illusions of movement (Bergenheim, Ribot-Ciscar & Roll, 2000; Roll, Bergenheim & Ribot-Ciscar, 2000). Co-contractions may involve greater fusimotor drive to the contracting muscles than occurs during isolated contractions producing equivalent EMG (Nielsen *et al.*, 1994).

Primary and secondary spindle endings

'Dynamic' and 'static' endings, presumably primary and secondary endings respectively, behave in a qualitatively similar manner in the different contractions tested: shortening and lengthening contractions, with or without additional load (Burke, Hagbarth & Löfstedt, 1978b).

Fusimotor activity when reliant on proprioceptive feedback during standing

When a subject is standing freely on a horizontal platform, there is little or no EMG activity in the pretibial muscles, there is a poorly sustained spindle afferent activity, and manoeuvres that increase the reliance on the proprioceptive feedback do not significantly alter the fusimotor drive in the absence of muscle contraction. However, when the receptor-bearing muscles are activated tonically or phasically to maintain balance their contraction is accompanied by an increase in fusimotor drive sufficient to affect spindle discharge (Aniss *et al.*, 1990b).

Activation of fusimotor neurones during voluntary effort

Static fusimotor motoneurones

The discharge of both primary and secondary spindle endings increases during voluntary contractions (Figs. 3.7(*b*), (*c*) and 3.5(*d*), respectively), and this constitutes evidence that the increase in γ drive involves γ_s neurones. Further evidence indicating a γ_s action consists of an increase in static sensitivity, a decrease in the dynamic response of primary endings to stretch (though this could be due to a change in the damping effect of the stiffness of muscle and tendon), and a loss of the pause in discharge that primary endings undergo following passive shortening (Vallbo, 1973, 1974; Vallbo *et al.*, 1979). In addition, there is an increase in the variability of spindle discharge, and the appearance of a negative serial correlation between successive interspike intervals (Burke, Skuse & Stuart, 1979), something that is a feature of γ_s drive (see Matthews & Stein, 1969; p. 127).

Dynamic fusimotor motoneurones

There is some evidence that γ_d drive is increased in addition to γ_s (Kakuda & Nagaoka, 1998). However, the study compared the dynamic responses to stretch of spindle endings in relaxed and contracting muscles. The experiments were well controlled, the results appear sound, and the conclusions may well be correct, but it would be wise to retain a reservation in mind because it is difficult to be certain that spindle endings are subjected to identical stimuli when the muscle and tendon are stiff and when they are slack.

Skeleto-fusimotor motoneurones

There is also some evidence that voluntary activity activates β motoneurones in addition to γ motoneurones during wrist extension (Kakuda, Miwa & Nagaoka, 1998). This finding relied on the use of spike-triggered averaging to define an EMG potential closely linked to the afferent spikes, a technique that had previously yielded negative findings (Gandevia, Burke & McKeon, 1986a).

Possible role of the fusimotor system during normal movement

The role of the fusimotor system is still the subject of debate, and it is likely that its importance in the moment-to-moment control of movement differs in the cat and man – in part because of the species differences discussed earlier (see pp. 115–16). The view that some movements can be initiated by first activating γ efferents is now rejected for both species, but the extent to which the fusimotor system provides a necessary support to voluntary contractions has not been clarified. Microneurography has been used for ~35 years, but in this time we have learnt a lot about what the fusimotor system does not do and relatively little about its essential contribution to the control of human movement.

Role of afferent feedback

Is movement possible without afferent feedback?

Movement is possible without any afferent feedback from the contracting muscle. This has been demonstrated in patients with large-fibre sensory neuropathies (Rothwell *et al.*, 1982; Sanes *et al.*, 1985; Cole & Sedgwick, 1992; Gordon, Ghilardi & Ghez, 1995; Ghez, Gordon & Ghilardi, 1995) and in experiments in which the activity of α motor axons was recorded proximal to a complete block of the motor nerve using local anaesthetic (Gandevia *et al.*, 1990, 1993; Macefield *et al.*, 1993). Subjects were still able to activate α motor axons directed to acutely denervated muscles and could voluntarily modulate their firing rates.

Necessity for afferent feedback

However, in the absence of afferent feedback, subjects were unable to maintain a steady discharge of α motoneurones, and the discharge rates in weak,

moderate and strong contractions were less than those reached in control experiments on the same subjects. Clearly, not every aspect of even a simple unperturbed contraction can be programmed centrally. Afferent feedback is also critical when there are unexpected disturbances to movement, such that there is a mismatch between the intended and the achieved movement. Disturbances to the expected movement trajectory may be external (due, e.g. to an obstruction or its release) or internal (due, e.g. to a glitch in the motor programme, tremor or unexpected stiffness of moving parts). Some form of feedback is necessary for skilled movement particularly when in novel circumstances, such as walking over an uneven terrain.

Which feedback?

The above data do not identify whether the necessary feedback is of cutaneous, muscle or joint (or even visual) origin. It is likely that the inputs from all appropriately responding mechanoreceptors are integrated to provide a consistent view of the prevailing circumstances and that all can play a role in shaping the compensatory motor response. The evidence is cogent for cutaneous and muscle afferents, but less convincing for human joint afferents, which seem to act more as multi-directional stress detectors: few joint afferents are capable of encoding joint movement throughout the physiological range (Burke, Gandevia & Macefield, 1988). Much information about the role of different afferent inputs has come from removing individual afferent cues by blocking specific nerves or from artificially boosting the impulse traffic in a selected group of afferents (e.g. by using vibration to activate muscle spindles). It is important to remember that these manoeuvres create an artificial environment and could give a distorted view of the importance of different afferent inputs. For example, exclusion one by one of the cues contributing to the control of upright quiet stance may be compensated for in normal subjects with a minimal increase in body sway (see Chapter 11, p. 536). This does not mean that the excluded cues were not important or that there was redundancy. It merely indicates that the nervous system will always compensate as well as it can before the system breaks down.

Speculations on the functional role of γ drive in various motor tasks

Accepting that muscle afferent feedback is critical to normal motor control and to movement-related sensations, it is still not clear the extent to which it is important to retain an ability to adjust muscle spindle responsiveness and, in particular, an ability to make such adjustments independently of the drive on α motoneurones. Some speculations are therefore in order.

All movements are learnt

While this book focuses on spinal circuitry and its role in movement, it should be remembered that muscle spindles are sensory receptors, that they project to higher centres including the sensorimotor cortex, and that they contribute significantly to kinaesthetic sensations. It is likely that the importance of γ drive involves more than its spinal reflex role. γ drive is likely to be critical for the maintenance of a coherent input to the supraspinal centres involved in formulating and crafting the motor programme.

Lower-limb muscles

Contractions of lower-limb muscles are usually weight-bearing and often cyclical, often eccentric. Normal gait is relatively slow, so that many muscles undergo slow loaded contractions that may be concentric or eccentric. These are circumstances when the co-activated γ drive can represent a powerful input to muscle spindle endings (see Chapter 11, p. 544).

Hand and forearm muscles

The muscles of the hand and forearm are required to perform discrete manual tasks, while more proximal

upper-limb muscles have a load-bearing and limb-positioning function (see Chapter 11, pp. 521–2). Skilled tasks such as playing the piano involve rapid essentially unloaded movements in which afferent-induced changes in motoneurone discharge could lag far behind the phase of movement that generated the feedback. Reflex feedback would have deleterious effects, unless it was based on prediction rather than actual performance. It would be sensible if such movements were performed under feedforward control, because feedback could be disruptive. Under these circumstances, the limited efficacy of γ drive in maintaining spindle discharge when movement is rapid and unloaded is not inappropriate: indeed, for it to be otherwise could do more harm than good. Awareness of limb position and movement would then depend more on the activity in stretched antagonistic muscles than in the actively contracting muscles (see p. 135).

Motor learning

When learning a discrete motor task, movements are slower and often involve co-contraction of antagonists to brace the joint. Such contractions are associated with an effective increase in γ drive to the contracting muscles, and there is evidence suggesting even greater fusimotor drive to co-contracting muscles (Nielsen *et al.*, 1994). The feedback from spindle endings would be important, not only for smoothing the movement trajectory but also for providing the sensory cues that allow a more refined voluntary drive. Setting up and maintaining a motor program depends on detailed information from both the re-afferent cues activated by the movement and the spinal circuitry ('the lower motor centres') fed by these cues (see Chapter 11, pp. 530–1). It is not unreasonable to postulate that γ drive is important in motor learning. As skill is acquired, its importance would lessen, in parallel with a change in movement performance that decreases the efficacy of the γ drive. Unfortunately, as mentioned above (p. 133), attempts by Vallbo's group to demonstrate that γ drive plays an important role in the acquisition of the skill necessary to perform an initially unfamiliar manual task have been unsuccessful. However, it is possible that this was due to the difficulty of designing a task that would test the hypothesis but still allow full control over experimental variables, and the hypothesis remains attractive.

Cutaneous control of gamma drive

Cutaneous reflex control of γ drive is unlikely to play a significant role in the moment-to-moment control of cyclical movements because of the extra lags in the reflex pathway. Cutaneous (and joint) afferent inputs to γ motoneurones are more likely to play a role in setting the operating level of the system, such that it is more responsive to changes in supraspinal drives.

Separate control of γ_d and γ_s

That there is separate control of γ_d and γ_s suggests that the nervous system relies on and can distinguish between the static and dynamic components of muscle spindle afferent discharge. As discussed above, the available evidence for human subjects does not favour a role for γ_d in alerting responses or the prepar-zation for movement. It is likely that the role of γ_d is to maintain the dynamic responsiveness of primary spindle endings so that they can signal irregularities in movement, and appropriately adjust the timing of motor unit discharge when there is a mismatch between the intended and the achieved movement (see pp. 136–7). However, in human experiments, it is technically difficult to infer γ_d activity from muscle spindle discharge, and these views must be advanced with caution. On the other hand, γ_s could function to provide an increase in background discharge and thereby supportive excitation to active muscles.

Studies in patients and clinical implications

Four decades ago, it was popularly held that disturbances of muscle tone occurred because of

overactivity of γ motoneurones (spasticity, rigidity) or their underactivity (hypotonia). The basis for these views has been discussed above, and have been the subject of a number of reviews (e.g. Burke, 1983, 1988; Van der Meche & Van Gijn, 1986). Intellectually satisfying at the time, the γ hypothesis of motor disturbance corresponded with the view that some movements could be driven through the fusimotor action, like a follow-up servo.

Potentially, fusimotor dysfunction in patients with motor disturbances could include the following.

Increased background fusimotor drive

In spasticity, heightened γ_d drive might result in tendon jerk hyperreflexia and a spastic increase in muscle tone, with loss of dexterity because of the resulting interference with voluntary movement. In parkinsonian rigidity, heightened γ_s drive might produce the more plastic increase in tone typical of rigidity.

Disordered fusimotor activation

In attempts to contract paretic, spastic or rigid muscles, this might lead to an inappropriate level of spindle activity for EMG (or effort), and thereby to disturbed reflex support to the contraction.

Disinhibited cutaneo-fusimotor reflexes

Reflex disinhibition might lead to a fusimotor contribution to spasms and spasticity, particularly in spinal patients, in whom these manifestations are more prominent.

Though the database of spindle recordings from such patients is restricted, there are cogent arguments against the view that fusimotor dysfunction drives these motor disturbances. This conclusion is consistent with other data suggesting that merely increasing spindle discharge with, e.g. vibration, does not produce spasticity or rigidity (Matthews, 1976; Burke, 1983).

Spasticity

Hemiplegia

Absence of γ hyperactivity

Some early recordings based on the timing of spindle discharge on the falling phase of electrically evoked twitch contractions led Szumski *et al.* (1974) to suggest that there was heightened background γ_d activity in spastic patients. However, it is likely that these findings were due to changes in the twitch properties of triceps surae rather than fusimotor action. Recordings have been made from spindle afferents in triceps surae of two hemiplegic patients (Hagbarth, Wallin & Löfstedt, 1973) and in the forearm extensor muscles of 14 hemiplegic patients (Wilson *et al.*, 1999a). In neither study was the background discharge or the response to stretch of spindle endings in relaxed muscles greater than those in control subjects. In addition, there was no evidence of 'inappropriate' spindle behaviour (i.e. changes in discharge that could not be correlated with a change in muscle length or the development of EMG in the receptor-bearing muscles), and there was no evidence that reinforcement manoeuvres could activate spindle endings without causing contraction of the relevant muscle. Most of the patients suffered from tendon jerk hyperreflexia, with or without an obvious increase in muscle tone, and these findings therefore support the view that spasticity occurs through mechanisms largely independent of the level of γ drive (Chapter 12; see also Burke, 1983, 1988). These results argue against a contribution of γ overactivity to spasticity. However, it would be imprudent to discard completely heightened fusimotor excitability as a possible contributing factor to spasticity in stroke patients: (i) only in two patients were triceps surae afferents studied; (ii) in the upper limb, spasticity is preferentially distributed on forearm flexors, not extensors (see Chapter 12, pp. 564–5).

Absence of α/γ co-activation in clonus

Spindle activity has been recorded during ankle clonus in patients with hemiplegic spasticity

(Hagbarth *et al.*, 1975c). Spindles were activated during the stretching phase of the oscillating clonic movement, and their activation appeared to drive the next clonic contraction, presumably through the same spinal pathways that underlie the tendon jerk reflex. The contraction itself was not accompanied by spindle activation, though this was seen when normal subjects made rapid alternating contractions mimicking clonus (Hagbarth, Wallin & Löfstedt, 1975b). This led Hagbarth and colleagues to suggest that proprioceptive spinal reflexes do not involve significant activation of γ motoneurones in addition to α motoneurones, i.e. that these reflexes constituted an exception to the principle of α/γ co-activation. This view was supported by similar findings with the tonic vibration reflex (Burke *et al.*, 1976b), and is consistent with relatively weak (or absent) excitatory projections of group Ia afferents onto γ motoneurones.

Fusimotor dysfunction probably contributes little to the motor deficit

A hypothesis of the study of Wilson *et al.* (1999a) had been that the corticospinal lesion might disrupt the balance normally present between the α and γ drives to a voluntarily contracting muscle, but they found no evidence of greater ease or greater difficulty in activating spindle endings voluntarily in paretic muscles. Disappointingly, there was also no evidence for disinhibition of cutaneous reflex pathways to γ motoneurones.

Spinal spasticity

Reflex activation of γ motoneurones

There are, as yet, no published reports of recordings from spindle endings in patients with spinal spasticity, though intuitively one might expect there to be disinhibition of reflex pathways acting on γ and β motoneurones, such that normally innocuous stimuli such as stroking the skin would cause a heightened spindle discharge. If this proved to be the case, it is possible that the skin, joint, bladder and bowel complications of paraplegia would result in a steady afferent input to γ motoneurones in such patients, producing widespread γ activity even in the absence of EMG activity. It remains to be proven whether heightened γ drive contributes to spinal spasticity and to flexor and extensor spasms.

Possible group II excitation of γ motoneurones

In patients with spinal cord lesions, there is evidence that increased group II excitation might be an important spinal mechanism underlying spasticity (cf. Chapter 12, p. 581). The disinhibition of pathways mediating group II excitation is probably due to damage to descending monoaminergic pathways that gate the transmission of group II excitation. The absence of a correlation between the increased electrically-induced group II excitation and the stretch reflex exaggeration could be because the former does not test the projections of group II-activated lumbar propriospinal neurones to γ motoneurones (see Chapter 7, p. 325). Reflex activation of γ motoneurones because of disinhibition of group II pathways deserves to be mentioned separately to disinhibition of cutaneous pathways to γ motoneurones (cf. above) because the former would cause positive feedback if the target neurones were γ_s.

Parkinson's disease

The data are particularly sparse for Parkinson's disease: multi-unit recordings that have been presumed to be dominated by muscle spindle activity (Hagbarth, Hongell & Wallin, 1970; Wallin, Hongell & Hagbarth, 1973), a subsequent re-analysis of precisely the same data (Burke, Hagbarth & Wallin, 1977), and some single-unit recordings during parkinsonian tremor (Hagbarth *et al.*, 1975c).

Rigidity

In these recordings, fluctuations in rigidity were associated with parallel fluctuations in muscle

afferent activity and EMG, but with the latter leading the former. Voluntary efforts were associated with the increase in muscle afferent discharge expected from studies in normal subjects. In other words, there was no evidence of selective or disproportionate γ drive to spindle endings in these patients, and no evidence that the rigidity was driven by enhanced fusimotor drive. However, as in the case of spasticity, it would be imprudent to discard completely the possibility that fusimotor neurones play a role in parkinsonian rigidity. Any enhanced γ motoneurone discharge need not result from enhanced descending drive onto fusimotor neurones: it could also result from abnormal gating of the transmission of group II excitation to γ motoneurones (see Chapter 12, p. 584). Clarification of this issue requires detailed studies under identical conditions of the responses of single spindle afferents in patients and control subjects.

Parkinsonian resting tremor

In parkinsonian resting tremor, muscle spindles discharged during two phases: during the shortening phase of the tremor cycle, with the EMG burst, and again in the opposite phase of the cycle as the endings were stretched (Hagbarth *et al.*, 1975c). This pattern is similar to that seen with voluntary alternating movements (Hagbarth, Wallin & Löfstedt, 1975b) but not clonus (Hagbarth *et al.*, 1975c). Such behaviour suggests that the supraspinal activity driving the resting tremor of Parkinson's disease activates both α and γ motoneurones.

Conclusions

The sensitivity of the muscle spindle

The muscle spindle is a more sensitive transducer of changes in muscle length and in the derivatives of length than could be constructed by humans or fixed to the limbs of volunteers. This complicates experiments that use muscle spindle activity as a measure of γ efferent drive. Evidence for selective activation of γ motoneurones should be viewed with an open mind, scepticism being warranted when the data are based on only an occasional recording from an afferent that could have been misclassified.

Background γ efferent drive to relaxed muscles

There is considerable evidence suggesting that there is little activity in static γ motoneurones innervating resting muscles and, if there is any, it is insufficient to alter muscle spindle discharge materially. The tendon jerk does not require that spindle endings be sensitised by γ_d drive to be sufficiently responsive that percussion evokes a tendon jerk. Regardless of whether reinforcement manoeuvres can activate some γ_d motoneurones, the reflex potentiation produced by the Jendrassik manoeuvre or in response to some other alerting stimulus is not mediated by selective activation of γ_d motoneurones.

γ efferent activation by corticospinal drives

Corticospinal drives, whether associated with voluntary effort or produced by transcranial magnetic or electrical stimulation of the motor cortex, can increase the discharge of spindle endings due, primarily, to activation of γ motoneurones (but also due to activation of β motoneurones), largely in parallel with α motoneurones. In voluntary contractions, the spindle activation parallels the effort put into the contraction, and an effective increase in γ drive is directed only to the contracting muscle. The increase in γ drive is translated into an enhanced spindle discharge when the contraction is near-isometric. The γ drive is even more effective when the contracting muscle is lengthening, and is much less so if the muscle is shortening. Increased spindle feedback accompanies shortening contractions only when the contractions are relatively slow or the muscle is working against a load. There will probably be little increase in spindle feedback from the contracting muscle in unloaded rapid shortening movements, i.e. proprioceptive cues probably then come from the stretched antagonists.

γ efferent activity in patients with motor disturbances

There are few studies in patients, but these do not support the view that an abnormality of γ motoneurone activity is the primary disturbance responsible for the clinical manifestations. This leads to the conclusion that, if there is an abnormality of fusimotor function in patients, it is unlikely to represent a causal association.

Résumé

Background from animal experiments

The number of spindles in different muscles varies from <50 for intrinsic muscles of the hand to >1000 for quadriceps femoris, but the density is higher in the former. Muscle spindles contain modified muscle fibres (intrafusal fibres). The bag_1 intrafusal fibre is innervated by dynamic fusimotor (γ_d) axons, and the bag_2 and chain fibres by static fusimotor (γ_s) axons. There are two types of sensory endings: primary endings wrap around both the bag and chain fibres, and are sensitive to both the static and dynamic components of muscle stretch and to high-frequency vibration; secondary endings are located on chain fibres and the static bag_2 fibre, are sensitive to the static component of stretch, are less sensitive to the dynamic component of stretch, and are much less sensitive to vibration. The primary ending gives rise to a single large group Ia afferent, while the secondary endings give rise to several group II afferent axons per spindle. The properties of the bag_2 fibre largely determine both the background firing rate of Ia afferents and the dynamic response to stretch of passive spindles. The fusimotor-induced enhancement of the resting dynamic responsiveness depends on activation of bag_1 fibre. The static and dynamic sensitivity of muscle spindle primary endings can be controlled independently by γ_s and γ_d, respectively. There are different supraspinal projections onto α and γ motoneurones, but there are also striking parallels, and this led to the suggestion that voluntary movement involved an α-γ linkage (or co-activation), a suggestion supported by microneurographic studies. β (skeleto-fusimotor) efferents innervate both intra- and extra-fusal muscle fibres.

Methodology

Discredited methods

(i) There is now substantial evidence against the view that comparisons of the H reflex and tendon jerk can be used to provide a reliable measure of fusimotor activity. While the tendon jerk and the H reflex are both dependent on the monosynaptic excitation from homonymous Ia afferents, the H reflex bypasses the muscle spindle while the tendon jerk does not. However, the two reflexes differ in so many other respects that comparison of them as a measure of fusimotor function is invalid.

(ii) Local anaesthetic nerve blocks: because of the large size of human nerves, diffusion of local anaesthetic through perineural and fascicular tissues results in non-selective effects because of involvement of closer rather than smaller axons. Microneurographic studies have shown that anaesthetic blocks are extremely difficult to control and cannot be used as a technique for selective denervation of muscle spindles.

Acceptable methods

(i) Microneurography is the most reliable technique for determining the level of fusimotor activity. The microelectrode is inserted manually through the skin into the peripheral nerve trunk. When the tip is within an appropriate fascicle, tapping on the appropriate muscle tendon will activate mechanoreceptors, and auditory feedback is then used to make further small adjustments of the electrode to bring the desired neural activity into focus. Criteria to identify spindle endings and Golgi tendon organs include the response to a twitch contraction of the

receptor-bearing muscle, the presence or absence of background activity, the regularity of any background discharge, behaviour during voluntary contractions and on abrupt relaxation, and the responses to stretch and vibration. There is a bias in microneurographic recordings towards axons that are large and have a background discharge. Muscle spindle endings are extremely sensitive to minute perturbations. Small disturbance to the spindle's environment within the muscle may not be apparent to inspection. EMG electrodes and force and length transducers must be used to be certain that the receptor-bearing muscle is truly relaxed when seeking evidence for selective activation of γ motoneurones.

(ii) Studies that exploit the thixotropic properties of intrafusal fibres. In human subjects, voluntary activity can produce long-lasting enhancements in spindle discharge. These changes may persist long after the contraction and are due to the thixotropic properties of the intrafusal fibres that contracted under γ drive during the voluntary contraction. This behaviour can be exploited to study fusimotor action in human subjects indirectly. The thixotropic properties of intrafusal muscle fibres can distort spindle discharge and must be considered when interpreting unexpected changes in spindle discharge, reflex behaviour or perception.

Critique of the tests to study fusimotor drive

Microneurography

Conclusions about fusimotor activity from recordings of muscle spindle discharge are valid only if all disturbances to the spindle are rigidly controlled, and this is rarely possible in human subjects; the identification of an axonal recording must be beyond dispute, particularly when the conclusions are based on only a couple of 'positive' findings from a larger sample; the movement repertoire that can be studied is quite limited; the technique is traumatic and technically demanding.

Studies of intrafusal thixotropy

These studies can allow stronger contractions to be assessed and can be of value in patients for assessing fusimotor activity. However, the technique is indirect, and a complicating factor is that extrafusal muscle fibres also display thixotropic behaviour.

Organisation and pattern of connections

Background fusimotor drive

Human spindle endings behave as if passive receptors without static fusimotor drive in the relaxed state. There may be some background γ_d activity. Firing rates are much lower and responses to stretch smaller than in the cat, and the regularity of discharge is similar to that of de-efferented feline endings. In addition, de-efferenting spindles does not alter the muscle spindle behaviour. This suggests a very low level of γ drive, insufficient to affect spindle discharge materially. In addition, the responses to muscle stretch or to tendon percussion do not change in relaxed muscle when subjects perform reinforcement manoeuvres, are provided with alerting stimuli or anticipate the need to contract the test muscle, provided that the receptor-bearing muscle remains relaxed.

Effects of cutaneous afferents on fusimotor neurones

Evidence for reflex activation of γ motoneurones has been found for human lower limb muscles, but only when subjects were standing without support. This finding suggests that fusimotor reflexes may be task-dependent, active when performing an appropriate motor task. In the relaxed forearm extensor muscles, such reflexes may be active even at rest. There may be some background γ_d drive to the resting forearm muscles.

Corticospinal volleys

Single transcranial magnetic or electrical stimuli can alter the discharge of muscles spindles, presumably through effects on γ and probably β motoneurones. However, an effective γ discharge cannot be generated without discharging α motoneurones and producing EMG activity in the test muscle.

Effects of muscle vibration on human mechanoreceptors

When applied transversely to a muscle tendon of an intact subject, vibration is usually not selective for muscle spindle primary endings in the vibrated muscle. The majority of human primary endings respond vigorously to tendon vibration, though often at subharmonics of the vibration frequency, particularly if the amplitude of vibration is small. Human secondary endings may respond to vibration, discharging at high subharmonics of the vibration frequency. Some tendon organs can respond to tendon vibration in relaxed muscles and many probably do so during voluntary contractions. Most cutaneous mechanoreceptors respond to vibration, and it is probable that Ruffini endings in joints do so as well. Like any mechanical stimulus, vibration of a tendon will spread widely through bone, exciting receptors in skin, muscles, fascia and joints remote from the site of vibration. In contracting muscles, fusimotor drive can enhance the spindle response to vibration, but the contraction itself may unload the ending and thereby decrease the spindle discharge.

Motor tasks and physiological implications

Reinforcement of tendon jerks by remote muscle contraction

Performance of the Jendrassik manoeuvre potentiates tendon jerks in uninvolved non-contracting muscles, but there is now cogent evidence that this is not due to widespread activation of γ_d motoneurones. There are central changes in the gain of the tendon jerk, changes which, together with the fact that the H reflex is also potentiated by the manoeuvre, indicate that the reflex enhancement involves central processes.

Effects of voluntary effort on fusimotor drive to the contracting muscle

(i) Deliberate voluntary contractions increase the discharge of primary and secondary spindle endings due, at least in part, to the activation of γ motoneurones. This afferent inflow has an overall autogenetic excitatory effect at spinal level and contributes to maintaining the firing of α motoneurones. It increases with the degree of effort but only or predominantly for spindles in the contracting muscle. It has a limited role in compensating for muscle fatigue.

(ii) The increase in spindle discharge follows the appearance of EMG in the contracting muscle. Attempts to produce consistent spindle activation in advance of EMG by, e.g. providing a warning cue, by using biofeedback training or in learning paradigms, have been unsuccessful.

(iii) The efficacy of γ drive in activating spindle endings depends on whether the contraction produces changes in length of the spindle. Shortening (as in a concentric contraction) unloads spindle endings, and an increase in spindle discharge occurs only in slow contractions or when greater effort is required to perform the same movement. There will probably be little increase in spindle feedback from the contracting muscle in unloaded rapid shortening movements and it is then likely that proprioceptive cues come from stretched antagonists. Stretching a contracting muscle (an eccentric contraction) greatly enhances any fusimotor effect on spindle discharge. There is some evidence that voluntary activity activates β motoneurones in addition to γ motoneurones, and that γ_d drive is increased in addition to γ_s.

(iv) The exact role of the fusimotor system in normal motor control remains speculative. However, it is possible that the γ-driven feedback from muscle spindles plays an important role in learning motor tasks.

Changes in fusimotor activity in patients

There are cogent arguments against the view that fusimotor dysfunction drives motor disturbances, but the database of spindle recordings from patients is restricted.

Spasticity

No abnormal spindle behaviour could be identified for spindle afferents from triceps surae and the forearm extensor muscles of patients with hemiplegia. These findings support the view that spasticity in stroke patients occurs through mechanisms largely independent of the level of γ drive. During ankle clonus, spindles are activated during the stretching phase of the oscillating clonic movement, and their activation drives the next clonic contraction. This suggests that spinal proprioceptive reflexes do not involve significant activation of γ motoneurones in addition to α motoneurones, i.e. that these reflexes are an exception to the principle of α/γ co-activation. There are, as yet, no published reports of recordings from spindle endings in patients with spinal spasticity, but the possibility exists that reflex activation of γ motoneurones by, e.g. cutaneous afferents and group II muscle afferents, contributes to the reflex disturbances of these patients.

Parkinson's disease

The data consist of multi-unit recordings, presumed to be dominated by muscle spindle activity and some single-unit recordings during parkinsonian tremor. These have revealed no evidence of selective or disproportionately increased γ drive in these patients, but the question needs to be addressed quantitatively using a large number of single unit recordings from identified afferents. In parkinsonian resting tremor, spindle discharge occurs in two phases: during the shortening phase of the tremor cycle, with the EMG burst, and again as the endings were stretched, a pattern similar to that seen with voluntary alternating movements but not clonus.

REFERENCES

Al-Falahe, N. A. & Vallbo, Å. B. (1988). Role of the human fusimotor system in a motor adaptation task. *Journal of Physiology (London)*, **401**, 77–95.

Al-Falahe, N. A., Nagaoka, M. & Vallbo, Å. B. (1990a). Lack of fusimotor modulation in a motor adaptation task in man. *Acta Physiologica Scandinavica*, **140**, 23–30.

(1990b). Response profiles of human muscle afferents during active finger movements. *Brain*, **113**, 325–46.

Aniss, A. M., Gandevia, S. C. & Burke, D. (1988). Reflex changes in muscle spindle discharge during a voluntary contraction. *Journal of Neurophysiology*, **59**, 908–21.

Aniss, A. M., Diener, H. C., Hore, J., Burke, D. & Gandevia, S. C. (1990a). Reflex activation of muscle spindles in human pretibial muscles during standing. *Journal of Neurophysiology*, **64**, 671–9.

Aniss, A. M., Diener, H. C., Hore, J., Gandevia, S. C. & Burke, D. (1990b). Behavior of human muscle receptors when reliant on proprioceptive feedback during standing. *Journal of Neurophysiology*, **64**, 661–70.

Bergenheim, M., Ribot-Ciscar, E. & Roll, J. P. (2000). Proprioceptive population coding of two-dimensional limb movements in humans: I. Muscle spindle feedback during spatially oriented movements. *Experimental Brain Research*, **134**, 301–10.

Bessou, P., Emonet-Dénand, F. & Laporte, Y. (1965). Motor fibres innervating extrafusal and intrafusal muscle fibres in the cat. *Journal of Physiology (London)*, **180**, 649–72.

Brown, M. C., Goodwin, G. M. & Matthews, P. B. C. (1969). After-effects of fusimotor stimulation on the response of muscle spindle primary afferent endings. *Journal of Physiology (London)*, **205**, 677–94.

Burg, D., Szumski, A. J., Struppler, A. & Velho, F. (1973). Afferent and efferent activation of human muscle receptors involved in reflex and voluntary contraction. *Experimental Neurology*, **41**, 754–68.

(1974). Assessment of fusimotor contribution to reflex reinforcement in humans. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 1012–21.

Burke, D. (1981). The activity of human muscle spindle endings in normal motor behavior. In *International Review of Physiology*, vol. 25, *Neurophysiology IV*, ed. R. Porter, pp. 91–126. Baltimore: University Park Press.

(1983). Critical examination of the case for or against fusimotor involvement in disorders of muscle tone. In *Advances in Neurology*, vol. 39, *Motor Control Mechanisms in Health*

and Disease, ed. J. E. Desmedt, pp. 133–50. New York: Raven Press.

(1988). Spasticity as an adaptation to pyramidal tract injury. In *Advances in Neurology*, vol. 47, *Functional Recovery in Neurological Disease*, ed. S. G. Waxman, pp. 401–23. New York: Raven Press.

Burke, D. & Gandevia, S. C. (1992). Selective activation of human fusimotor neurons innervating human tibialis anterior. In *Muscle Afferents and Spinal Control of Movement*, ed. L. Jami, E. Pierrot-Deseilligny & D. Zytnicki, pp. 151–6. Oxford: Pergamon Press.

Burke, D., Hagbarth, K.-E., Löfstedt, L. & Wallin, B. G. (1976a). The responses of human muscle spindle endings to vibration of non-contracting muscles. *Journal of Physiology (London)*, **261**, 673–93.

(1976b). The responses of human muscle spindle endings to vibration during isometric contraction. *Journal of Physiology (London)*, **261**, 695–711.

Burke, D., Hagbarth, K.-E. & Wallin, B. G. (1977). Reflex mechanisms in Parkinsonian rigidity. *Scandinavian Journal of Rehabilitation Medicine*, **9**, 15–23.

Burke, D., Hagbarth, K.-E. & Löfstedt, L. (1978a). Muscle spindle responses in man to changes in load during accurate position maintenance. *Journal of Physiology (London)*, **276**, 159–64.

(1978b). Muscle spindle activity in man during shortening and lengthening contractions. *Journal of Physiology (London)*, **277**, 131–42.

Burke, D., Hagbarth, K.-E. & Skuse, N. F. (1979a). Voluntary activation of spindle endings in human muscles temporarily paralysed by nerve pressure. *Journal of Physiology (London)*, **287**, 329–36.

Burke, D., Skuse, N. F. & Stuart, D. G. (1979b). The regularity of muscle spindle discharge in man. *Journal of Physiology (London)*, **291**, 277–90.

Burke, D., McKeon, B., Skuse, N. F. & Westerman, R. A. (1980). Anticipation and fusimotor activity in preparation for a voluntary contraction. *Journal of Physiology (London)*, **306**, 337–48.

Burke, D., McKeon, B. & Skuse, N. F. (1981a). The irrelevance of fusimotor activity to the Achilles tendon jerk of relaxed humans. *Annals of Neurology*, **10**, 547–50.

(1981b). Dependence of the Achilles tendon reflex on the excitability of spinal reflex pathways. *Annals of Neurology*, **10**, 551–6.

Burke, D., Gandevia, S. C. & McKeon, B. (1983). The afferent volleys responsible for spinal proprioceptive reflexes in man. *Journal of Physiology (London)*, **339**, 535–52.

Burke, D., Gandevia, S. C. & McKeon, B. (1984). Monosynaptic and oligosynaptic contributions to the human ankle jerk and H reflex. *Journal of Neurophysiology*, **52**, 435–48.

Burke, D., Aniss, A. M. & Gandevia, S. C. (1987). In-parallel and in-series behavior of human muscle spindle endings. *Journal of Neurophysiology*, **58**, 417–26.

Burke, D., Gandevia, S. C. & Macefield, V. G. (1988). Responses to passive movement of receptors in joint, skin and muscle of the human hand. *Journal of Physiology (London)*, **402**, 347–61.

(2003). Microneurography and motor disorders. In *Handbook of Clinical Neurophysiology*, series ed. J. R. Daube & F. Mauguière, vol. 1, *Movement Disorders*, ed. M. Hallett, pp. 153–62. Amsterdam: Elsevier.

Bussel, B., Morin, C. & Pierrot-Deseilligny, E. (1978). Mechanism of monosynaptic reflex reinforcement during Jendrassik manoeuvre in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **41**, 40–4.

Clark, F. J., Matthews, P. B. C. & Muir, R. B. (1981). Response of soleus Ia afferents to vibration in the presence of the tonic vibration reflex in the decerebrate cat. *Journal of Physiology (London)*, **311**, 97–112.

Cole, J. D. & Sedgwick, E. M. (1992). The perceptions of force and of movement in a man without large myelinated sensory afferents below the neck. *Journal of Physiology (London)*, **449**, 503–15.

Cordo, P., Gandevia, S. C., Hales, J. P., Burke, D. & Laird, G. (1993). Force and displacement-controlled tendon vibration in humans. *Electroencephalography and Clinical Neurophysiology*, **89**, 45–53.

Edin, B. B. (1991). The 'initial burst' of human primary muscle spindle afferents has at least two components. *Acta Physiologica Scandinavica*, **143**, 169–75.

Edin, B. B. & Vallbo, Å. B. (1987). Twitch contraction for identification of human muscle afferents. *Acta Physiologica Scandinavica*, **131**, 129–38.

(1988). Stretch sensitization of human muscle spindles. *Journal of Physiology (London)*, **400**, 101–11.

(1990a). Dynamic response of human muscle spindle afferents to stretch. *Journal of Neurophysiology*, **63**, 1297–306.

(1990b). Muscle afferent responses to isometric contractions and relaxations in humans. *Journal of Neurophysiology*, **63**, 1307–13.

(1990c). Classification of human muscle stretch receptor afferents: a Bayesian approach. *Journal of Neurophysiology*, **63**, 1314–22.

Emonet-Dénand, F., Jami, L. & Laporte, Y. (1975) Skeletofusimotor axons in hind-limb muscles of the cat. *Journal of Physiology (London)*, **249**, 153–66.

Gandevia, S. C. & Burke, D. (1985). Effect of training on voluntary activation of human fusimotor neurons. *Journal of Neurophysiology*, **54**, 1422–9.

(1992). Does the nervous system depend on kinesthetic information to control natural limb movements? *Behavioral Brain Sciences*, **15**, 614–32.

(2004). The peripheral motor system. In *The Human Nervous System*, 2nd edn, ed. G. Paxinos & J. K. Mai, pp. 113–33. New York: Academic Press.

Gandevia, S. C., Burke, D. & McKeon, B. (1986a). Coupling between human muscle spindle endings and motor units assessed using spike-triggered averaging. *Neuroscience Letters*, **71**, 181–6.

Gandevia, S. C., Miller, S., Aniss, A. M. & Burke, D. (1986b). Reflex influences on muscle spindle activity in relaxed human leg muscles. *Journal of Neurophysiology*, **56**, 159–70.

Gandevia, S. C., Macefield, V. G., Burke, D. & McKenzie, D. K. (1990). Voluntary activation of human motor axons in the absence of muscle afferent feedback. The control of the deafferented hand. *Brain*, **113**, 1563–81.

Gandevia, S. C., Macefield, V. G., Bigland-Ritchie, B., Gorman, R. B. & Burke, D. (1993). Motoneuronal output and gradation of effort in attempts to contract acutely paralysed leg muscles in man. *Journal of Physiology (London)*, **471**, 411–27.

Gandevia, S. C., Wilson, L., Cordo, P. J. & Burke, D. (1994). Fusimotor reflexes in relaxed forearm muscles produced by cutaneous afferents from the human hand. *Journal of Physiology (London)*, **479**, 499–508.

Ghez, C., Gordon, J. & Ghilardi, M. F. (1995). Impairments of reaching movements in patients without proprioception. II. Effects of visual information on accuracy. *Journal of Neurophysiology*, **73**, 361–72.

Gioux, M., Petit, J. & Proske, U. (1991). Responses of cat muscle spindles that lack a dynamic fusimotor supply. *Journal of Physiology (London)*, **432**, 557–71.

Gordon, J., Ghilardi, M. F. & Ghez, C. (1995). Impairments of reaching movements in patients without proprioception. I. Spatial errors. *Journal of Neurophysiology*, **73**, 347–60.

Granit, R. (1955). *Receptors and Sensory Perception*. 369 p. New Haven: Yale University Press.

Gregory, J. E., Wise, A. K., Wood, S. A., Prochazka, A. & Proske, U. (1998). Muscle history, fusimotor activity and the human stretch reflex. *Journal of Physiology (London)*, **513**, 927–34.

Gregory, J. E., Wood, S. A. & Proske, U. (2001). An investigation into mechanisms of reflex reinforcement by the Jendrassik manoeuvre. *Experimental Brain Research*, **138**, 366–74.

Grillner, S. (1969). Supraspinal and segmental control of static and dynamic gamma-motoneurones in the cat. *Acta Physiologica Scandinavica*, **Suppl. 327**, 1–34.

Hagbarth, K.-E. (1967). EMG studies of stretch reflexes in man. *Electroencephalography and Clinical Neurophysiology*, **Suppl. 25**, 74–9.

(1979). Exteroceptive, proprioceptive, and sympathetic activity recorded with microelectrodes from human peripheral nerves. *Mayo Clinic Proceedings*, **54**, 353–65.

Hagbarth, K.-E., & Vallbo, Å. B. (1968). Discharge characteristics of human muscle afferents during muscle stretch and contraction. *Experimental Neurology*, **22**, 674–94.

Hagbarth, K.-E., Hongell, A. & Wallin, B. G. (1970). Parkinson's disease: afferent muscle nerve activity in rigid patients. A preliminary report. *Acta Societas Medicalis Upsaliensis*, **75**, 70–6.

Hagbarth, K.-E., Wallin, G. & Löfstedt, L. (1973). Muscle spindle responses to stretch in normal and spastic subjects. *Scandinavian Journal of Rehabilitation Medicine*, **5**, 156–9.

Hagbarth, K.-E., Wallin, G., Burke, D. & Löfstedt, L. (1975a). Effects of the Jendrassik manoeuvre on muscle spindle activity in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 1143–53.

Hagbarth, K.-E., Wallin, G. & Löfstedt, L. (1975b). Muscle spindle activity in man during voluntary fast alternating movements. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 625–35.

Hagbarth, K.-E., Wallin, G., Löfstedt, L. & Aquilonius, S. M. (1975c). Muscle spindle activity in alternating tremor of Parkinsonism and in clonus. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 636–41.

Hulliger, M. (1984). The mammalian muscle spindle and its central control. *Reviews of Physiology, Biochemistry and Pharmacology* **101**, 1–110.

Hunt, C. C. (1951). The reflex activation of mammalian small nerve fibres. *Journal of Physiology (London)*, **115**, 456–69.

Hunt, C. C. & Kuffler, S. W. (1951). Stretch receptor discharges during muscle contraction. *Journal of Physiology (London)*, **113**, 298–315.

Hunt, C. C. & Paintal, A. S. (1958). Spinal reflex regulation of fusimotor neurones. *Journal of Physiology (London)*, **143**, 195–212.

Jahnke, M. T., Proske, U. & Struppler, A. (1989). Measurements of muscle stiffness, the electromyogram and activity in single muscle spindles of human flexor muscles following conditioning by passive stretch or contraction. *Brain Research*, **493**, 103–12.

Kakuda, N. & Nagaoka, M. (1998). Dynamic response of human muscle spindle afferents to stretch during voluntary contraction. *Journal of Physiology (London)*, **513**, 621–8.

Kakuda, N., Miwa, T. & Nagaoka, M. (1998). Coupling between single muscle spindle afferent and EMG in human wrist extensor muscles: physiological evidence of skeletofusimotor (beta) innervation. *Electroencephalography and Clinical Neurophysiology*, **109**, 360–3.

Kuffler, S. W., Hunt, C. C. & Quilliam, J. P. (1951). Function of medullated small-nerve fibres in mammalian ventral roots: efferent muscle spindle innervation. *Journal of Neurophysiology*, **14**, 29–54.

Lance, J. W. & De Gail, P. (1965). Spread of phasic muscle reflexes in normal and spastic subjects. *Journal of Neurology, Neurosurgery and Psychiatry*, **28**, 328–34.

Landau, W. M. & Clare, M. H. (1964). Fusimotor function. Part IV. Reinforcement of the H-reflex in normal subjects. *Archives of Neurology*, **10**, 117–22.

Leksell, L. (1945). The action potential and excitatory effects of the small ventral root fibres to skeletal muscle. *Acta Physiologica Scandinavica*, **10**, suppl. 31, 1–84.

Macefield, V. G., Hagbarth, K.-E., Gorman, R. B., Gandevia, S. C. & Burke, D. (1991). Decline in spindle support to alpha-motoneurones during sustained voluntary contractions. *Journal of Physiology (London)*, **440**, 497–512.

Macefield, V. G., Gandevia, S. C., Bigland-Ritchie, B., Gorman, R. B. & Burke, D. (1993). The firing rates of human motoneurones voluntarily activated in the absence of muscle afferent feedback. *Journal of Physiology (London)*, **471**, 429–43.

Mackenzie, R. A., Burke, D., Skuse, N. F. & Lethlean, A. K. (1975). Fibre function and perception during cutaneous nerve block. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 865–73.

Marchand-Pauvert, V., Nicolas, G., Burke, D. & Pierrot-Deseilligny, E. (2002). Suppression of the H reflex in humans by disynaptic autogenetic inhibitory pathways activated by the test volley. *Journal of Physiology (London)*, **542**, 963–76.

Matthews, B. H. C. (1933). Nerve endings in mammalian muscle. *Journal of Physiology (London)*, **78**, 1–53.

Matthews, P. B. C. (1972). *Mammalian Muscle Receptors and their Central Actions*, 630 pp. London: Arnold.

(1976). Absence of gross action of prolonged vibration on mouse motor behaviour. *Journal of Physiology (London)*, **260**, 2P.

(1981). Evolving views on the internal operation and functional role of the muscle spindle. *Journal of Physiology (London)*, **320**, 1–30.

Matthews, P. B. C. & Rushworth, G. (1957a). The selective effect of procaine on the stretch reflex and tendon jerk of soleus muscle when applied to its nerve. *Journal of Physiology (London)*, **135**, 245–62.

(1957b). The relative sensitivity of muscle nerve fibres to procaine. *Journal of Physiology (London)*, **135**, 263–9.

Matthews, P. B. C. & Stein, R. B. (1969). The regularity of primary and secondary muscle spindle afferent discharges. *Journal of Physiology (London)*, **202**, 59–82.

McKeon, B. & Burke, D. (1980). Identification of muscle spindle afferents during in vivo recordings in man. *Electroencephalography and Clinical Neurophysiology*, **48**, 606–8.

(1981). Component of muscle spindle discharge related to arterial pulse. *Journal of Neurophysiology*, **46**, 788–96.

(1983). Muscle spindle discharge in response to contraction of single motor units. *Journal of Neurophysiology*, **49**, 291–302.

Merton, P. A. (1951). The silent period in a muscle of the human hand. *Journal of Physiology (London)*, **114**, 183–98.

(1953). Speculations on the servo control of movement. In *The Spinal Cord, Ciba Foundation Symposium*, ed. J. L. Malcolm & J. A. G. Gray, pp. 84–91. Baltimore: University Park Press.

Meunier, S. & Morin, C. (1989). Changes in presynaptic inhibition of Ia fibres to soleus motoneurones during voluntary dorsiflexion of the foot. *Experimental Brain Research*, **76**, 510–18.

Morgan, D. L., Prochazka, A. & Proske, U. (1984). Can fusimotor activity potentiate the responses of muscle spindles to a tendon tap? *Neuroscience Letters*, **50**, 209–15.

Morita, H., Petersen, N., Christensen, L. O., Sinkjaer, T. & Nielsen, J. (1998). Sensitivity of H-reflexes and stretch reflexes to presynaptic inhibition in humans. *Journal of Neurophysiology*, **80**, 610–20.

Nielsen, J., Nagaoka, M., Kagamihara, Y., Kakuda, N. & Tanaka, R. (1994). Discharge of muscle afferents during voluntary co-contraction of antagonistic ankle muscles in man. *Neuroscience Letters*, **170**, 277–80.

Nordh, E., Hulliger, M. & Vallbo, Å. B. (1983). The variability of inter-spike intervals of human spindle afferents in relaxed muscles. *Brain Research*, **271**, 89–99.

Paillard, J. (1955). *Réflexes et régulations d'origine proprioceptive chez l'Homme*. Thèse de Sciences, 289 pp. Paris: Arnette.

Prochazka, A. & Hulliger, M. (1983). Muscle afferent function and its significance for motor control mechanisms during voluntary movements in cat, monkey, and man. *Advances in Neurology*, **39**, 93–132.

Proske, U. (1997). The mammalian muscle spindle. *News in Physiological Sciences*, **12**, 37–42.

Proske, U., Morgan, D. L. & Gregory, J. E. (1993). Thixotropy in skeletal muscle and in muscle spindles: a review. *Progress in Neurobiology*, **41**, 705–21.

Ribot, E., Roll, J. P. & Vedel, J. P. (1986). Efferent discharges recorded from single skeletomotor and fusimotor fibres in man. *Journal of Physiology (London)*, **375**, 251–68.

Ribot-Ciscar, E. & Roll, J. P. (1998). Ago-antagonist muscle spindle inputs contribute together to joint movement coding in man. *Brain Research*, **791**, 167–76.

Ribot-Ciscar, E., Vedel, J. P. & Roll, J. P. (1989). Vibration sensitivity of slowly and rapidly adapting cutaneous mechanoreceptors in the human foot and leg. *Neuroscience Letters*, **104**, 130–5.

Ribot-Ciscar, E., Tardy-Gervet, M. F., Vedel, J. P. & Roll, J. P. (1991). Post-contraction changes in human muscle spindle resting discharge and stretch sensitivity. *Experimental Brain Research*, **86**, 673–8.

Ribot-Ciscar, E., Rossi-Durand, C. & Roll, J. P. (2000). Increased muscle spindle sensitivity to movement during reinforcement manoeuvres in relaxed human subjects. *Journal of Physiology (London)*, **523**, 271–82.

Roll, J. P. & Vedel, J. P. (1982). Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Experimental Brain Research*, **47**, 177–90.

Roll, J. P., Vedel, J. P. & Ribot, E. (1989). Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study. *Experimental Brain Research*, **76**, 213–22.

Roll, J. P., Bergenheim, M. & Ribot-Ciscar, E. (2000). Proprioceptive population coding of two-dimensional limb movements in humans: II. Muscle-spindle feedback during 'drawing-like' movements. *Experimental Brain Research*, **134**, 311–21.

Rothwell, J. C., Traub, M. M., Day, B. L., Obeso, J. A., Thomas, P. K. & Marsden, C. D. (1982). Manual motor performance in a deafferented man. *Brain*, **105**, 515–42.

Rothwell, J. C., Gandevia, S. C. & Burke, D. (1990). Activation of fusimotor neurones by motor cortical stimulation in human subjects. *Journal of Physiology (London)*, **431**, 743–56.

Rushworth, G. (1960). Spasticity and rigidity: an experimental study and review. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 99–118.

Sanes, J. N., Mauritz, K. H., Dalakas, M. C. & Evarts, E. V. (1985). Motor control in humans with large-fiber sensory neuropathy. *Human Neurobiology*, **4**, 101–14.

Scott, J. J. (1991). Responses of Ia afferent axons from muscle spindles lacking a bag1 intrafusal muscle fibre. *Brain Research*, **543**, 97–101.

Szumski, A. J., Burg, D., Struppler, A. & Velho, F. (1974). Activity of muscle spindles during muscle twitch and clonus in normal and spastic human subjects. *Electroencephalography and Clinical Neurophysiology*, **37**, 589–97.

Takada, Y., Miyahara, T., Tanaka, T., Ohyama, T. & Nakamura, Y. (2000). Modulation of H reflex of pretibial muscles and reciprocal Ia inhibition of soleus muscle during voluntary teeth clenching in humans. *Journal of Neurophysiology*, **83**, 2063–70.

Taylor, A., Gladden, M. H. & Durbaba, R. (eds.) (1995). *Alpha and Gamma Motor Systems*, 639 pp. New York: Plenum.

Torebjörk, H. E. & Hallin, R. G. (1973). Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. *Experimental Brain Research*, **16**, 321–32.

Vallbo, Å. B. (1971). Muscle spindle response at the onset of isometric voluntary contractions in man. Time difference between fusimotor and skeletomotor effects. *Journal of Physiology (London)*, **218**, 405–31.

(1973). Muscle spindle afferent discharge from resting and contracting muscles in normal human subjects. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 251–62. Basel: Karger.

(1974). Human muscle spindle discharge during isometric voluntary contractions. Amplitude relations between spindle frequency and torque. *Acta Physiologica Scandinavica*, **90**, 319–36.

Vallbo, Å. B. & Al-Falahe, N. A. (1990). Human muscle spindle response in a motor learning task. *Journal of Physiology (London)*, **421**, 553–68.

Vallbo, Å. B. & Hagbarth, K.-E. (1968). Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. *Experimental Neurology*, **21**, 270–89.

Vallbo, Å. B., Hagbarth, K.-E., Torebjörk, H. E. & Wallin, B. G. (1979). Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. *Physiological Reviews*, **59**, 919–57.

Van der Meche, F. G. & Van Gijn, J. (1986). Hypotonia: an erroneous clinical concept? *Brain*, **109**, 1169–78.

Wallin, B. G., Hongell, A. & Hagbarth, K.-E. (1973). Recordings from muscle afferents in Parkinsonian rigidity. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 263–72. Basel: Karger.

Wilson, L. R., Gandevia, S. C. & Burke, D. (1995). Increased resting discharge of human spindle afferents following voluntary contractions. *Journal of Physiology (London)*, **488**, 833–40.

Wilson, L. R., Gandevia, S. C., Inglis, J. T., Gracies, J. M. & Burke, D. (1999a). Muscle spindle activity in the affected upper limb after a unilateral stroke. *Brain*, **122**, 2079–88.

Wilson, L. R., Gracies, J. M., Burke, D. & Gandevia, S. C. (1999b). Evidence for fusimotor drive in stroke patients based on muscle spindle thixotropy. *Neuroscience Letters*, **264**, 109–12.

Wise, A. K., Gregory, J. E. & Proske, U. (1998). Detection of movements of the human forearm during and after co-contractions of muscles acting at the elbow joint. *Journal of Physiology (London)*, **508**, 325–30.

Wood, S. A., Morgan, D. L., Gregory, J. E. & Proske, U. (1994). Fusimotor activity and the tendon jerk in the anaesthetised cat. *Experimental Brain Research*, **98**, 101–9.

Wood, S. A., Gregory, J. E. & Proske, U. (1996). The influence of muscle spindle discharge on the human H reflex and the monosynaptic reflex in the cat. *Journal of Physiology (London)*, **497**, 279–90.

Zehr, E. P. & Stein, R. B. (1999). Interaction of the Jendrassik maneuver with segmental presynaptic inhibition. *Experimental Brain Research*, **124**, 474–80.

4

Recurrent inhibition

Recurrent inhibition was the first spinal pathway identified, and there was detailed knowledge of its morphology, physiology and pharmacology from animal experiments well before other spinal pathways could be investigated. After reciprocal Ia inhibition, the recurrent pathway was the first pathway for which a reliable selective method of investigation became available for use in human subjects. This is due to the simplicity of its organisation and to its unique feature of being activated by the final motor output rather than by a special afferent input. Human experiments have helped understand what could be the functional role of this form of negative feedback, but its exact function(s) remain(s) debated.

Background from animal experiments

Initial findings

Renshaw (1941) demonstrated that, in animals with dorsal roots sectioned, antidromic impulses in motor axons could evoke a short-latency long-lasting inhibition of the monosynaptic reflex in homonymous and synergistic motoneurones. The inhibition depends on motor axon recurrent collaterals activating interneurones, that have been called Renshaw cells, the discharge of which inhibits motoneurones (Eccles, Fatt & Koketsu, 1954). The following description of the recurrent pathway in the cat (see Fig. 4.1) is based on a comprehensive review by Baldissera, Hultborn & Illert (1981), and emphasis is placed on data that can enlighten studies in human subjects.

General features

Morphology

Renshaw cells are funicular cells located ventrally in lamina VII, medial to motoneurones (near their emergent axons), with axons that enter the spinal white matter to project over distances >12 mm rostrally or caudally (Jankowska & Lindström, 1971).

The organisation of the disynaptic recurrent pathway

Some relevant connections are sketched in Fig. 4.1: motor axons give off recurrent collaterals activating Renshaw cells, which have inhibitory projections to homonymous and synergistic motoneurones.

Pharmacology

Recurrent collaterals excite Renshaw cells using acetylcholine as the transmitter, much as do motoneurone terminals at the neuromuscular junction (Eccles, Fatt & Koketsu, 1954). This characteristic provides the unique possibility in human studies of studying transmission through the pathway by altering it pharmacologically.

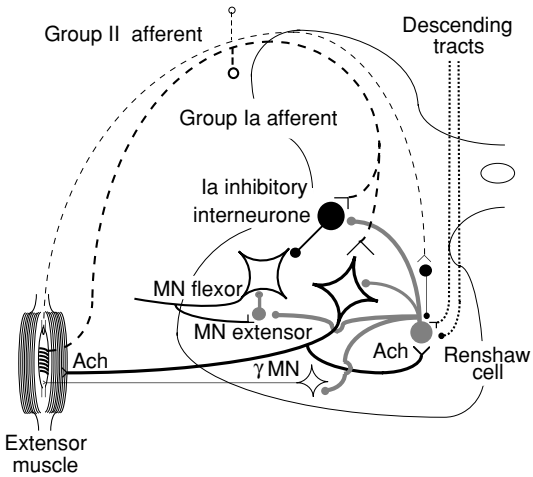


Fig. 4.1. Wiring diagram of the connections of the recurrent inhibitory pathway in the cat. In this and subsequent figures, excitatory synapses are represented by Y-shape bars, inhibitory synapses by small filled circles, and inhibitory interneurones by larger filled circles. Renshaw cells, their axons and their inhibitory projections are in grey. An individual Renshaw cell activated by the recurrent collateral from an extensor motoneurone (MN) has inhibitory projections to motoneurones of this pool (and MNs of synergistic muscles, not represented), on γ MNs of the same muscle(s), on Ia inhibitory interneurones which are activated by Ia afferents from the extensor muscle and inhibit antagonistic flexor MNs, and on Renshaw cells activated from flexor MNs. Group II afferents inhibit Renshaw cells disynaptically. Descending tracts elicit both excitation and inhibition of Renshaw cells. There is the same transmitter, acetylcholine (Ach), at the neuromuscular junction and at the synapse between recurrent collaterals and Renshaw cells. From data in Baldissera, Hultborn & Illert (1981).

Electrophysiology

A single volley in α motor axons produces a repetitive discharge of Renshaw cells, due to a prolonged EPSP from the recurrent collaterals. Accordingly, the maximal recurrent IPSP in motoneurones from a given heteronymous nerve (i.e. that elicited by antidromic stimulation of all motor axons in the nerve) has a central latency of slightly more than 1 ms (disynaptic pathway), reaches its maximum 5 ms after its onset, and has a total duration of ~40 ms (Eccles, Fatt & Koketsu, 1954).

Strength of recurrent inhibition

Conflicting results have been reported. Lindsay & Binder (1991) found a very low gain, which contradicted older results (Granit & Renkin, 1961). In reviewing the function of the recurrent pathway, Windhorst (1996) proposed that the gain of recurrent inhibition: (i) may be low, albeit alterable; (ii) does not need to be high to have significant effects; (iii) depends on the relative location on the motoneurone dendritic tree of Renshaw cell synapses and of excitatory synapses that they 'oppose' (the depressive effect being greater in cases of extensive overlap; see Hultborn *et al.*, 2003).

Input–output relationship

In individual Renshaw cells the relationship between the amount of injected current and the number of spikes produced by the cell is sigmoid (Hultborn & Pierrot-Deseilligny, 1979b). The output from the Renshaw cell pool caused by a *phasic* motor volley may be therefore facilitated when Renshaw cells receive a *tonic* excitatory input sufficient to move them to the steeply rising phase of the input-output relationship.

Input to Renshaw cells

Input from α motoneurones

In the cat hindlimb, recurrent collaterals are always given off by motoneurones innervating ankle and knee muscles but are absent from motoneurones of short plantar foot muscles (Cullheim & Kellerth, 1978). Similarly, recurrent collaterals are absent from motoneurones of long digit extensors in the cat forelimb (Hörner, Illert & Kümmel, 1991). Motor axon collaterals spread a distance of less than 1 mm from their parent cell body, so that excitation of a given Renshaw cell can be obtained only from

motor nuclei located in the immediate neighbourhood (Cullheim & Kellerth, 1978). Each individual Renshaw cell is excited by axon collaterals of many motoneurones, as evidenced both by their smoothly growing response to increasing intensity of stimulation of individual nerves and by their excitation from several nerves (Eccles, Fatt & Koketsu, 1954; Eccles *et al.*, 1961b). Renshaw cells are excited mainly by motoneurones of synergistic muscles and not by those of strict antagonists, and this indicates that convergence onto Renshaw cells is based, not only on proximity, but also on functional factors. This holds true also in the baboon hindlimb (Hultborn, Jankowska & Lindström, unpublished data, cited by Baldissera, Hultborn & Illert, 1981). It has long been believed that Renshaw cells were preferentially activated from large motoneurones (fast-twitch fatigue-sensitive motor units) (Eccles *et al.*, 1961a). However, because of the small force contribution of the earliest recruited units, the excitatory drive on Renshaw cells from motoneurones increases linearly with the developed force (Hultborn *et al.*, 1988a).

Segmental afferents

Apart from the excitation produced by motoneurone discharges, polysynaptic excitation of Renshaw cells may occur after stimulation of cutaneous afferents (Ryall & Piercey, 1971) and ipsilateral group II and III muscle afferents (Piercey & Goldfarb, 1974). There are also inhibitory inputs to Renshaw cells from cutaneous and group II afferents (Wilson, Talbot & Kato, 1964; Fromm, Haase & Wolf, 1977).

Descending inputs

There is ample evidence that Renshaw cells may be facilitated or inhibited, independently of an alteration in motoneurone discharge by stimulation of various higher centres (cerebral cortex, internal capsule, red nucleus, cerebellum, reticular formation and thalamus; for references, see Baldissera, Hultborn & Illert, 1981). For instance, stimulation of the internal capsule increases the monosynaptic reflex discharge and decreases the resulting Renshaw cell activity, thus de-coupling Renshaw cells from their input motoneurones (Koehler *et al.*, 1978).

Projections of Renshaw cells

Projections to α motoneurones

Following activation of the motoneurones of a given muscle, recurrent inhibition is evoked in a number of motor nuclei. The largest recurrent IPSPs are found in homonymous motoneurones, but many other motoneurones are also strongly inhibited (Eccles, Fatt & Koketsu, 1954; Eccles *et al.*, 1961b). This heteronymous recurrent inhibition is distributed to motoneurones of synergistic muscles acting at the same joint or even at another joint, and there is a striking overlap between the distribution of Renshaw inhibition and monosynaptic Ia excitation (Hultborn, Jankowska & Lindström, 1971b). However, there may be little or no recurrent inhibition to motor nuclei receiving strong Ia excitation (e.g. the distal forelimb muscles; Illert & Wietelmann, 1989) and recurrent inhibition may occur without Ia excitation (e.g. phrenic motoneurones; Lipski, Fyffe & Jodkowski, 1985). Thus, the 'rules' underlying the distribution of Ia excitation and recurrent inhibition are basically independent, even though they are often convergent (Hultborn, 1989). It has long been believed that small motoneurones (slow-twitch fatigue-resistant motor units) were subject to stronger recurrent inhibition than large motoneurones (Granit, Pascoe & Steg, 1957). However, the differences in the output from Renshaw cells, measured as recurrent inhibitory current elicited in different motoneurone types close to their firing threshold, disappear (Hultborn, Katz & Mackel, 1988b).

Projections to γ motoneurones

Both γ_s and γ_d motoneurones receive recurrent inhibition from α motoneurones. Recurrent inhibition is less potent and less evenly distributed in γ than in α motoneurones of the same motor nucleus (Ellaway, 1971; Ellaway & Murphy, 1980).

Ia inhibitory interneurones

Renshaw cells inhibit the interneurones mediating disynaptic reciprocal Ia inhibition to α motoneurones antagonistic to those giving off the recurrent collaterals that excite them (Hultborn, Jankowska & Lindström, 1971a). α motoneurones and 'corresponding' Ia interneurones (i.e. those with the same Ia excitatory input, see Fig. 4.1) receive recurrent inhibition in a strictly parallel fashion. This inhibition of Ia interneurones is responsible for recurrent facilitation (i.e. the facilitation elicited in antagonistic motoneurones by motor discharges), which was described by Renshaw (1941), operates predominantly between antagonists, and is due to inhibition of tonically active Ia interneurones (Hultborn *et al.*, 1971c).

Other Renshaw cells

Renshaw cells also inhibit other Renshaw cells quite efficiently (Ryall, 1970). The principal pattern of mutual inhibition appears to be such that Renshaw cells excited by extensors strongly inhibit those excited by flexors (see Fig. 4.1) and vice versa (Ryall, 1981).

Ventral spinocerebellar tract

Finally, Renshaw cells have inhibitory projections to the cells of origin of the ventral spinocerebellar tract (VSCT, cf. Baldissera, Hultborn & Illert, 1981).

Conclusions

Hypotheses about the role of the recurrent pathway have centred around four themes: '(i) control of the spatial pattern of motoneuronal activity (stretching from theories of a ≪sharpening≫ of motor contrast to the hypothesis that the particular distribution of recurrent inhibition may support specific ≪synergic≫ motor patterns; (ii) control of the temporal pattern (e.g. synchronisation, suppression of oscillations, change of dynamic properties of motoneurones); (iii) control of the relative activity of slow and fast units; (iv) proposal that the Renshaw system functions as a variable gain regulator at the output level' (Hultborn, 1989; cf. p. 179). So far, the functional role of recurrent inhibition remains unknown, and it is possible that it varies with motor tasks (see Windhorst, 1996).

Methodology

Using homonymous antidromic motor volleys is a flawed technique in humans

Presumed recurrent effects

Taking advantage of the fact that very brief (50 μs) stimuli favour motor axons over Ia afferents (see Paillard, 1955; Chapter 1, p. 6), Veale & Rees (1973) conditioned the soleus H reflex by a brief stimulus evoking a pure M wave. This produced triphasic modulation of the test reflex with early inhibition at interstimulus intervals (ISIs) of 2–3 ms, facilitation peaking at 5–8 ms, followed by further inhibition. It was claimed that these changes were due to recurrent effects elicited by the antidromic motor volley: recurrent inhibition on which a phase of recurrent facilitation due to mutual inhibition of Renshaw cells would be superimposed.

This interpretation is erroneous

(i) A similar curve can be obtained using a conditioning stimulus of 50 μs duration subthreshold for a motor response, whether H or M, due to excitation of Ia afferents (Pierrot-Deseilligny & Morin, 1980). The afferents in the test volley would be refractory at short ISIs of 2–3 ms and supernormal at slightly longer ISIs of 5–8 ms (see Chapter 1, p. 11; Fig. 1.5(*b*)). In addition, the conditioning Ia volley would create subliminal excitation in the motoneurone pool, explaining the phase of excitation. The absence of an H-reflex response does not indicate the absence of activation of Ia afferents: it takes only one motor axon to produce a detectable M wave, but many Ia afferents must

be activated for there to be a reflex response. In this respect, the threshold for the H response elicited by such brief stimuli (50 μs) may be higher than the threshold for the M wave but it is close to it (see Veale, Rees & Mark, 1973, their Fig. 4.2(*a*)).

(ii) In the cat, recurrent facilitation is observed between antagonistic motoneurones, never between homonymous or synergistic motoneurones (Hultborn *et al.*, 1971c).

Other issues with stimuli >1 × MT

Using an antidromic motor discharge to activate Renshaw cells has been extensively used in experiments on animals with dorsal roots sectioned, but cannot be achieved in intact human subjects without extreme care (see p. 168). When the dorsal roots are intact, it is impossible to elicit an antidromic motor volley without producing two complicating factors: (i) an orthodromic group I volley, the effects of which may interfere with recurrent inhibition (see above); and (ii) a complex afferent discharge evoked by the muscle twitch due to the orthodromic motor volley.

The paired H reflex technique to investigate homonymous recurrent inhibition

Underlying principles

The paired H reflex technique relies on a collision in motor axons, and is an attempt to bypass the difficulties of studying homonymous recurrent inhibition when dorsal roots are intact (see below for details, and Pierrot-Deseilligny & Bussel, 1975; Bussel & Pierrot-Deseilligny, 1977).

(i) Renshaw cells are activated orthodromically by a conditioning monosynaptic reflex discharge, but a collision in motor axons prevents the conditioning reflex from reaching the muscle, and producing a twitch-induced afferent discharge.

(ii) The test reflex cannot be an ordinary H reflex, because motoneurones that discharged in the conditioning reflex undergo post-spike afterhyperpolarisation (AHP), while those that did not will be subliminally excited. Because of this, a second (test) H reflex will recruit predominantly the latter (Pierrot-Deseilligny *et al.*, 1976). The larger the conditioning reflex, the smaller will be the test reflex, independent of recurrent inhibition. The particular technique of collision used to test recurrent inhibition creates a homogeneous population of motoneurones available for assessment by the test reflex. Only those motoneurones that discharged in the conditioning reflex (and have undergone the AHP) can be involved in the test reflex (see below).

(iii) Long conditioning-test intervals (≥10 ms) prevent Ib inhibition evoked by the conditioning volley from contaminating the recurrent inhibition (Pierrot-Deseilligny, Katz & Morin, 1979; Chapter 6, p. 255).

Conditioning and test reflexes

The method was originally described for soleus. The conditioning and test stimuli are delivered to the posterior tibial nerve through the same unipolar electrode. As sketched in Fig. 4.2(*a*), the Ia volley elicited by the conditioning stimulus (S1) discharges a group of motoneurones (motoneurones 'X' and 'Y') to produce the conditioning reflex (Fig. 4.2(*e*)), hereafter referred to as H1. This reflex volley activates Renshaw cells orthodromically via recurrent collaterals. The test stimulus (SM) is supramaximal for α-motor axons and, when given by itself, is not followed by a reflex response in the EMG (Fig. 4.2(*f*)), because of collision between the antidromic volley set up in motor axons and the reflex discharge (cf. Chapter 1, p. 7 and the sketch of Fig. 4.2(*b*)). Providing that the ISI is appropriate, the H1 conditioning reflex discharge will collide with this antidromic α volley (Fig. 4.2(*c*)) and eliminate it in the corresponding motor axons (axons 'X' and 'Y') so that the H′ test reflex due to the supramaximal test stimulus can now pass (cf. axon 'X' in Fig. 4.2(*d*)) and appear in the EMG (Fig. 4.2(*g*)). Thus, the population of motoneurones responsible for the H′ test reflex evoked by SM is homogeneous, because all of them have already discharged in the H1 conditioning reflex. As a result,

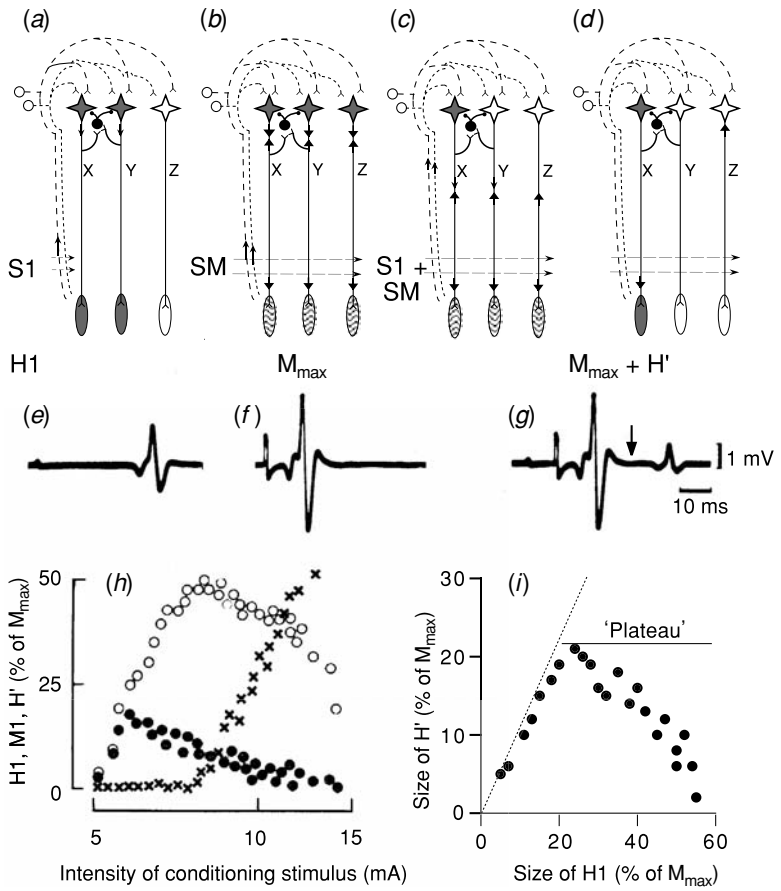


Fig. 4.2. The paired H reflex technique. (*a*)–(*g*) Volleys in Ia afferents and motor axons ((*a*)–(*d*)), and corresponding EMG responses ((*e*)–(*g*)). Motoneurones (MNs) and muscle fibres activated in the H reflex are grey; muscle fibres activated in the M wave are speckled; orthodromic and antidromic volleys are indicated by vertical arrows. (*a*) Conditioning stimulation (S1) activates some Ia afferents (dashed line) and discharges MNs 'X' and 'Y', and the resulting H1 response is shown in (*e*). (*b*) Supramaximal (SM) stimulation recruits all Ia afferents (dashed and dotted lines) and all motor axons, producing the maximal M wave in (*f*), which is not followed by a reflex response, because the antidromic motor volley collides with and eliminates any reflex volley in motor axons. (*c*) When S1 precedes SM by 10 ms, the EMG contains the M max response (*g*). The antidromic volley evoked by SM collides with the conditioning H1 reflex discharge elicited by S1 in MNs 'X' and 'Y', and eliminates it in the corresponding axons, so that the H1 discharge disappears from the EMG (the arrow in *G* indicates its predicted site). (*d*) Because of the collision between the SM antidromic volley and the H1 reflex discharge, the axons of MNs 'X' and 'Y' are freed from antidromic impulses, and the reflex response due to SM (H') can appear in the EMG in (*g*). However, due to recurrent inhibition brought about by the H1 reflex discharge, the strong Ia volley due to SM cannot fire MN 'Y' ((*c*), (*d*)), and H′ is smaller than H1. Because MN 'Z' is not involved in the conditioning reflex, it cannot be assessed by the test reflex (see p. 161). (*h*) H1 (○) and the corresponding M wave (×) elicited by S1, and H′ (●, when SM is preceded by S1 by 10 ms), expressed as a percentage of M_{max}, are plotted against the logarithm of the S1 intensity. (*i*) 'Bell-shaped' curve illustrating the variation of H′ (as a percentage of M_{max}) when the size of H1 (as a percentage of M_{max}) is increased. The dotted oblique line represents the theoretical curve which would be obtained if H′ equalled H1. Note that initial data points fall on or just below this line of identity. The horizontal line ('plateau') represents the maximal inhibition of H′ due to the AHP of the MNs (see p. 159). Each symbol in (*h*), (*i*) is the mean of five measurements. Modified from Pierrot-Deseilligny & Bussel (1975) ((*e*)–(*h*)) and Bussel & Pierrot-Deseilligny (1977) (*i*), with permission.

(i) they all undergo the post-spike AHP, and (ii) the action potential has eliminated the underlying EPSP evoked in these motoneurones by the conditioning Ia volley (Coombs, Eccles & Fatt, 1955b). The H′ test reflex can, at most, be equal to H1, and the amplitude of H1 can be considered the unconditioned value of the H′ test reflex. Because of the collision, H1 does not appear in the EMG when followed by SM (arrow in Fig. 4.2(*g*)), and it is necessary to alternate the combined S1-SM stimulation and the S1 conditioning stimulus alone to measure it. Several characteristics of H′ show that it is not an F wave: (i) very stable latency, (ii) large amplitude (up to 40% of M_{max}), which contrasts with the small size of F waves in soleus (Chapter 1, p. 23), (iii) strong depression produced by post-activation depression at the Ia afferent-motoneurone synapse when the frequency of stimulation is increased or the response conditioned by vibration (Pierrot-Deseilligny *et al.*, 1976).

Evidence for recurrent inhibition

Inhibition of the test reflex after the conditioning discharge

Initially the H′ test reflex increases as the stimulus intensity for the H1 conditioning reflex increases. Then increasing the size of the H1 conditioning reflex results in a decrease in the amplitude of the H′ reflex (Fig. 4.2(*h*)). Accordingly, at low conditioning reflex amplitudes H′ equals (or nearly equals) H1, i.e. the motoneurones recruitable into the test reflex are those in whose motor axons collision has eliminated the antidromic impulses. As the H1 conditioning reflex continues to increase, there is a gradual decrease in the amplitude of H′. Three factors could contribute to the decrease: (i) activation of a larger number of group I afferent fibres producing non-reciprocal group I (Ib) inhibition of soleus motoneurones and/or presynaptic inhibition of Ia terminals; (ii) post-spike AHP of motoneurones, preventing the less excitable motoneurones from being recruited by the test volley (Coombs, Eccles & Fatt, 1955a); and (iii) increasing recurrent inhibition brought about by the increasingly large conditioning reflex discharge.

Reflex inhibition is related to the size of the conditioning reflex discharge

Non-reciprocal group I inhibition should have subsided by the 9-ms ISI and cannot account for the test reflex inhibition illustrated in Fig. 4.2(*h*), which was recorded at a 10 ms ISI (see Chapter 6, p. 255). In addition, the increase in the inhibition of the H′ test reflex is not related to the intensity of S1, i.e. not to the number of afferent fibres *per se*, but to the H1 motor discharge they evoke. This was demonstrated by facilitating the conditioning reflex either by stimulation of a remote nerve (superficial radial) or by a soleus stretch (cf. Fig. 4.3(*c*)–(*e*), and its legend). When the amplitude of H′ is plotted against the intensity of the S1 conditioning stimulus, for a given intensity of S1, activating a fixed number of afferent fibres, the H′ test reflex amplitude is smaller when the conditioning reflex is facilitated than in the control situation (Fig. 4.3(*d*)). This indicates that the inhibition of H′ is a function of the number of motoneurones involved in the H1 conditioning discharge. Accordingly, when the amplitude of H′ is plotted against that of the corresponding conditioning reflex, for each given amplitude of H1, the test reflex amplitude is identical whether the conditioning reflex is facilitated or not (Fig. 4.3(*e*)).

Possible role of AHP

The above findings indicate that the amplitude of the H′ test reflex is related only to the amplitude of the conditioning reflex discharge. The 'bell-shaped' curve in Fig. 4.2(*i*) shows the variations of the H′ test reflex expressed as a percentage of M_{max} (hereafter referred to as the 'absolute' size of H′) vs that of H1. The dotted oblique line represents the curve which would be obtained if H′ equalled H1. Values below this theoretical curve indicate a depression of H′ with respect to H1. This depression could be explained in terms of differences in susceptibility to the Ia test volley of the different motoneurones (early and late recruited) undergoing the AHP. As long as the H1 conditioning reflex is small, motoneurones which are the most sensitive to the Ia input are recruited

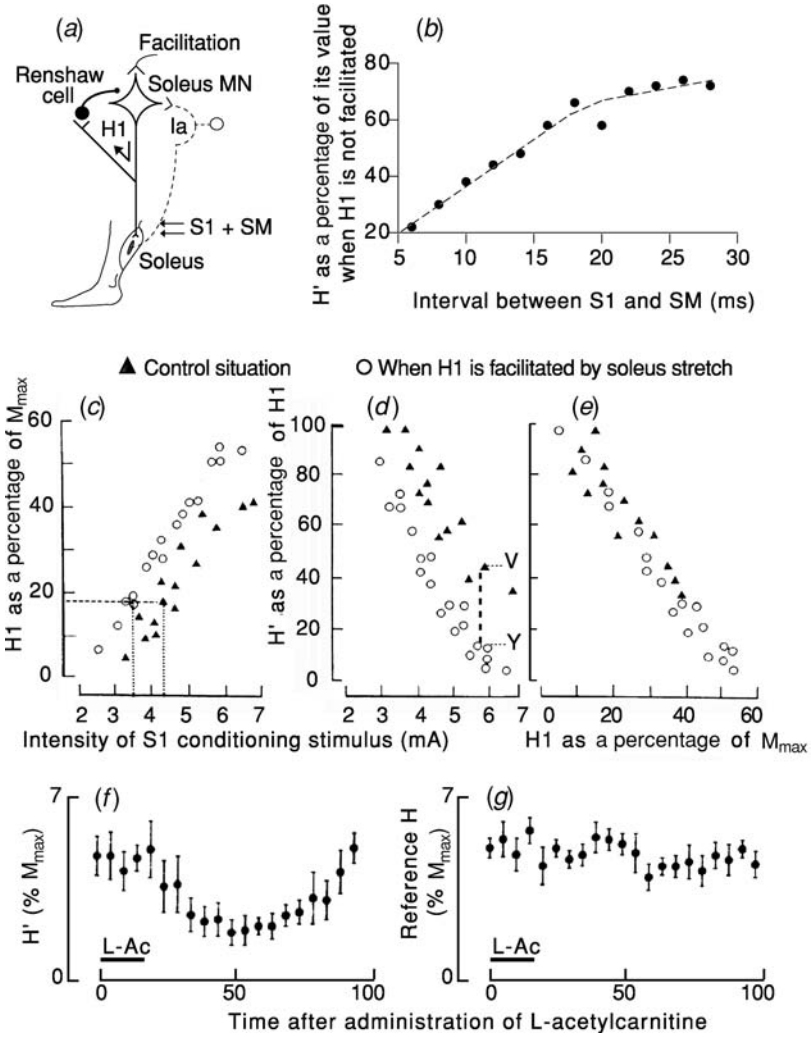


Fig. 4.3. Evidence for recurrent inhibition. (*a*) Sketch of the presumed pathways. The arrow (H1) represents the conditioning reflex discharge. (*b*) Time course of the supplementary recurrent inhibition due to facilitation of H1 by stretch of soleus: the amplitude of H′ when H1 is facilitated, expressed as a percentage of its value when H1 is not facilitated (e.g. Y as a percentage of V in panel (*d*)), is plotted against the ISI between S1 and SM. (Ib inhibition may contribute to H′ inhibition at short ISIs, but this factor may be neglected when considering the supplementary recurrent inhibition brought about by the facilitation of H1, since Y and V in (*d*) were obtained with the same S1 intensity). Note that the need for collision limits the extent to which the ISI can be altered, so that the full time course cannot be explored. (*c*)–(*e*) Augmentation of the inhibition of H′ due to stretch-induced enhancement of the H1 conditioning reflex. Stretch of triceps surae was produced by a twitch of intrinsic foot muscles due to tibial nerve stimulation at the ankle, while the nerve was blocked proximally with xylocaïne; Bussel & Pierrot-Deseilligny, 1977, their Fig. 3). Control (▲) and responses obtained after H1 facilitation (○) are compared at the 10-ms ISI. (*c*) Amplitude of H1 (as a percentage of M_{max}) is plotted against intensity of S1 (mA); an H1 reflex of a given amplitude (horizontal dashed line) was obtained with a S1 intensity larger in the control situation than when H1 was facilitated (dotted vertical lines). (*d*), (*e*) Amplitude of H′ (as a percentage of H1) is plotted against the intensity of S1 (*d*) and the amplitude of H1 (as a percentage of M_{max} (*e*)). (*f*), (*g*) Time course of the changes in the amplitudes of H′ ((*f*) conditioned by an H1 reflex of 45% of M_{max}, H′ being well in its decay phase, 10 ms ISI) and of a reference H reflex of similar amplitude (*g*) during (thick horizontal bars) and after administration of L-acetylcarnitine (L-Ac). Each symbol is the mean of 10 (*b*), 5 ((*d*)–(*e*)) or 6 ((*f*), (*g*)) measurements. Modified from Bussel & Pierrot-Deseilligny (1977) ((*b*)–(*e*)), and Mazzocchio & Rossi (1989) ((*f*), (*g*)), with permission.

(see Chapter 1, pp. 3–4), and the SM test volley, which activates all Ia fibres, can overcome the AHP in them. H′ will then equal H1. Further increases in H1 will recruit motoneurones that are less sensitive to the Ia input. It is conceivable that, in these motoneurones, the AHP cannot be overcome by the test volley, and would therefore prevent them from firing in the test reflex. This is one reason why the test reflex does not follow the conditioning reflex at high amplitudes. However, if the AHP were acting alone to suppress H′ (i.e. if there was no recurrent inhibition), there would be at most a fixed limit to the number of motoneurones available for the test reflex. As a result, increasing the conditioning reflex beyond a certain value (20% of M_{max} in the case illustrated in Fig. 4.2(*i*)) would result in a fixed number of motoneurones that SM could discharge, and this would produce a 'plateau' in the absolute size of H′. However, this could not produce the characteristic 'bell-shaped' pattern seen in Fig. 4.2(*i*), where the H′ amplitude having reached its maximum gradually decreases as H1 increases.

Decrease in the absolute size of H′

The decrease in the absolute size of H′ implies increasing failure of motoneurone recruitment, as Renshaw cell activation increases with the size of the conditioning reflex discharge.

Under these conditions, the extent of inhibition of H′ between the dotted oblique line and the plateau in Fig. 4.2(*i*) represents the maximal inhibition possible due to the AHP alone. Accordingly, in intrinsic muscles of the hand and foot, where there is no homonymous recurrent inhibition, there is no decay phase of the H′ test reflex (see p. 169).

Time course of recurrent inhibition

In order to ensure collision between the conditioning reflex and the antidromic test volley, the ISI between S1 and SM must be adjusted so that the S1-induced reflex volley does not reach the site of peripheral stimulation before SM is delivered: thus, the maximal ISI that can be used depends on the length of the conduction paths, the extreme values found being 21 ms for a subject 1.56 m tall, and 33 ms for a subject 1.98 m tall (Pierrot-Deseilligny *et al.*, 1976). For each S1–SM ISI, the ratio of the test reflex amplitudes obtained in the two conditions, with and without facilitation of H1 (e.g. *Y* as a percentage of *V* in Fig. 4.3(*d*)), can be used to estimate the supplementary recurrent inhibition brought about by facilitation of the conditioning reflex: the smaller the ratio, the larger the supplementary recurrent inhibition. Supplementary recurrent inhibition is maximal at the shortest ISI explored (6 ms), and progressively decreases at longer ISIs (Fig. 4.3(*b*)), much as does recurrent inhibition assessed by the size of a monosynaptic reflex in animal experiments (Renshaw, 1941).

Validation

Animal experiments

Some assumptions on which the method relies have been tested in animal experiments (Hultborn, Pierrot-Deseilligny & Wigström, 1979b).

(i) There is a linear increase in recurrent inhibition with increasing conditioning reflex size and even small monosynaptic reflexes are able to produce measurable recurrent inhibition of motoneurones.

(ii) In the spinal cat, maximal homonymous recurrent inhibition and AHP are of the same order of magnitude. This is one of the prerequisites for the paired H reflex method. If the depression due to recurrent inhibition was minor compared to that caused by AHP, the method would produce results that were difficult to interpret.

Pharmacological validation

An important finding validating the method was that of Mazzocchio & Rossi (1989) who showed in human experiments that recurrent inhibition, as assessed by the paired H reflex technique, was selectively potentiated by intravenous injection of L-acetylcarnitine (L-Ac). L-Ac is a derivative of acetylcholine with a stereospecific facilitatory action on nicotine receptors, thereby affecting the synapses responsive to

acetylcholine. It has few or no systemic side effects in human subjects (see Mazzocchio & Rossi, 1989). Intravenous injection of L-Ac decreases the amplitude of the H′ test reflex, but does not change that of a 'reference' H reflex of similar amplitude (Fig. 4.3(*f*), (*g*)). Nor does it change Ib inhibition or the AHP (Rossi & Mazzocchio, 1992). The L-Ac-induced increase in depression of the H′ test reflex therefore indicates potentiation of recurrent inhibition and confirms that the decrease in the size of H′ expressed as a percentage of M_{max} ('absolute size') results from greater Renshaw cell activation. The inhalation of tobacco smoke also results in a rapid and dramatic decrease in H′ lasting for ~50 min, without altering H1 reflex significantly (Shefner, Berman & Young, 1993). Given the potentiation of recurrent inhibition by nicotine demonstrated in the cat (Eccles, Fatt & Koketsu, 1954), this provides further pharmacological support for the view that the inhibition of H′ by the H1 reflex discharge is due to activation of Renshaw cells.

Critique: limitations, advantages, conclusions

Assessing changes in recurrent inhibition requires attention to methodology

Criteria are required for the valid use of the size of the H′ test reflex to assess changes in recurrent inhibition

(i) The size of the H1 conditioning reflex discharge must be identical in the two situations which are compared. (ii) The H1 conditioning reflex must be within the range where its increase results in a progressive decrease in the absolute size of the H′ test reflex. This is not always possible, particularly in motor nuclei other than the soleus. This problem can be overcome by facilitating H1 by a conditioning stimulus subthreshold for the H reflex, preceding S1 by 3–5 ms so that S1 will recruit more motoneurones (Mazzocchio & Rossi, 1997a), but this introduces the additional complication of another afferent volley. (iii) The conditioning-test ISI must be >9 ms so that Ib inhibition evoked by the conditioning stimulus has subsided. Then, the smaller the H′ test reflex amplitude, the larger the recurrent inhibition elicited by a given H1 conditioning reflex discharge.

Comparison with a reference H reflex

The amplitude of the H′ test reflex depends not only on the recurrent inhibition produced by H1, but also on experimentally produced changes in motoneurone excitability (e.g. enhanced motoneurone excitability during a voluntary contraction of soleus). Thus, the excitability of the motoneurones must also be evaluated by an ordinary H reflex (reference H) of the same size as H′ under control conditions (see Hultborn & Pierrot-Deseilligny, 1979a; Fig. 4.8(*b*)). Apart from the depression due to H1, H′ and the reference H are subject to the same peripheral and supraspinal influences during the test. A differential net effect on these two reflexes can therefore be taken to reflect variations in the recurrent inhibition elicited by the constant conditioning reflex discharge (however, see below).

Limitations

A sizeable H′ reflex can be obtained in only 65% of the normal subjects

It has been shown that in those subjects without an H′ response the threshold of the M wave in the soleus and/or gastrocnemius muscle(s) is below that of the soleus H reflex. This suggests that the additional recurrent inhibition caused by the antidromic volley from the conditioning stimulus is responsible for the absence of the H′ test reflex (Katz & Pierrot-Deseilligny, 1982).

Ib contribution

The timing of SM 10 ms after S1 ensures that Ib afferents in the S1 volley will not affect the H′ reflex (cf. Chapter 6, p. 255). However, Ib afferents in a test volley can limit the size of the test H reflex (see Chapter 1, pp. 14–16), and Ib afferents in the strong SM volley could do so. This might account for the finding that initially H′ is often slightly smaller than H1 (as evidenced by the data points below the beginning of the dotted oblique line in Fig. 4.2(*i*)).

However, such a contribution would not explain the subsequent divergence of H′ from H1 at larger H1 amplitudes, and is unlikely to explain the differential changes in H′ and in a reference H reflex during voluntary activity or in pathology (see pp. 173–87).

Underestimation of the extent of recurrent inhibition

While recurrent inhibition can only be assessed for those motoneurones that produce a reflex EMG potential, the H1 discharge could have produced recurrent inhibition in motoneurone 'Z' in Fig. 4.2(*a*)–(*d*). Whether or not this occurs cannot be determined because this motoneurone cannot contribute to the reflex EMG potential, since it is not involved in the conditioning reflex. Owing to the orderly recruitment and de-recruitment of motoneurones in the monosynaptic reflex (see Chapter 1, pp. 3–4), the earliest changes in recurrent inhibition could occur in those motoneurones that cannot be assessed.

Possible changes in the post-spike AHP

Because the depression of the test reflex after the H1 conditioning reflex discharge depends on both the AHP of the motoneurones and the recurrent inhibition brought about by H1, the suppression of H′ will not measure only recurrent inhibition. AHP is not a fixed parameter, as was thought when the method was developed, but can vary: (i) activation of descending monoaminergic pathways can reduce the AHP of target motoneurones in the cat (see Hultborn *et al.*, 2004); (ii) plateau potentials can probably be triggered in motoneurones during voluntary contractions in human subjects (see Chapter 1, p. 20), and it remains to be seen how this change in motoneurone behaviour would influence the AHP; (iii) AHP following a spike may also summate with that resulting from a preceding spike (Ito & Oshima, 1962), and this factor must be taken into account in situations, such as soleus contractions, where temporal summation of the AHP might occur.

Lesser sensitivity of H′ than of the reference H to PSPs

Changes in membrane conductance during the AHP reduce the sensitivity of motoneurones discharging in the H′ test reflex to synaptic inputs. As a result, identical excitatory or inhibitory inputs to motoneurones cause smaller changes in the H′ test reflex than in a reference H reflex (Hultborn & Pierrot-Deseilligny, 1979a; Katz & Pierrot-Deseilligny, 1984). Thus, no conclusions concerning changes in recurrent inhibition can be drawn if both reflexes vary in the same direction and the variation of the test reflex is less than that of the reference H reflex. Conversely, larger changes in the H′ test reflex than that in the reference H reflex (and *a fortiori* in the opposite direction) indicate a change in recurrent inhibition. Provided that there is no change in the AHP (see above), greater facilitation reflects decreased recurrent inhibition and greater inhibition reflects increased recurrent inhibition. The weaker sensitivity to synaptic inputs of the motoneurones fired in H′ may then lead to an underestimation of the changes in recurrent inhibition.

Conclusions

Although the paired H reflex technique may seem complex, it is simple to use. It is the only available method allowing assessment of homonymous recurrent inhibition at rest and during various motor tasks in normal subjects and patients. However, interpretations concerning the changes in H′ in physiological and pathological conditions must take into account the fact that the size of H′ also depends on the AHP, and this is not a fixed parameter.

Methods for investigating heteronymous recurrent inhibition

Underlying principles

A conditioning motor discharge, whether a reflex or antidromic motor volley, is used to activate Renshaw cells and the resulting recurrent inhibition

is assessed in a heteronymous muscle by one of the methods exploring the excitability of the motoneurones: PSTHs of single units, H reflex, modulation of the on-going EMG or the MEP. The criteria by which the resulting inhibition can be attributed to recurrent inhibition are given below (pp. 166–7).

Inhibition evoked by an orthodromic (reflex) discharge

Inhibition may be produced by the tendon jerk

In Fig. 4.4, the PSTHs of a tibialis anterior unit are conditioned by patellar tendon taps of increasing strength. The early increase in firing probability, due to heteronymous monosynaptic Ia excitation (see Chapter 2), was followed by a trough that appeared with the tendon jerk (*e*)–(*g*) and increased with it in size and duration (*h*)–(*m*) (Meunier *et al.*, 1990).

Inhibition may be produced by an H reflex

Thus, Fig. 4.6 shows inhibition evoked in tibialis anterior and soleus motoneurones by femoral nerve stimulation sufficient to produce a quadriceps H reflex discharge, as assessed using the H reflex (*c*), the PSTH of a single unit ((*d*), (*e*)), on-going EMG ((*f*), (*g*)) or the MEP ((*h*), (*i*)). In each case, there is an initial facilitation due to monosynaptic Ia excitation, followed by inhibition, which appears in the PSTHs with a short central delay of 2 ms and has a long duration (30–40 ms).

Inhibition is related to the conditioning reflex discharge

The above inhibition could result from the afferent volley *per se* or from the motor discharge it evoked. To distinguish between these two possibilities either the reflex discharge can be changed without modifying the intensity of the conditioning stimulus, or the afferent volley can be altered without changing the reflex discharge. Thus, a constant stimulus to the femoral nerve, subthreshold for the quadriceps H reflex at rest and without inhibitory effect in the PSTH of a tibialis anterior unit, produced inhibition in the PSTH after the early Ia excitation when a voluntary contraction of the quadriceps caused the H reflex to appear (Meunier *et al.*, 1990; Fig. 4.5(*d*)–(*g*)). Similarly, the inhibition of the soleus H reflex elicited by a quadriceps H reflex discharge disappeared when a stimulus of the same intensity but eliciting no reflex discharge was applied to the branch of the femoral nerve supplying the vastus lateralis (Barbeau *et al.*, 2000; Fig. 4.6(*c*) and its legend). Conversely, it has been verified that quadriceps tendon jerks and H reflexes of the same size evoke similar inhibition in the PSTHs of leg muscle single units (Meunier, Pierrot-Deseilligny & Simonetta-Moreau, 1994), even though there are differences in the composition of the two afferent volleys (see Chapter 3, pp. 117–18).

Conditioning-test combinations

Such evidence for recurrent inhibition produced orthodromically by reflex discharges has been described: (i) in various heteronymous lower limb muscles with quadriceps and soleus H reflexes and tendon jerks (cf. Meunier, Pierrot-Deseilligny & Simonetta-Moreau, 1994; Table 4.1), and (ii) in proximal upper limb muscles after H reflexes and tendon jerks of forearm and arm muscles (cf. Katz *et al.*, 1993; Table 4.2).

Inhibition elicited by an antidromic motor volley

To compare the distribution of recurrent inhibition in humans and cats requires conditioning discharges from a number of motor nuclei. However, reflexes cannot be confined to selected muscles, and it is generally impossible to evoke a reflex involving only one head of a complex muscle: e.g. the gastrocnemius medialis (triceps surae) or the vastus lateralis (quadriceps). In such cases, an antidromic motor volley can be used, but note that here heteronymous recurrent inhibition is tested, unlike the situation critiqued earlier, supposedly testing homonymous recurrent inhibition (pp. 154–5). Qualitatively

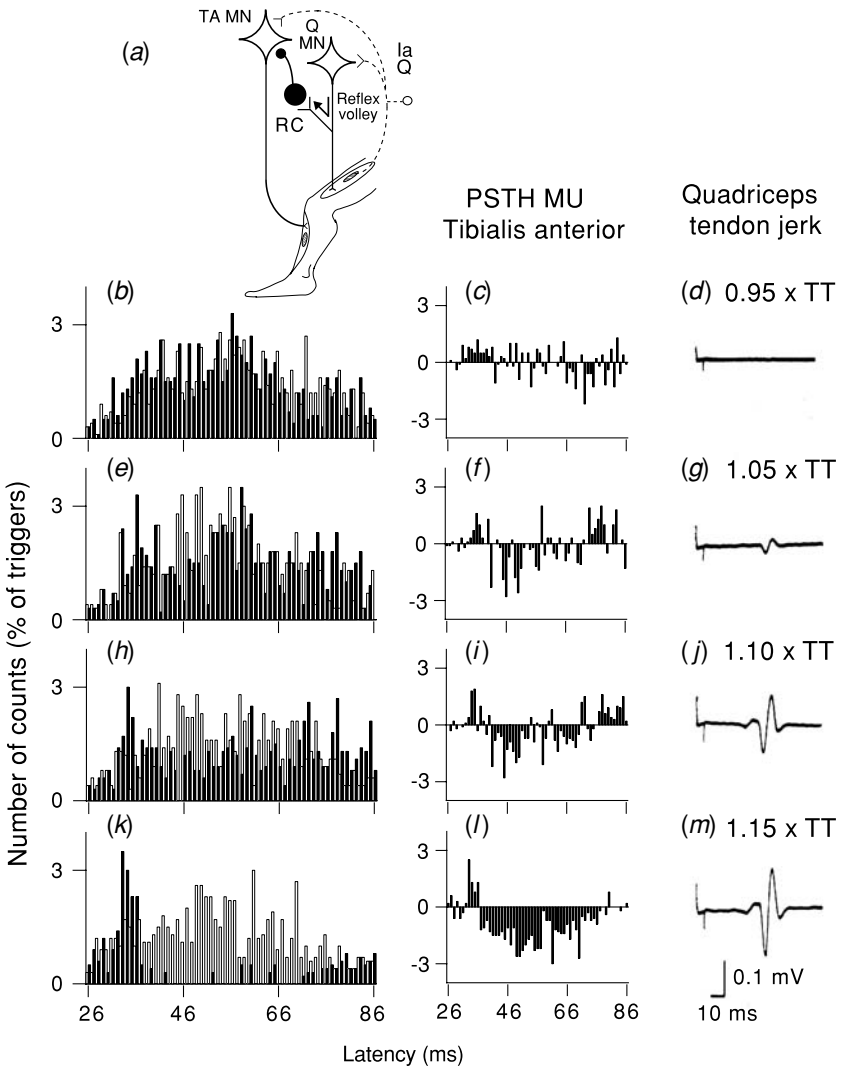


Fig. 4.4. Evidence for recurrent inhibition from quadriceps to tibialis anterior. (*a*) Sketch of the presumed pathways of heteronymous Ia excitation and recurrent inhibition from quadriceps (Q) to tibialis anterior (TA). The arrow represents the conditioning reflex discharge that activates Renshaw cells (RC). (*b*), (*e*), (*h*), (*k*) Changes in firing probability evoked in PSTHs (1 ms bin width) for a TA unit by a Q tendon tap (■) are compared with the control histograms (without stimulation, □). The number of counts as a percentage of number of triggers is plotted against the latency after the stimulation. (*c*), (*f*), (*i*), (*l*) Differences between conditioned and control histograms. (*d*), (*g*), (*j*), (*m*) The conditioning reflex response in the Q. The strength of the tendon tap was increased from top to bottom: 0.95 × tendon jerk threshold (TT) ((*b*)–(*d*)), 1.05 × TT ((*e*)–(*g*)), 1.10 × TT ((*h*)–(*i*)), 1.15 × TT ((*k*)–(*m*)), and the reflex response assessed as a percentage of M_{max} increased accordingly (0% in (*d*), 3% in (*g*), 12% in (*j*), 20% in (*m*)). The tap evoked an early increase in firing probability, the latency of which (33 ms) reflects heteronymous monosynaptic Ia excitation (see Chapter 2), and this was followed by a trough when the tap produced a tendon jerk ((*e*)–(*m*)). Modified from Meunier *et al.* (1990), with permission.

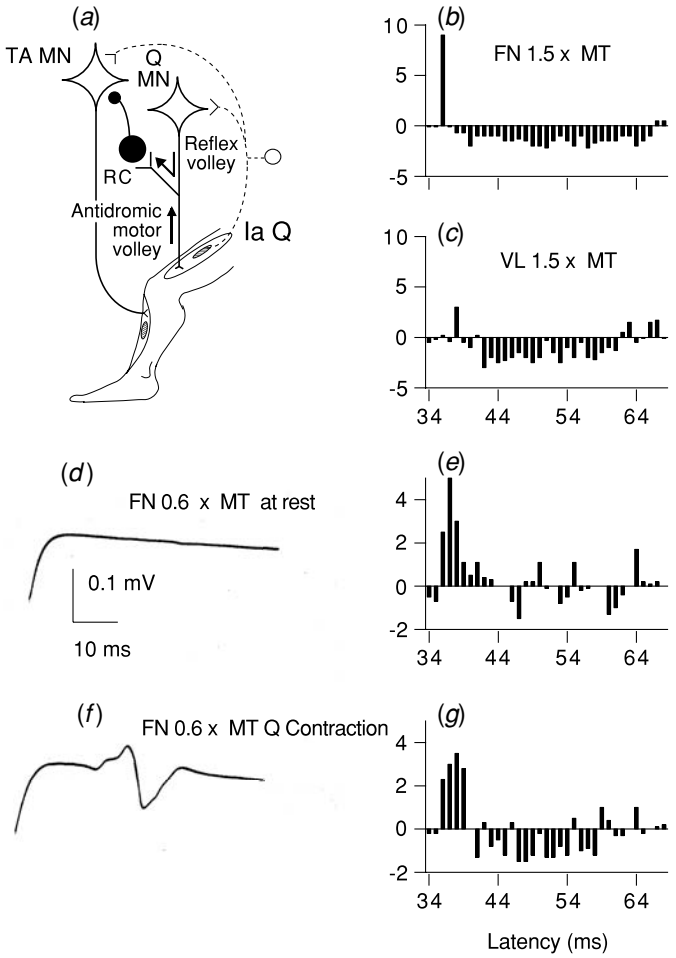


Fig. 4.5. Further evidence for recurrent inhibition from quadriceps to tibialis anterior. (*a*) Sketch of the presumed pathways of heteronymous Ia excitation and recurrent inhibition from quadriceps (Q) to tibialis anterior (TA). Conditioning motor discharges (reflex or antidromic motor volley) activate Renshaw cells (RC), as indicated by arrows. (*b*), (*c*), (*e*), (*g*) Changes in firing probability evoked in PSTHs for a tibialis anterior (TA) unit by femoral nerve (FN) volleys (after subtraction of the background firing, 1 ms bin width). The number of counts as a percentage of number of triggers is plotted against the latency after the stimulation. (*b*) Stimulation of the femoral nerve (FN, 1.5 × MT). (*c*) Stimulation of its branch to the vastus lateralis (VL, 1.5 × MT). The latency difference between the peaks in (*b*) and (*c*) is largely due to the supplementary conduction time for a volley arising more distally in the VL nerve, and this suggests that the excitation and inhibition elicited by stimulation of the FN and of its branch to the VL have the same origin. (*d*)–(*g*) Stimulation of the FN (0.6 × MT) at rest ((*d*), (*e*)) and during Q contraction ((*f*), (*g*)). At rest, there was no H reflex (*d*), and no inhibition followed the early excitation in the PSTH (*e*). During Q contraction, an H reflex appeared in the Q (*f*), and the early excitation was followed by an inhibition in the PSTH (*g*). Despite a similar amount of early Ia facilitation in (*e*) and (*g*), the trough was only observed in (*g*), where there was a conditioning reflex discharge. This indicates that the AHP following the peak of Ia excitation is insufficient by itself to explain the following suppression. Modified from Meunier *et al.* (1990), with permission.

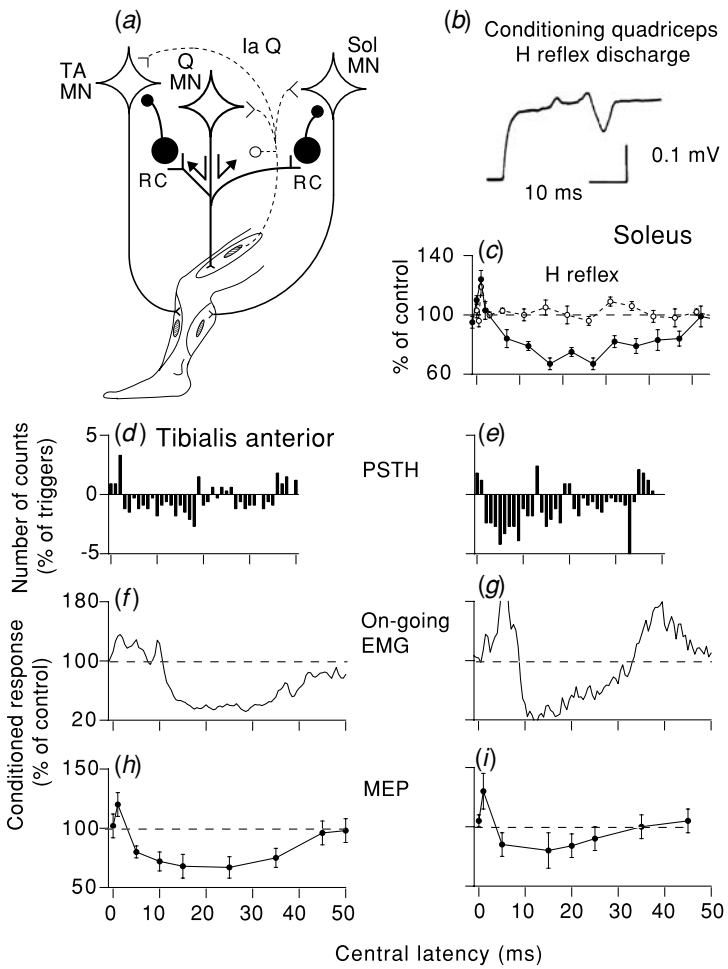


Fig. 4.6. Recurrent inhibition from quadriceps to tibialis anterior and soleus demonstrated by different methods. (*a*) Sketch of the presumed pathways of heteronymous Ia excitation and recurrent inhibition from quadriceps (Q) to tibialis anterior (TA) and soleus (Sol) motoneurones (MN). Arrows indicate the conditioning reflex discharges that activate Renshaw cells (RC). (*b*) Conditioning Q H reflex elicited by femoral nerve (FN) stimulation (1.1 × MT) producing the heteronymous recurrent inhibition shown in (*d*), (*e*). (*c*)–(*i*) Heteronymous Ia excitation and recurrent inhibition elicited in Sol (*c*), (*e*), (*g*), (*i*) and TA (*d*), (*f*), (*h*) MNs, assessed using the H reflex (*c*), the PSTHs of single units (after subtraction of the background firing, 1 ms bin width (*d*), (*e*)), the modulation of voluntary on-going EMG ((*f*), (*g*)), the initial excitation is truncated in (*g*)) or the MEP ((*h*), (*i*)). Conditioned responses (expressed as a percentage of control responses in (*c*) and (*f*)–(*i*), while the difference between conditioned and control histograms expressed as a percentage of the number of triggers is shown in (*d*)–(*e*)), are plotted against the central latency (i.e. the zero of the abscissa corresponds to the expected time of arrival of the FN Ia volley at the level of the MN tested). (*c*) Comparison of the modulation of the soleus H reflex by stimulation of the same intensity (0.95 × MT) applied to the FN eliciting a Q H reflex (●, 24% of M_{max}) and the vastus lateralis (VL) nerve eliciting no motor or reflex response (○, after allowance for the extra peripheral conduction time; note, however, that displacing the stimulating electrodes to activate only VL would have also changed the afferent volley). The finding that the conditioning stimulation evokes a similar inhibition of the MEP ((*h*), (*i*)) indicates that the inhibition of the H reflex (*c*), PSTH ((*d*), (*e*)) and on-going EMG ((*f*), (*g*)) is not due to FN-induced presynaptic inhibition of Ia terminals mediating the afferent volley of the H reflex or contributing to the on-going EMG or the motor unit discharge required for PSTH experiments (see Chapter 8, pp. 343–4). Modified from Meunier *et al.* (1990) ((*b*), (*d*), (*e*)), and Barbeau *et al.* (2000) ((*c*), (*f*)–(*i*)), with permission.

Table 4.1. Heteronymous recurrent inhibition and Ia excitation to human leg and thigh muscles

Nerve / MN	Sol	GM	SP	DP	FN	TN
Sol		***	*	NE	***	
GM	***		*		***	
Per brev		*			***	
TA	0	0	0		**	
Q	*	*	0			
Bi	***	***	*	0	NE	

homonymous | RI alone | No RI–No Ia | 0

Ia + RI | Ia alone | Not explored | NE

Columns: nerve stimulated: Sol (inferior soleus), GM (nerve to the gastrocnemius medialis), SP (superficial peroneal), DP (deep peroneal), FN (femoral nerve), TN (tibial nerve at the ankle). Lines: motoneurone (MN) pools investigated with the PSTH method: Sol (soleus), GM (gastrocnemius medialis), Per Brev (peroneus brevis), TA (tibialis anterior), Q (quadriceps), Bi (biceps femoris). The number of asterisks indicates the strength of the inhibition (see p. 169). Grey cells: recurrent inhibition and Ia excitation (crossed cells correspond to homonymous pathways). Horizontally hatched cells: recurrent inhibition without Ia excitation. Vertically hatched cells: Ia excitation without recurrent inhibition. 0 = absence of recurrent inhibition and Ia excitation. NE = not explored. From Meunier *et al.* (1990), Meunier, Pierrot-Deseilligny & Simonetta-Moreau (1994) and P. Marque, G. Nicolas & E. Pierrot-Deseilligny (unpublished data on projections from the tibial nerve).

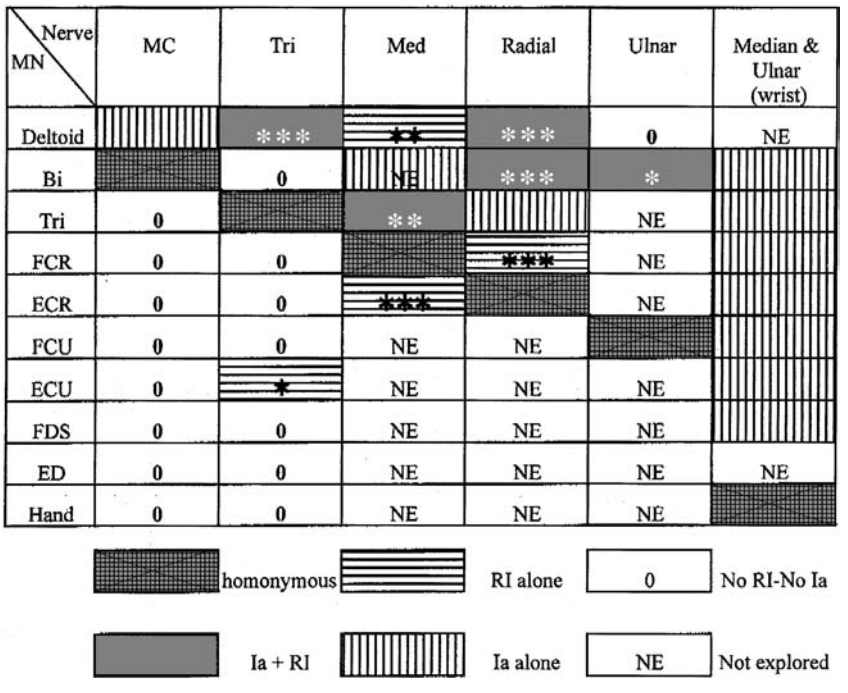
similar results, with initial heteronymous monosynaptic Ia excitation immediately followed by a long-lasting inhibition, have then been obtained, whether stimulating the nerve supplying the whole muscle or one of its branches (Meunier *et al.*, 1990; Fig. 4.5(*b*), (*c*) and its legend). Inhibition that has a short central delay and parallels the size of the conditioning M response is likely to be due to the antidromic motor volley (see below). In some cases, such as the inferior soleus nerve, the conditioning stimulation evokes both direct (M) and reflex (H) discharges. To scale the inhibition with respect to the conditioning motor discharge, Iles & Pardoe (1999) then simply summed the two conditioning motor responses.

Evidence for recurrent inhibition

Arguments for recurrent inhibition

The depressions illustrated in Figs. 4.4–4.6 have characteristics consistent with recurrent inhibition: (i) They appear and increase with the conditioning motor discharge, whether it be due to a reflex (Fig. 4.4) or M response. (ii) They are independent of the conditioning stimulus intensity *per se* (Fig. 4.5(*d*)–(*g*)). (iii) They have a short central delay, 1–2 ms longer than monosynaptic Ia excitation. (iv) They have a long duration, more than 15 ms. In addition, the suppressions are generally, though not always, preceded by a peak of monosynaptic Ia excitation,

Table 4.2. Heteronymous recurrent inhibition and Ia excitation in the human upper limb



Columns: nerve stimulated: MC (musculo-cutaneous), Tri (nerve of the triceps brachii), Med (median), Radial (radial at the elbow), Ulnar (ulnar), Median & Ulnar (wrist) median and ulnar at the wrist. Lines: motoneurone (MN) pools investigated with the PSTH method: Deltoid, Bi (biceps brachii), Tri (triceps brachii), FCR (flexor carpi radialis), ECR (extensor carpi radialis), FCU (flexor carpi ulnaris), ECU (Extensor carpi ulnaris), FDS (flexor digitorum superficialis), ED (extensor digitorum), Hand (intrinsic hand muscles). The number of asterisks indicates the strength of the inhibition (see pp. 169–71). Grey cells: recurrent inhibition and Ia excitation (crossed cells correspond to homonymous pathways). Horizontally hatched cells: recurrent inhibition without Ia excitation. Vertically hatched cells: Ia excitation without recurrent inhibition. 0 = absence of recurrent inhibition and Ia excitation. NE = not explored. From Créange *et al.* (1992), Katz *et al.* (1993) and V. Marchand-Pauvert, C. Iglesias, G. Lourenço & E. Pierrot-Deseilligny (unpublished data on projections from intrinsic hand muscles).

and there is a striking overlap between the distribution of heteronymous Ia excitation and recurrent inhibition in the lower limb (see p. 170). None of these arguments, by itself, provides unequivocal evidence for recurrent inhibition, but their conjunction makes it highly probable.

Arguments against other mechanisms

There are cogent arguments against a significant contribution of other mechanisms or pathways to the inhibitions brought about by conditioning reflex discharges.

(i) In the PSTH of a discharging motoneurone, the post-spike AHP following the discharge of the motoneurone in a heteronymous monosynaptic Ia peak could contribute to the suppression following the excitation. In fact, the AHP does not play a major role in the suppression because the trough appears to be independent of the heteronymous monosynaptic peak (Meunier *et al.*, 1990; Fig. 4.5(*d*)–(*g*) and its legend) and, in any case, the peak of monosynaptic excitation contains few discharges when compared with the subsequent trough (e.g. see Fig. 1.15(*c*)).

(ii) Conditioning stimulation evokes a group I volley able to produce non-reciprocal group I inhibition. However, evidence for Ib inhibition is rarely seen in PSTHs, probably because transmission in Ib pathways to motoneurones responsible for the contraction is depressed during the steady contractions required for PSTHs (see Chapter 6, p. 252). In addition, a similar inhibition can be observed with a tendon tap (Meunier *et al.*, 1990; Fig. 4.4), which, in a 'conditioning' muscle at rest, is much less effective in eliciting Ib inhibition than electrical stimulation (cf. Chapter 6, pp. 252–3).

(iii) The conditioning volley could evoke presynaptic inhibition of Ia terminals mediating the afferent volley of the test H reflex, or contributing to the on-going EMG or the motor unit discharge required for PSTH experiments. However, such a contribution is unlikely because the MEP is similarly suppressed (Barbeau *et al.*, 2000; Fig. 4.6(*h*)–(*i*), cf. Chapter 8, pp. 343–4).

(iv) A contribution from group II afferents is also unlikely when the conditioning electrical stimulation is below 1 × MT (Chapter 7, p. 303).

(v) The twitch-induced afferent discharge following the reflex response can be discounted because it cannot produce spinal effects for several tens of milliseconds (see Meunier *et al.*, 1990).

Electrical stimuli above 1 × MT

When the inhibition is evoked by electrical stimuli above 1 × MT, its Renshaw origin may appear more debatable, because the afferent volley elicited by the conditioning shock is more complex. It may then include both group II afferents, the threshold for which is 1.2 × MT (see Chapter 7, p. 303) and the twitch-induced afferent discharge evoked by the M response. However, the resulting effects appear later than the recurrent inhibition: a group II volley elicited at knee level produces effects in motoneurones ~10 ms later than the monosynaptic Ia excitation (Chapter 7, pp. 293–7), and the twitch-induced Ib inhibition would start to manifest itself in motoneurones even later after the orthodromic monosynaptic Ia facilitation (because of the time to and from the muscle, plus the time between the onset of the twitch and the activation of Golgi tendon organs; see Binder *et al.*, 1977). Three additional arguments support the Renshaw origin of this inhibition.

(i) Inhibition evoked in motor nuclei by the reflex discharge of triceps surae or quadriceps motoneurones is in all likelihood of Renshaw origin (see above), and it is reasonable to assume that inhibition induced in the same motor nuclei, with the same central delay and duration, by motor discharges from one head of these muscles (e.g. vastus lateralis in Fig. 4.5(*c*)) results from recurrent inhibition set up by the antidromic motor volley.

(ii) Intravenous administration of L-Ac increases the long-lasting inhibition produced by antidromic volleys above 1 × MT from gastrocnemius medialis to soleus and from wrist extensors to FCR (Rossi, Zalaffi & Decchi, 1994; Aymard *et al.*, 1997), and does so without altering the early low-threshold group I inhibition.

(iii) Similar results have been obtained in the upper limb of a deafferented patient (V. Marchand-Pauvert, J. B. Nielsen, B. Conway, J. C. Lamy & H. Hultborn, unpublished data).

Critique: limitations, conclusions

Limitations

Group I EPSPs and IPSPs elicited by the conditioning volley can overlap the onset of recurrent inhibition, and could affect the test response. This is important because the relative strengths of monosynaptic Ia

excitation and recurrent inhibition in motoneurones are similar (cf. p. 170). Recurrent inhibition should therefore be assessed at a long ISI where Ia EPSPs and group I IPSPs have subsided but recurrent IPSPs are still present.

Conclusions

In routine clinical studies, a simple method is preferable, and the modulation of the on-going EMG is the simplest method to compare the amount of recurrent inhibition elicited by a conditioning motor discharge in different motor tasks (Meunier *et al.*, 1996; Barbeau *et al.*, 2000). However, the modulation of the H reflex should be used to investigate changes in heteronymous recurrent inhibition during motor tasks with respect to rest (Iles & Pardoe, 1999).

Organisation and pattern of connections

Homonymous recurrent projections to motoneurones

Homonymous recurrent inhibition in proximal muscles

With the paired H reflex technique, evidence for homonymous recurrent inhibition has been found not only in the soleus (Bussel & Pierrot-Deseilligny, 1977), but also in quadriceps and the peroneal muscles (Rossi & Mazzocchio, 1991), FCR and ECR (Katz *et al.*, 1993). In these different motor nuclei, supportive evidence for the Renshaw origin of the inhibition came from its potentiation by L-Ac. Evidence for recurrent inhibition of soleus motoneurones following an antidromic motor volley has also been found in PSTHs (Kudina & Pantseva, 1988; Miles, Le & Türker, 1989). Similarly, in the deltoid, triceps brachii, FCU and ECU, an antidromic motor volley evoked by selective stimulation of the parent nerve just above 1 × MT has been shown to produce long-lasting inhibition, probably due to recurrent inhibition (Rossi & Mazzocchio, 1992; Katz *et al.*, 1993). Recurrent inhibition of ECR motoneurones elicited by a pure antidromic volley has been documented in a deafferented patient (Mattei, Schmied & Vedel, 2003).

Absence of homonymous recurrent inhibition in distal muscles

The paired H reflex technique has also been used to look for homonymous recurrent inhibition in intrinsic muscles of the foot (abductor hallucis brevis; Rossi & Mazzocchio, 1991) and hand muscles (opponens pollicis and abductor digiti minimi; Katz *et al.*, 1993). In these distal muscles, increasing the size of the H1 conditioning reflex discharge resulted in a plateau-like pattern, where H′ reflex remained the same once it had reached its maximum. In addition, H′ was not altered by administration of L-Ac. There are no recurrent collaterals from the axons of motoneurones innervating distal limb muscles of the cat (see p. 152), and the absence of evidence for recurrent inhibition in the human studies probably reflects an absence of such collaterals in humans.

Heteronymous recurrent projections to motoneurones in the lower limb

Pattern of distribution

Strength and distribution of heteronymous recurrent inhibition in the lower limb

Table 4.1 shows the distribution of heteronymous recurrent inhibition to leg and thigh muscles, determined using PSTHs (Meunier *et al.*, 1990; Meunier, Pierrot-Deseilligny & Simonetta-Moreau, 1994; P. Marque, G. Nicolas & E. Pierrot-Deseilligny, unpublished data). An attempt has been made to estimate the strength of recurrent inhibition (number of asterisks in each cell), based on (i) the frequency of occurrence (i.e. the percentage of units in which there was a significant recurrent inhibition), and (ii) the mean duration of the recurrent inhibition elicited by a conditioning discharge ~50% of M_{max}. In the human lower limb, recurrent connections are much more

widely distributed than in the cat hindlimb with, in particular, the appearance of transjoint connections that do not exist in the cat (apart from quadriceps to soleus) between quadriceps and all tested muscles operating at the ankle, and from triceps surae to quadriceps.

Comparison with the pattern of monosynaptic Ia excitation

Overlap between recurrent and Ia projections

The grey cells in Table 4.1 indicate that in the human lower limb, as in the cat hindlimb (cf. p. 153), most of the recurrent connections, and in particular most transjoint connections, are matched by parallel monosynaptic Ia excitatory projections. Comparison of Table 4.1 with the Table 2.1 of Chapter 2 shows that this parallel remains true in quantitative terms: the stronger the Ia excitation, the more marked the recurrent inhibition (e.g. both Ia excitation and recurrent inhibition from gastrocnemius medialis are strong on biceps and weak on quadriceps motoneurones).

Recurrent inhibition without Ia excitation

The overlap in the expression of Ia excitation and recurrent inhibition in different motoneurone pools is not total: recurrent connections from gastrocnemius medialis to soleus and peroneus brevis are not paralleled by corresponding Ia projections (horizontally hatched cells). Additional recurrent connections also exist in the cat, and this 'extended pattern' (Hultborn, Jankowska & Lindström, 1971b) has been presumed to link muscles that act in functional synergism although they are not connected by the Ia input. The functional synergism between two heads of the triceps surae (gastrocnemius medialis and soleus) is obvious. The absence of Ia input from gastrocnemius medialis to soleus may be related to a particular requirement of plantigrade gait (cf. Chapter 2, p. 93).

Ia excitation without recurrent inhibition

Ia excitatory connections without their recurrent counterpart (vertically hatched cells) also exist between some muscles acting on the ankle. Such Ia connections essentially link ankle muscles that are not synergists in flexion–extension movements (soleus and peroneus brevis, tibialis anterior and gastrocnemius medialis), but are believed to contribute to the stabilisation of the ankle during the stance phase of locomotion (cf. Chapter 11, p. 546). This finding is reminiscent of the Ia connections without recurrent inhibition found between flexors of the digits in the cat (Hamm, 1990), and suggests that the pattern of recurrent inhibition is determined by function during locomotion rather than anatomical synergism. The finding that the extensive Ia projections from intrinsic foot muscles to leg and thigh muscles in humans (see Table 2.1 in Chapter 2) are not paralleled by recurrent connections is most probably due to the absence of recurrent collaterals from motoneurones innervating distal muscles. The absence of recurrent inhibition in all combinations tested from the deep peroneal nerve (Table 4.1) raises the question of whether recurrent collaterals from pretibial flexors exist in man.

Functional implications

It has been assumed that, in the cat, the recurrent pathway has a focusing action, which helps limit the extent of Ia excitation (Hultborn, Jankowska & Lindström, 1971b). Similarly, it will be suggested on pp. 183–4 that transjoint recurrent connections found in the human lower limb have probably evolved to control matched Ia excitatory connections during postural co-contractions of bipedal stance (see Chapter 11, p. 538).

Heteronymous recurrent projections to motoneurones in the upper limb

Pattern of distribution

The pattern of heteronymous recurrent inhibition in the cat forelimb differs from that in the hindlimb: more extended transjoint connections, and projections from proximal to distal muscles (see Illert & Kümmel, 1999). In contrast, transjoint connections

are more restricted in the upper than in the lower limb of human subjects (Créange *et al.*, 1992; Katz *et al.*, 1993). Table 4.2 is arranged as Table 4.1, and shows that, as for heteronymous Ia excitation (see Chapter 2, p. 84), there are no proximal-to-distal projections, if one ignores the weak projection from triceps to ECU (which is not matched by an equivalent Ia connection). The deltoid motor nucleus, supplying the most proximal muscle investigated, receives the largest number of recurrent heteronymous projections from distal muscles, but some of them (from muscles supplied by the median nerve) are not matched by equivalent Ia connections. An interesting finding, also described in the cat (Illert & Wietelmann, 1989), is that ECR-coupled Renshaw cells inhibit FCR motoneurones and vice versa (Aymard *et al.*, 1997). This is in keeping with the finding that Renshaw cells activated by FCR or ECR motor discharges do not inhibit reciprocal inhibition directed to the antagonistic motor nucleus (see below). As in the lower limb, Ia projections from intrinsic hand muscles are not matched by equivalent recurrent connections, presumably because the corresponding motor axons lack recurrent collaterals.

Functional implications

The distribution of recurrent inhibition in the human upper limb is more restricted than in the cat forelimb, a difference that is the opposite of that for the human lower limb and the cat hindlimb. Heteronymous Ia projections from distal to proximal muscles presumably provide support to the hand during manipulatory movements (see Chapter 2, p. 94). However, the motor repertoire of the upper limb is much more versatile, and heteronymous recurrent connections from forearm to proximal muscles might be used (together with the corticospinal facilitation of presynaptic inhibition of Ia terminals, see Chapter 8, p. 353) to counteract excitatory Ia connections and bias the motoneurones in favour of the transmission of the descending excitation in those movements for which the assistance of Ia excitatory projections is not critical.

Recurrent inhibition of interneurones mediating reciprocal Ia inhibition

A characteristic feature of the recurrent pathway in the cat is the projection of Renshaw cells to interneurones mediating disynaptic reciprocal Ia inhibition (p. 154; Fig. 4.1).

Evidence for recurrent inhibition of Ia inhibitory interneurones

Reciprocal inhibition produced by an electrical volley to the triceps brachii nerve and assessed with the biceps tendon jerk was conditioned by a preceding tendon reflex discharge in the triceps (Katz, Pénicaud & Rossi, 1991; Fig. 4.7(*a*), (*b*)). The triceps motor discharge strongly depressed reciprocal Ia inhibition, with a short central delay and a long duration, i.e. a time course closely resembling that of recurrent inhibition of motoneurones (Fig. 4.7(*b*)). Figure 4.7(*b*) also shows that the suppression of reciprocal inhibition was not seen when the conditioning tendon tap was just subthreshold for the tendon jerk and therefore did not activate Renshaw cells (Δ), although it would have produced similar post-activation depression at the synapse of the Ia fibre and the Ia interneurone. It is therefore likely to be due to recurrent inhibition and not to the tap-induced afferent volley. A similar suppression was observed in the opposite direction, from biceps brachii to triceps, indicating that Renshaw cells coupled to elbow motor nuclei project to Ia interneurones mediating reciprocal Ia inhibition between elbow muscles. Recurrent inhibition from soleus similarly depresses reciprocal Ia inhibition from soleus to tibialis anterior (Baret *et al.*, 2003; Chapter 5, p. 206; Fig. 5.5(*b*)).

Absence of recurrent inhibition of reciprocal inhibition at wrist level

Different results have been obtained at the wrist (Aymard *et al.*, 1995). Recurrent inhibition evoked by a flexor or extensor motor discharge has no effect on group I inhibition directed to the 'antagonistic'

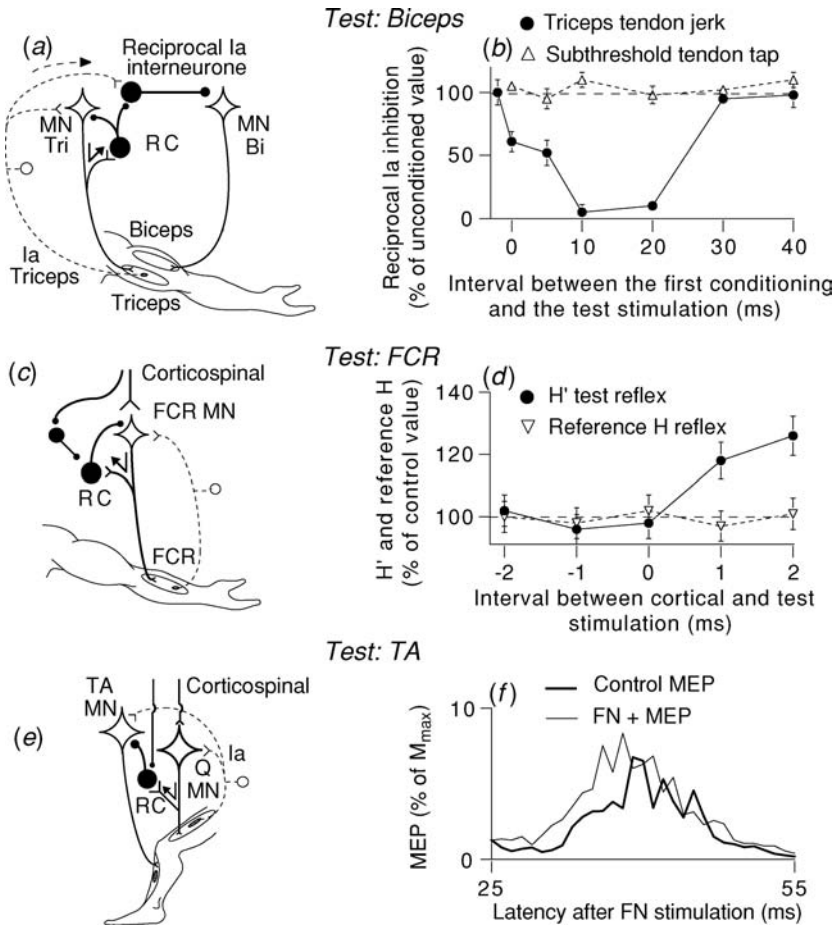


Fig. 4.7. Recurrent inhibition of reciprocal Ia inhibition and cortical depression of recurrent inhibition. (*a*), (*c*), (*e*) Sketches of the presumed pathways. Continuous arrows indicate the conditioning reflex discharges. (*a*) Renshaw cells (RC) activated from recurrent collaterals of triceps brachii (Tri) motoneurones (MN) inhibit interneurones mediating reciprocal inhibition from Tri to biceps (Bi). The dashed arrow indicates the conditioning volley eliciting reciprocal Ia inhibition. (*b*) The test response is the reciprocal Ia inhibition of the Bi tendon jerk elicited by an electrical volley to the Tri nerve (0.95 × MT) at the –3-ms ISI (cf. Fig. 5.3(*b*)). Reciprocal Ia inhibition was conditioned by a Tri tendon jerk, and the resulting amount of reciprocal inhibition (●, expressed as a percentage of the unconditioned value of reciprocal inhibition) is plotted against the ISI between this tendon tap and the test stimulus. △, Results obtained with a tap just subthreshold for the Tri tendon jerk for a single subject. Each symbol, mean of 20 measurements; vertical bars ±1 SEM. (*c*) Sketch of the corticospinal inhibition of homonymous recurrent inhibition to FCR MNs. (*d*) The onset of the cortical effect on the reference (▽) and the H′ (●) test reflexes in FCR. Reflexes (expressed as a percentage of their control value) are plotted against the ISI between cortical and test stimulation (TMS given at time zero). The intensity of TMS was set to produce no significant effect on the reference H reflex. Each point is the grand mean of results from four subjects. Vertical bars ±1 SEM. (*e*) Sketch of the pathway of corticospinal inhibition of heteronymous recurrent inhibition from quadriceps (Q) to tibialis anterior (TA) MNs. (*f*) Rectified averaged (15 sweeps) MEP (TMS = 38% of the maximal stimulator output) in the TA conditioned by a preceding Q H reflex discharge (thick line, ~20% of M_{max}, 5 ms ISI) and unconditioned (thin line), expressed as a percentage of M_{max}, are plotted against the latency after femoral (FN) stimulation. Adapted from Katz, Pénicaud & Rossi (1991) (*b*), Mazzocchio, Rossi & Rothwell (1994) (*d*), Barbeau *et al.* (2000) (*f*), with permission.

motor nucleus (cf. Chapter 5, pp. 207–8; Fig. 5.5(*d*)). This is in keeping with the mutual recurrent inhibition between 'antagonistic' ECR and FCR (see above) and raises the question whether the so-called 'reciprocal inhibition' between wrist muscles truly represents reciprocal Ia inhibition (see Chapter 5, pp. 211–14).

Corticospinal suppression of recurrent inhibition

Corticospinal depression of homonymous recurrent inhibition

Changes in recurrent inhibition of FCR and soleus motoneurones, assessed with the paired H reflex technique, have been investigated after cortical stimulation (Mazzocchio, Rossi & Rothwell, 1994). TMS produced significant facilitation of the H′ test reflex in the FCR at an intensity that produced no facilitation of the reference H reflex (Fig. 4.7(*c*), (*d*)). At soleus level, TMS elicited a similar facilitation of the H′ test reflex, whereas the reference H reflex was inhibited. A change in the AHP was eliminated, and these findings presumably reflect corticospinal depression of Renshaw cells, as has been observed in the cat after stimulation of the pericruciate cortex (MacLean & Leffman, 1967) or the internal capsule (see Koehler *et al.*, 1978, and p. 153). Because the corticospinal inhibition of Renshaw cells has a lower threshold than the cortical facilitation of motoneurones, Mazzocchio, Rossi & Rothwell (1994) argued that TMS might also act by corticospinal suppression of a tonic excitatory drive from the reticular formation (specifically, the nucleus raphe magnus; there is also an indirect corticospinal inhibitory drive via the locus coeruleus; see the sketch in Fig. 4.11(*a*)). Regardless, the cortical effects on recurrent inhibition occur 3–4 ms later than the effects on motoneurones.

Corticospinal depression of heteronymous recurrent inhibition

Figure 4.7(*f*) shows that the MEP in tibialis anterior is depressed by the heteronymous recurrent inhibition produced by a quadriceps H reflex discharge, and that this involves the initial part of the MEP but not its later part (Barbeau *et al.*, 2000). The sparing of the later part can be explained because, in this experiment, the corticospinal volley produces two effects: activation of motoneurones responsible for the MEP (the test response), and depression of Renshaw cells. However, as seen above, the suppression of recurrent inhibition begins some milliseconds later than the facilitation of the corresponding motoneurones. Thus, the femoral-induced recurrent inhibition of the earliest motoneurones discharging in the MEP is not depressed by the corticospinal inhibition of Renshaw cells, whereas recurrent inhibition of motoneurones discharged by later corticospinal volleys is depressed by the action of the fastest cortical volley on Renshaw cells.

Motor tasks and physiological implications

The picture that emerges from the changes in recurrent inhibition during various motor tasks in human subjects suggests that recurrent inhibition might serve several functions, that are not exclusive. However, functional interpretations must be made with care because: (i) it cannot be taken for granted that the response of Renshaw cells to a tonic input is the same as the response to the phasic inputs explored in the experiments below, and (ii) experiments dealing with homonymous recurrent inhibition were performed using the paired H reflex technique, and would be affected by changes in the motoneuronal AHP (see p. 161).

Recurrent inhibition of motoneurones of a muscle involved in selective contractions

Methodology

These studies have focused on the changes in homonymous recurrent inhibition of soleus motoneurones, investigated with the paired H reflex technique during various voluntary contractions of

the gastrocnemius-soleus. The H′ test reflex was compared to a reference H reflex, and sample records in Fig. 4.8(*b*) show the different responses recorded in the EMG at rest and during a strong tonic voluntary contraction of the gastrocnemius-soleus. The intensity of the S1 conditioning stimulus (upper traces) was adjusted so that the H1 conditioning reflex was maximal at rest, thus ensuring that (i) its size was modified little by the contraction, and (ii) the corresponding H′ reflex was well within its decay phase (cf. p. 160), whatever the strength of contraction (see the vertical dashed line in Fig. 4.8(*c*)). S1 also evoked a small M wave, the stability of which was used to verify that stimulating conditions did not change during the contraction (Chapter 1, p. 8). The test stimulus (SM, second traces) can evoke a small late response, 'V1', at reflex latency during contraction, because: (i) the collision in a very few motor axons between natural impulses due to the voluntary effort and the antidromic motor volley frees them from the latter, and allows the reflex response due to SM to pass (Upton, McComas & Sica, 1971), and (ii) the contraction potentiates F waves (Chapter 1, p. 23). When present, this late response was subtracted from the H′ test reflex. Combined S1 and SM (10 ms ISI, third traces) resulted in M_{max} followed by the H′ test reflex. Changes in H′ during contraction were compared to those of a reference H reflex (bottom traces) of the same amplitude as H′ at rest. To investigate the period preceding the contraction, despite the silent period induced in the voluntary EMG by H and M waves, the subjects were trained to perform simultaneous contractions of soleus in both legs. The time interval between reflex responses in the ipsilateral limb and the onset of the on-going EMG in the contralateral soleus was then assessed.

Changes in H′ and reference H reflexes during various soleus voluntary contractions

Tonic contractions of gastrocnemius-soleus

During tonic contractions of gastrocnemius-soleus at various force levels, the H′ and reference H reflexes undergo different changes (Hultborn & Pierrot-Deseilligny, 1979a; Fig. 4.8(*d*)). The size of the reference H reflex increases with each level of contraction, though the greatest increase occurs from rest to weak contraction. By contrast, the amplitude of the H′ test reflex decreases during the weakest contractions. With greater contraction force, there is facilitation of H′, which then increases with contraction force, and finally exceeds the reference H reflex in the strongest contractions.

Effect of muscle fatigue

During a prolonged contraction of soleus at 20% of MVC for 10 min, the amplitude of the H′ test reflex is significantly greater at the end of the contraction, when there is evidence of muscle fatigue (Löscher, Cresswell & Thorstensson, 1996).

Ramp contractions

During ramp contractions, the H′ and reference H reflexes undergo almost reciprocal changes (Hultborn & Pierrot-Deseilligny, 1979a; Fig. 4.8(*e*)). At the earliest intervals following the EMG onset, the amplitude of H′ was smaller than at rest, as occurs during weak tonic contractions, but it then increased progressively until the end of the ramp. By contrast, the reference H reflex was maximal at the onset of the ramp and then decreased throughout the ramp phase. Thus, the greatest increase in H′ relative to the reference H reflex was towards the end of the ramp. During the plateau, the H′ test reflex decreased while the reference H reflex remained stable, so that the two reflexes became more similar in amplitude, much as occurs during tonic contractions of medium force. A similar reciprocal time course for H′ and reference H has been found for faster ramp contractions lasting 250 and 500 ms.

Changes prior to contraction

Throughout the 50 ms prior to a ramp contraction, the same changes have been observed as at the onset of contraction, i.e. an increase in the reference H but a decrease in the H′ test reflex with respect to rest values (Katz, Pierrot-Deseilligny & Hultborn, 1982).

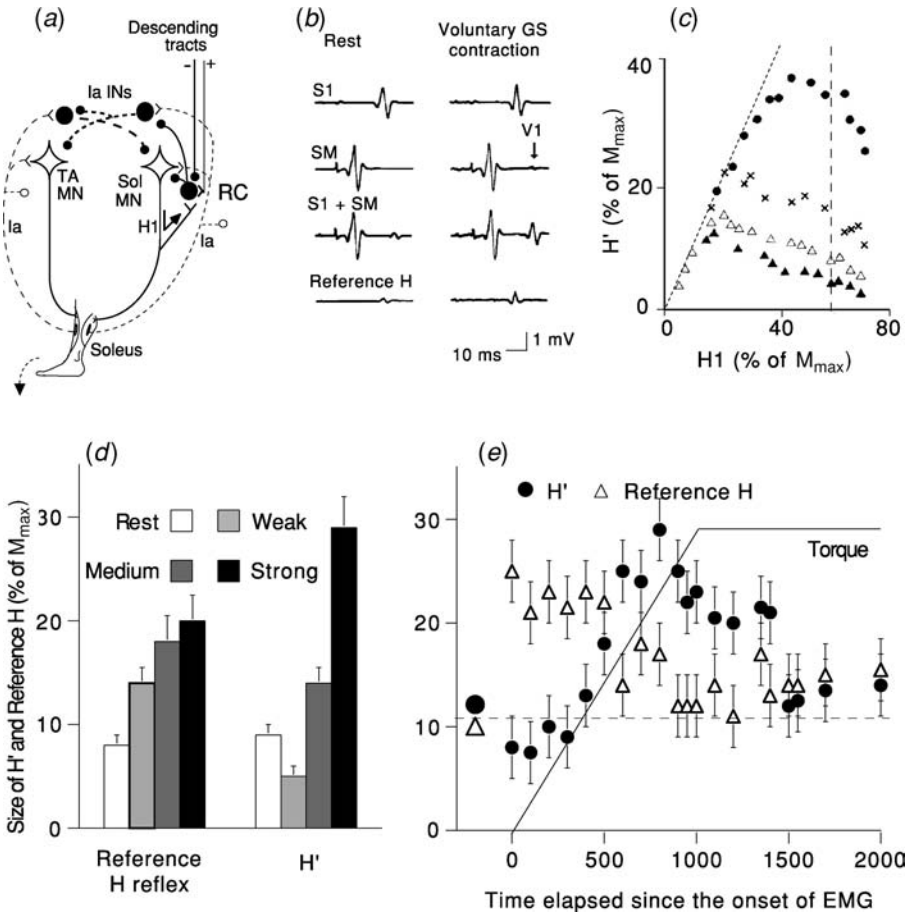


Fig. 4.8. Changes in homonymous recurrent inhibition to soleus motoneurones during voluntary contractions of gastrocnemius-soleus. (*a*) Sketch of the presumed pathways, with projections of Renshaw cells (RC) to both soleus (Sol) motoneurones (MN) and Ia inhibitory interneurones (INs) to tibialis anterior (TA) MNs, and mutual inhibition of 'opposite' Ia INs. Continuous arrow: conditioning reflex discharge (H1); dotted arrow: stretch of TA caused by Sol contraction. (*b*)–(*e*) Data from single subjects. (*b*) Sample records of EMG responses elicited at rest (left) and during strong tonic contraction of gastrocnemius-soleus (GS) (right). From top to bottom, responses elicited by S1 (6 mA, eliciting a maximal H reflex which did not increase during contraction), SM evoking a late response (V1, arrow) during contraction, S1 + SM (10 ms ISI), and a stimulus evoking a reference H reflex of the same size as H′ at rest. (*c*) The H′ test reflex (as a percentage of M_{max}) is plotted against H1 at rest (△) and during tonic GS contractions of 10% (▲), 40% (×) and 80% (●) of MVC (dotted oblique line, theoretical curve obtained if H′ = H1). (*d*) Reference (left group of histograms) and H′ test (right group of histograms) reflexes (as a percentage of M_{max}) are compared at rest (□) and during tonic GS contractions of increasing force: 10% (pale grey), 40% (dark grey) and 80% (■) of MVC. H′ was obtained with the H1 reflex at 60% of M_{max}, i.e. within the range where increases in H1 resulted in a progressive decrease in the absolute size of H′ (vertical dashed line in (*c*)). (*e*) Time course of the changes in H′ (●) and reference H (△) reflexes (as a percentage of M_{max}) during a ramp-and-hold contraction of 1 s. Torque (continuous thin line) increased over 1 s (ramp phase) to reach 60% of MVC and was then held at that level for a further 1 s. Large symbols on the left and horizontal dashed line indicate rest values. Each column or symbol in (*c*)–(*e*) is the mean of 20 measurements. Vertical bars 1 SEM (*d*), ±1 SEM (*e*). Modified from Hultborn & Pierrot-Deseilligny (1979a), with permission.

Period following contraction

H′ test and reference H reflexes are suppressed to the same extent immediately after relaxation of a tonic voluntary contraction of soleus (Schieppati & Crenna, 1985). This suggests that increased recurrent inhibition does not contribute to the termination of a voluntary contraction. (The reflex suppression is then probably due to post-activation depression following the activation of Ia afferents in the contraction, cf. Chapter 1, pp. 13–14).

Ballistic contractions

Both reference H and H′ test reflexes are facilitated at the onset of ballistic contractions with respect to their rest values, and this facilitation then progressively decreases, but the H′ test reflex is much less facilitated than the reference H reflex (Katz, Pierrot-Deseilligny & Hultborn, 1982).

Mechanisms underlying the changes in H′ during homonymous voluntary contractions

A number of mechanisms may contribute to the finding that H′ test and reference H reflexes are differentially changed during homonymous contractions. They include (i) the lesser sensitivity of H′ to excitatory inputs (p. 161), (ii) changes in the AHP (p. 178), (iii) changes in transmission in the recurrent pathway following its activation by the motor discharge, and (iv) changes in the descending control of Renshaw cells.

Mechanisms other than changes in recurrent inhibition

Both the lesser sensitivity of H′ to excitatory inputs and the summation of AHP following the H1 conditioning discharge with that resulting from a preceding voluntary spike could explain why H′ is less facilitated than the reference H during soleus contractions. However, the summation of the AHPs does not apply prior to ramp contractions, and the lesser sensitivity of H′ to *excitatory* inputs cannot explain the *depression* of H′ with respect to rest values during weak contractions. Nor can such mechanisms account for the opposite result (the greater facilitation of H′ than of reference H) observed during strong contractions and towards the end of ramps. The possible effects of a decrease in the AHP during strong contractions are considered below.

Effects of the voluntary motor discharge

Activation of Renshaw cells by the voluntary motor discharge via recurrent collaterals is the most obvious change in the input to Renshaw cells during homonymous contractions. The greater drive on Renshaw cells could facilitate their discharge or, paradoxically have the opposite effect, i.e. a reduced Renshaw cell output. The latter could occur through different 'occlusive' mechanisms between natural motor and conditioning reflex discharges: occlusion at Renshaw cell level (Eccles, Fatt & Koketsu, 1954), mutual inhibition of Renshaw cells (Ryall, 1970), and post-activation depression at the recurrent collateral terminals (Hultborn, Pierrot-Deseilligny & Wigström, 1979a). However, there are several arguments why occlusive mechanisms are unlikely to be responsible for the greater facilitation of H′ during strong contractions (an unexpected result, given the greater natural motor drive to Renshaw cells). (i) In cat experiments, the output from Renshaw cells and the resulting recurrent inhibition of motoneurones caused by a phasic motor volley is increased when Renshaw cells receive a tonic excitatory input (see p. 152; Hultborn & Pierrot-Deseilligny, 1979b). (ii) In human subjects, the same results were obtained with H1 conditioning reflexes of different size, but occlusion should be reduced with smaller conditioning reflex discharges (Hultborn & Pierrot-Deseilligny, 1979a,b). (iii) During ballistic contractions, H′ is less facilitated than reference H despite the strong voluntary drive (see above). (iv) H′ is profoundly inhibited towards the end of co-contraction of soleus and tibialis anterior with the same level of soleus EMG activity as during isolated plantar flexion (see pp. 180–1; Fig. 4.9(*d*), (*e*)).

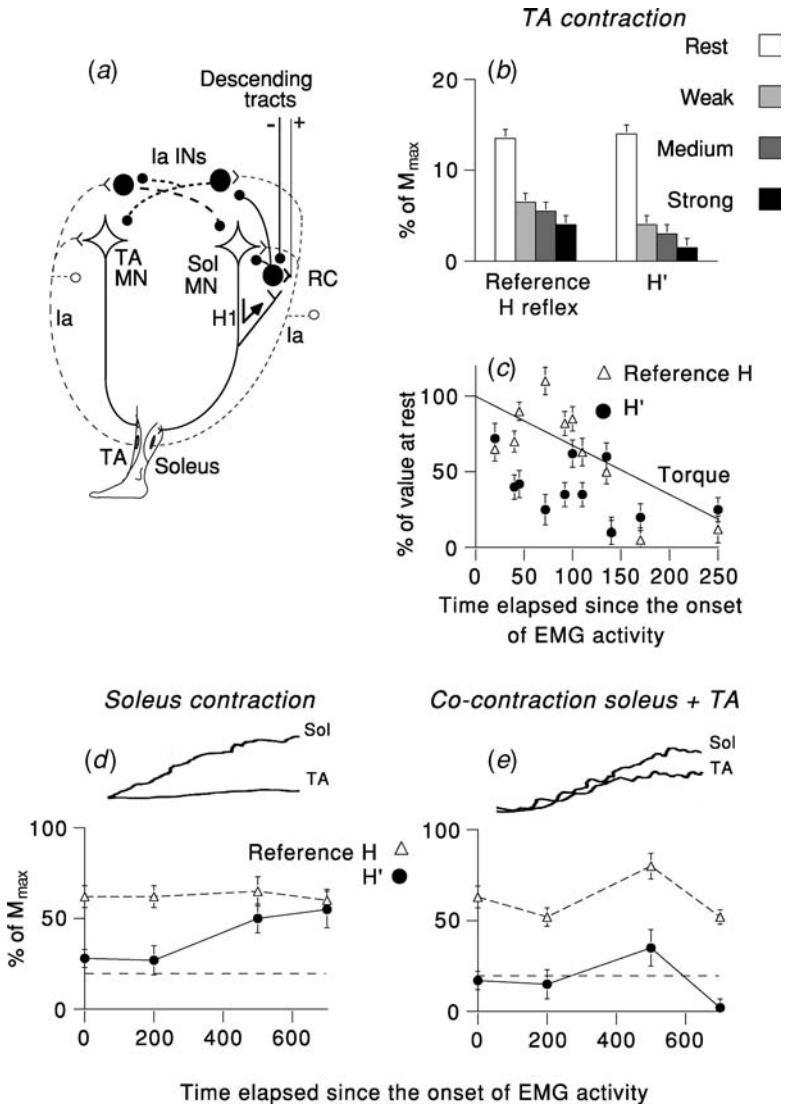


Fig. 4.9. Changes in homonymous recurrent inhibition to soleus motoneurones during contractions of tibialis anterior and soleus, separately and together. (*a*) Sketch of the presumed pathways, with projections of Renshaw cells (RC) to both soleus (Sol) motoneurones (MNs) and Ia inhibitory interneurones (INs) directed to tibialis anterior (TA) MNs, and mutual inhibition of 'opposite' Ia INs. The arrow (H1) indicates the conditioning reflex discharge. (*b*)–(*e*) show data from different subjects (same subject in (*d*), (*e*)). (*b*) Reference H (left group of histograms) and H′ test reflexes (right group of histograms) (as a percentage of M_{max}) are compared at rest (□) and during TA tonic contractions of increasing forces: 8% (pale grey), 30% (dark grey) and 45% (■) of MVC. (*c*) H′ (●) and reference H (△) reflexes (expressed as a percentage of their value at rest) are plotted against the time after onset of EMG activity during ramp dorsiflexion over 250 ms (torque, continuous thin line). (*d*), (*e*) H′ (●) and reference H (△) reflexes (expressed as a percentage of M_{max}) are plotted against the time after onset of EMG activity during a ramp-and-hold plantar flexion (*d*) and co-contraction of Sol and TA (*e*). The EMG activity progressively increased over 700 ms. Horizontal dashed lines indicate the rest value of the reflexes. Sample records at the top of (*d*), (*e*) show the integrated EMG traces (time constant 120 ms) from Sol and TA. Each column or symbol in (*b*)–(*e*) is the mean of 20 measurements. Vertical bars 1 SEM (*b*), ±1 SEM ((*c*)–(*e*)). Adapted from Katz & Pierrot-Deseilligny (1984) ((*b*), (*c*)) and Nielsen & Pierrot-Deseilligny (1996) ((*d*), (*e*)), with permission.

Decreased recurrent inhibition or reduction of the AHP?

During strong tonic contractions and towards the end of ramp contractions, H′ is more facilitated than the reference H, despite (i) its lesser sensitivity to excitatory inputs, (ii) the summation of the AHPs, and (iii) the facilitation of Renshaw cells by the strong motor discharge via recurrent collaterals. This cannot be attributed to occlusion in the recurrent pathway (see above). Inhibition of Renshaw cells therefore appears probable. Indeed, the degree of H′ inhibition is likely to be underestimated in these studies, because of the factors discussed above that would produce less facilitation of H′ than of the reference H. An alternative possibility would be a differential change in the AHP during weak and strong contractions. It might therefore be prudent to retain a reservation about the cause of the changes in H′ during contractions of different strengths until it is clarified (i) whether these contractions are accompanied by descending monoaminergic excitation depressing the AHP, (ii) whether they produce plateau potentials, and (iii) whether plateau potentials alter the AHP (and therefore H′) (see p. 161). Regardless of this unresolved issue, similar changes in *heteronymous* recurrent inhibition to voluntarily activated motoneurones have been observed using a method in which the test reflex did not undergo the AHP following the conditioning reflex discharge (Iles & Pardoe, 1999; see below). Because this finding was observed with a method independent of changes in AHP, it confirms that recurrent inhibition is decreased during strong contractions.

Origin of Renshaw cell inhibition

The possibility of Renshaw cell inhibition due to activation of cutaneous receptors by pressure on the sole of the foot has been excluded in specific experiments, in which similar pressure by itself did not modify recurrent inhibition (Hultborn & Pierrot-Deseilligny, 1979a). By exclusion, the inhibition of Renshaw cells is likely to be of supraspinal origin, and this conclusion is supported by direct evidence: stimulation of the motor cortex depresses transmission in the recurrent pathway (see p. 173).

Descending facilitation of Renshaw cells

The increase in recurrent inhibition observed during weak tonic contractions in normal subjects has not been observed in spastic patients, despite the same on-going motor activity and a normal level of recurrent inhibition at rest (see pp. 186–7). This suggests that the increase is not due to Renshaw cell activation by the natural motor discharge. Further support comes from the finding that the H′ test reflex is inhibited prior to a ramp contraction while reference H is facilitated, changes that occur in advance of any motoneurone discharge or afferent activation related to the contraction. This suggests supraspinal facilitation of Renshaw cells during moderate voluntary tonic contractions, as has been described in animal experiments after stimulation of different higher centres (p. 153).

Changes in heteronymous recurrent inhibition during voluntary contractions

Heteronymous recurrent inhibition of quadriceps motoneurones due to a soleus motor discharge has been assessed with the quadriceps H reflex during tonic voluntary contractions of the quadriceps (Iles & Pardoe, 1999). Recurrent inhibition progressively declined with the strength of the contraction, and fell to zero at ~35% of MVC. This resembles the inhibition of soleus-coupled Renshaw cells described during strong soleus contraction, but differs in two points: (i) absence of increased recurrent inhibition for the lowest levels of forces (which has been observed for homonymous recurrent inhibition at quadriceps level using the paired H reflex technique, Rossi & Mazzocchio, 1991), and (ii) the finding that recurrent inhibition was completely inhibited with a much lower level of force than during homonymous soleus contraction. Two reasons could account for the lesser decrease in homonymous than in heteronymous recurrent inhibition of the

motoneurones involved in voluntary contractions: (i) as discussed above, the decrease in homonymous recurrent inhibition is underestimated with the paired H reflex technique, given the lesser sensitivity of H′ to excitatory inputs, and the summation of the AHPs; (ii) if homonymous and heteronymous inhibitions operate through different pathways, the summation in Renshaw cells of the natural motor activity and the conditioning discharge would facilitate homonymous recurrent inhibition (see above), but not heteronymous recurrent inhibition.

Conclusions and functional implications

The main finding is that, during a strong contraction or towards the end of ramp contractions, recurrent inhibition directed to active motoneurones is depressed despite the activation of Renshaw cells by the natural motor discharge via recurrent collaterals. A similar result was obtained with heteronymous recurrent inhibition, i.e. with a method independent of possible changes in the motoneuronal AHP during contraction.

Descending inhibition of Renshaw cells

The decreased recurrent inhibition occurs because Renshaw cells receive potent descending inhibition which is likely to be corticospinal in origin. This interpretation is consistent with the decrease in recurrent inhibition observed after stimulation of the motor cortex (cf. p. 173). The reduction of recurrent inhibition of motoneurones during strong contractions ensures a high input–output gain for the motoneurone pool, and this would favour large tension output. During sustained long-lasting contractions, the absence of recurrent inhibition of silent homonymous motoneurones would facilitate their recruitment, thus helping overcome fatigue.

Inhibition of Renshaw cells favours reciprocal Ia inhibition

It has been a general feature that, for a given level of force reached towards the end of phasic ramp contractions, Renshaw cells are more inhibited than when the same force is developed in a tonic contraction (Fig. 4.8(*e*)). This particular control probably occurs because effective reciprocal Ia inhibition of the antagonistic muscle is required during phasic contractions (Pierrot-Deseilligny, Katz & Hultborn, 1983). Indeed, agonist contractions (e.g. soleus) produce a stretch-induced Ia discharge from the antagonistic muscle (here tibialis anterior, Fig. 4.8(*a*)), and this is greater during a ramp contraction than during a tonic contraction, because the stretch is then both dynamic and static. This Ia discharge tends to produce two undesirable effects: excitation of antagonistic motoneurones (tibialis anterior) and of 'corresponding' Ia interneurones inhibiting agonist motoneurones (soleus). These effects may be opposed by the reciprocal Ia inhibition from soleus to tibialis anterior motoneurones and of 'opposite' Ia interneurones, provided that soleus-coupled Ia interneurones are not inhibited by recurrent inhibition. Thus, Renshaw cell inhibition during flexion–extension movements allows reciprocal Ia interneurones to exert their necessary inhibitory action (Fig. 4.8(*a*); Chapter 5, p. 222; Chapter 11, p. 519).

The gain hypothesis

The facilitation of Renshaw cells during weak contractions would be explained if recurrent inhibition served as 'a variable gain control' on the 'final common path' (Hultborn, Lindström & Wigström, 1979a): if the recurrent pathway is active, it will reduce the slope (the gain) of the input–output relation for the motoneurone pool. This reduction will be maximal when Renshaw cells are facilitated, as occurs during weak contractions. The resulting low gain for the motoneurone pool would allow supraspinal centres to operate over a large part of their working range and cause only small changes in muscle force. As a result, a facilitated recurrent pathway would improve resolution in the control of motor output. In contrast, an inhibited recurrent pathway would give rise to a high output gain allowing the central command to generate larger forces for a given drive, despite the strong motor discharge reaching Renshaw cells via recurrent collaterals.

Recurrent inhibition during contraction of the antagonistic muscle

The paired H reflex technique has been used to investigate changes in homonymous recurrent inhibition directed to soleus motoneurones during voluntary contraction of the antagonistic pretibial flexors (Katz & Pierrot-Deseilligny, 1984). With contractions of the antagonist, it is likely that there would be no change in the AHP of the agonist to complicate the interpretation of the changes in H′. Because of the AHP, the H′ test reflex is less sensitive than the reference H reflex to the inhibitory inputs related to the antagonistic contraction (see p. 161), and greater inhibition of H′ than of the reference H may be attributed to increased homonymous recurrent inhibition.

Changes during various contractions

Whatever the force of tonic voluntary ankle dorsiflexion, the H′ test reflex in the antagonistic soleus was more inhibited than the reference H reflex, indicating an increase in recurrent inhibition, as compared to rest (Fig. 4.9(*b*)). During the ramp phase of a ramp-and-hold voluntary dorsiflexion, the H′ test reflex continuously decreases, whereas the reference H reflex, which is inhibited at the onset of voluntary dorsiflexion, undergoes a later 'relative facilitation' due to the stretch-induced Ia discharge from the antagonistic muscle (Fig. 4.9(*c*); see Morin & Pierrot-Deseilligny, 1977). The stronger inhibition of H′ when there is relative facilitation of the reference H reflex indicates an increase in recurrent inhibition.

Origin and significance of the changes in recurrent inhibition

It was suggested that the increased recurrent inhibition of soleus motoneurones during voluntary contraction of antagonistic pretibial flexors was due to a descending facilitation of soleus-coupled Renshaw cells (Katz & Pierrot-Deseilligny, 1984). This could be one of the mechanisms that prevent a stretch reflex in soleus (see Chapter 11, p. 520). Any discharging motoneurones would inhibit other motoneurones and thus curtail the stretch reflex. In this respect, it is of interest that the maximal Renshaw cell facilitation is observed when the stretch-induced Ia discharge from the antagonistic muscle elicits a 'relative facilitation' of the reference H reflex.

Recurrent inhibition of antagonistic muscles involved in co-contraction

Recurrent inhibition during voluntary co-contraction of antagonistic muscles

Homonymous recurrent inhibition of soleus motoneurones, assessed with the paired H reflex technique, has been measured during co-contraction of antagonistic ankle plantar and dorsiflexors and during plantar flexion alone, at matched levels of background activity in the soleus muscle (Nielsen & Pierrot-Deseilligny, 1996).

Depression of the H′ test reflex

In soleus, the H′ reflex is depressed during weak and facilitated during strong plantar flexion (cf. p. 174), but it is always strongly depressed during tonic co-contractions, regardless of their force level. This finding suggests differential control of recurrent inhibition during the two types of contraction (see below). Interestingly, heteronymous recurrent inhibition to quadriceps motoneurones, assessed with a method independent of possible changes in the motoneuronal AHP during contraction, is also differentially controlled during tonic contractions of quadriceps (decreased) and co-contraction of quadriceps and hamstrings (unchanged) (Iles & Pardoe, 1999). During a ramp contraction, the reference H reflex was facilitated with respect to its rest value in both types of contraction, but H′ underwent different changes: continuous increase throughout the ramp plantar flexion with complete suppression at the end of the ramp co-contraction (Fig. 4.9(*d*),(*e*)).

Specific control during co-contraction

It is unlikely that the control of soleus-coupled Renshaw cells during co-contraction is the sum of the opposite effects observed during isolated voluntary plantar and dorsiflexions.

(i) The inhibition observed during strong co-contraction is greater than the sum of the strong facilitation during strong plantar flexion and the moderate inhibition during strong dorsiflexion.

(ii) The strong inhibition of H′ observed during the first 100 ms of voluntary dorsiflexion (Fig. 4.9(*c*)) does not fit the finding that during co-contraction the H′ test reflex is inhibited towards the end of the ramp (Fig. 4.9(*e*)). This implies a specific control of recurrent inhibition during co-contraction, and would be in line with previous studies which have suggested that the descending control of spinal segmental pathways is conveyed by different descending pathways during co-contraction and during flexion–extension movements (see Chapter 11, p. 533).

Which control?

During strong contraction of the target muscle, the decreased recurrent inhibition to active motoneurones probably results from corticospinal inhibition of Renshaw cells (see above). The strong recurrent inhibition during co-contraction could be explained simply by suppression of this descending control, leaving the motor discharge-induced excitation of Renshaw cells unopposed by descending inhibition. If this were so, recurrent inhibition should parallel the on-going motor discharge. However, during ramp co-contractions, the inhibition of the H′ test reflex increases abruptly at the end of the ramp, and this suggests the existence of a supplementary descending facilitation of Renshaw cells.

Homonymous recurrent inhibition during active standing

Because contraction of either of the antagonistic ankle muscles may be required in postural tasks such as the maintenance of upright stance, recurrent inhibition of soleus motoneurones has been compared when standing with and without support (Pierrot-Deseilligny *et al.*, 1977). The H′ test reflex was significantly smaller during active stance than when standing with support (Fig. 4.10(*b*), (*c*)). The size of the reference H reflex was the same in the two situations, and increased recurrent inhibition of soleus motoneurones during active standing is therefore likely. The increased recurrent inhibition was not directly related to muscle contraction in the explored leg, because the same result has been observed in the absence of muscle contraction, when the subject placed most of the body weight on the unexplored leg. Neither was it due to the cutaneous afferent discharge from the sole of the foot because this discharge would be the same whether stance was supported or unsupported. The main difference between the two positions is that when equilibrium is unsteady, contractions may be required in either of the antagonistic muscles operating at the ankle, and this creates a situation where an increase in recurrent inhibition may be helpful in controlling body sway. The reinforcement of recurrent inhibition in active standing is probably due to a supraspinal mechanism, possibly vestibular. In this connection, homonymous recurrent inhibition of soleus motoneurones is enhanced during static backward tilt from 80° to 40° of a subject fixed to a tilting chair (Rossi, Mazzocchio & Scarpini, 1987).

Functional implications

Renshaw cells are facilitated during co-contractions of antagonistic muscles, contractions which, in the lower limbs, may be necessary in postural tasks. This is of functional interest, because: (i) transmission in the Ia inhibitory pathway must be depressed to allow the parallel activation of the two antagonistic muscles (see Chapter 5, p. 227), and Renshaw cell output contributes significantly to this depression; and (ii) it ensures that the gain of the stretch reflex is diminished at the output stage to prevent oscillations and clonus from developing during co-contractions (cf. Chapter 11, p. 534).

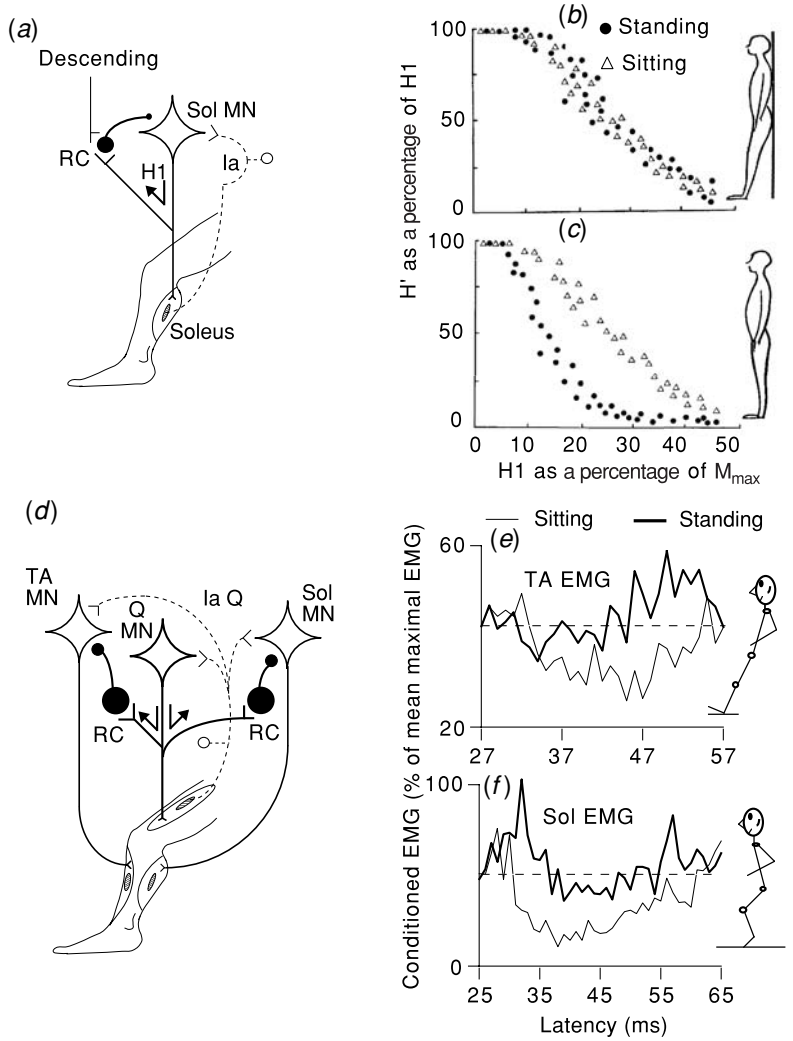


Fig. 4.10. Changes in recurrent inhibition during postural tasks. (*a*) and (*d*) Sketches of the presumed pathways of homonymous recurrent inhibition of soleus (Sol) motoneurones (MNs) (*a*), and heteronymous recurrent inhibition from quadriceps (Q) to Sol and tibialis anterior (TA) MNs (*d*). The arrows indicate the conditioning reflex discharges that activate Renshaw cells (RC). (*b*), (*c*) Homonymous recurrent inhibition to Sol MNs, assessed with the paired H reflex technique, in the sitting position (△) and in standing (●) with (*b*) and without (*c*) support of a wall. The size of the H′ test reflex of Sol (expressed as a percentage of the H1 conditioning reflex) is plotted against the size of H1 (expressed as a percentage of M_{max}). (*e*), (*f*) Heteronymous recurrent inhibition elicited by a Q H reflex discharge in the TA (*e*) and the Sol (*f*), assessed as the modulation on the on-going EMG of TA or Sol, during a voluntary co-contraction in sitting position on a high stool (thin lines) and postural co-contractions (thick lines) of Q and TA ((*e*), leaning backwards) or of Q and Sol ((*f*), preparation for hopping). The sketches on the right of each trace represent the postural task. Modified from Pierrot-Deseilligny *et al.* (1977) ((*b*), (*c*)), and Barbeau *et al.* (2000) ((*e*), (*f*)), with permission.

Heteronymous recurrent inhibition and heteronymous Ia excitation

The hypothesis that a function of heteronymous recurrent inhibition may be to limit the extent of Ia excitation has been examined by studying the changes in heteronymous recurrent inhibition during postural tasks requiring co-contraction of lower-limb muscles linked in Ia synergism.

Methodology

Recurrent inhibition of tibialis anterior and soleus motoneurones produced by a quadriceps H reflex discharge has been measured using three test responses: (i) the rectified and averaged ongoing EMG activity of tibialis anterior or soleus; (ii) the MEP elicited in these muscles by cortical stimulation; (iii) the soleus H reflex (Barbeau *et al.*, 2000). Recurrent inhibition from quadriceps was compared at matched levels of background EMG activity during voluntary co-contraction of quadriceps and of the relevant ankle muscle while sitting (control situation) and in different postural tasks. In the reverse paradigm (soleus to quadriceps), Renshaw cells were activated by a soleus H reflex and the resulting recurrent inhibition assessed with a quadriceps H reflex (Iles, Ali & Pardoe, 2000).

Decreased recurrent inhibition to motoneurones of the muscle involved in postural co-contraction

During postural co-contractions of quadriceps and tibialis anterior, as occur when standing and leaning backwards, heteronymous recurrent inhibition from quadriceps to tibialis anterior was reduced with respect to sitting, whether assessed with the on-going EMG activity (Fig. 4.10(*e*)) or the MEP. In the same situation, recurrent inhibition from quadriceps to soleus assessed with the H reflex was unchanged or increased. During postural co-contractions of quadriceps and soleus, as occur in preparation for hopping, recurrent inhibition from quadriceps to soleus was reduced with respect to sitting, whether assessed with the on-going EMG activity (Fig. 4.10(*f*)), the H reflex or the MEP, and recurrent inhibition to tibialis anterior was unchanged. In situations in which the soleus contraction was not associated with a quadriceps contraction (standing on tip of toes or leaning forwards during stance), heteronymous recurrent inhibition from quadriceps to soleus was unchanged. Similarly, heteronymous recurrent inhibition from soleus to quadriceps was reduced during postural stance involving quadriceps and soleus co-contraction when compared with similar voluntary muscle contractions when sitting (Iles, Ali & Pardoe, 2000).

Origin of the posture-related changes in recurrent inhibition

The decreased recurrent inhibition directed to muscles associated with the quadriceps in postural co-contractions is probably due to descending control because the on-going motor discharge reaching Renshaw cells via recurrent collaterals and the cutaneous activation due to the pressure of the foot sole would have been the same in the control and postural situations.

Functional implications

The above results support the view that the facilitation of heteronymous recurrent inhibition functions to limit the extent of heteronymous Ia excitation. As discussed in Chapter 2, prewired Ia connections link the quadriceps to both tibialis anterior and soleus operating at the ankle (and, similarly, the gastrocnemius-soleus to both quadriceps and biceps femoris). In functional terms this may be explained by the versatile synergisms required for various tasks (see Chapter 2, p. 94). These connections could become functionally inconvenient because any increase in activity of quadriceps Ia afferents might result in the simultaneous activation of antagonistic ankle flexor and extensor motoneurones. The Ia excitatory connection that is not appropriate for a particular movement (e.g. the quadriceps projections to soleus motoneurones when leaning

backwards) must therefore be controlled. This can be done through appropriate control of Renshaw cells: recurrent inhibition directed to motoneurones of the ankle muscle not involved in the co-contraction opposes Ia excitation, whereas Renshaw cells projecting onto motoneurones involved in the postural co-contraction are depressed (cf. Chapter 11, p. 538).

Studies in patients and clinical implications

In patients, only homonymous recurrent inhibition of soleus motoneurones has been studied using the paired H reflex technique. These investigations have involved mainly spastic patients.

Spasticity

On theoretical grounds, decreased recurrent inhibition could contribute to the stretch reflex exaggeration that characterises spasticity: activity of the motoneurone pool would then be less effectively opposed by recurrent inhibition, and so a greater discharge would ensue.

Changes in recurrent inhibition at rest

Three abnormal patterns have been observed in some patients (Katz & Pierrot-Deseilligny, 1982; 1998; Mazzocchio *et al.*, 1990): (i) absence of H′ test reflex, (ii) a plateau-like pattern, where the H′ reflex having attained its maximum remains unchanged (Fig. 4.11(*e*)), and (iii) a 'straight-line' pattern, in which H′ keeps increasing in parallel with H1 (Fig. 4.11(*f*)). The amplitude of H′ depends on the excitability of the monosynaptic reflex arc, which is enhanced in the lower limbs of spastic patients (as evidenced by an increased H_{max}/M_{max} ratio, see Chapter 12, p. 562). The greater excitability of motoneurones could protect them from the inhibition following the H1 discharge. Hence, an abnormally large H′ test reflex might reflect an increase in excitability of the monosynaptic reflex arc and/or a decrease in recurrent inhibition. The latter possibility can be explored by measuring the extent to which the H′ test reflex is modified by the acute injection or the chronic intake of L-Acetylcarnitine (L-Ac; pp. 159–60; Mazzocchio *et al.*, 1990; Mazzocchio & Rossi, 1997b). Abnormal patterns of H′ are unlikely to reflect a change in the AHP of the motoneurones because, in the cat, the AHP is not modified after chronic spinal transsection (Gustafsson, Katz & Malmsten, 1982).

Stroke patients

The absence of H′ is the most frequent finding on the affected side of stroke patients whatever the amplitude of H1. The H′ response cannot be elicited in ~30% of normal subjects and this is more frequent in stroke patients (53%, of 85 patients, Katz & Pierrot-Deseilligny, 1982). When present, H′ following a conditioning reflex discharge of 50% of M_{max} (i.e. within the range producing a decrease in the H′ test reflex in normal subjects) was of the same size as in normal subjects, and of equal or smaller amplitude than on their unaffected side (Katz & Pierrot-Deseilligny, 1982; Chaco *et al.*, 1984). Given that H_{max} is increased in soleus on the affected side of stroke patients (see Chapter 12, p. 576), the absence of H′ in most patients and lack of increase in its amplitude in others suggest enhanced recurrent inhibition in these patients.

Patients with spinal cord injury

There is evidence for an increase in recurrent inhibition in patients with complete or partial spinal cord injury at the cervical and thoracic levels. The soleus H′ reflex was absent in 13 of 18 patients and, when present, its amplitude was significantly smaller than in normal subjects (Shefner *et al.*, 1992).

Patients with amyotrophic lateral sclerosis

While H_{max} is not greater than in normal subjects, the amplitude of the H′ response was increased, suggesting a decrease in recurrent inhibition (Raynor & Shefner, 1994).

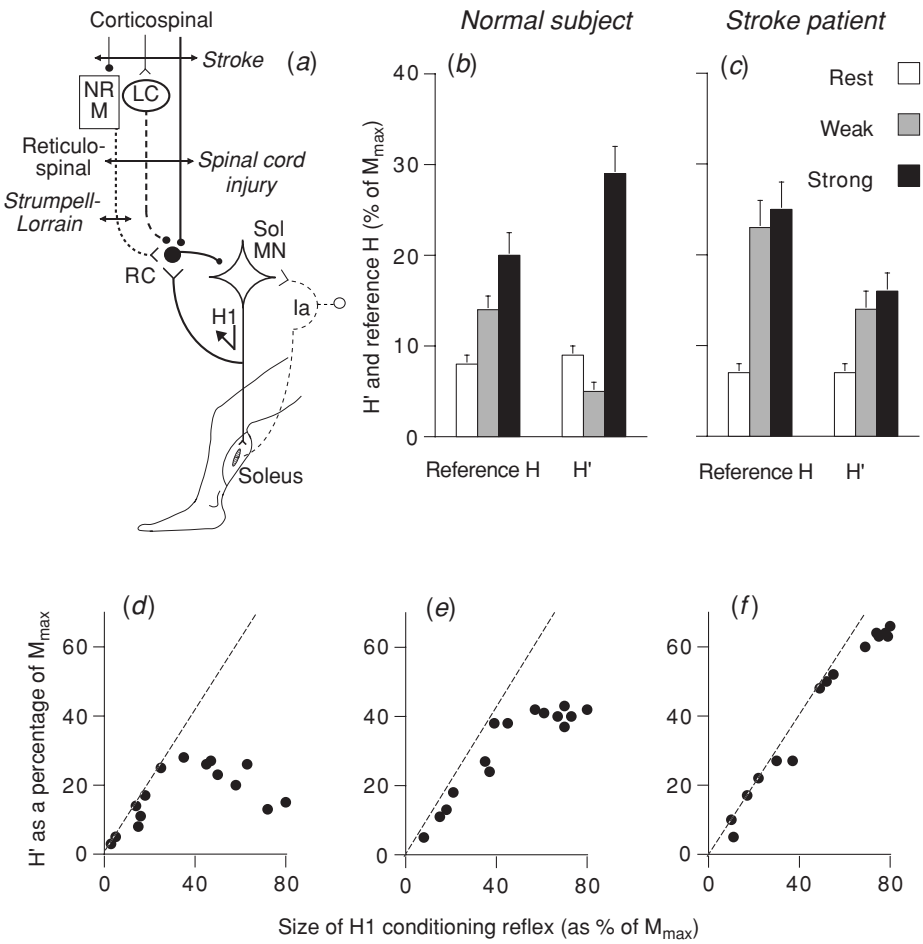


Fig. 4.11. Changes in recurrent inhibition in spastic patients. (*a*) Sketch of the presumed pathways. Renshaw cells (RC) mediating homonymous recurrent inhibition to soleus (Sol) motoneurones (MN) activated by the conditioning reflex discharge (arrow, H1) are inhibited by the corticospinal tract (continuous line) and a descending pathway (dashed line) from the locus coeruleus (LC) and are excited (dotted line) by a reticulospinal pathway from the nucleus raphe magnus (NRM). The LC is facilitated and the NRM inhibited by corticospinal projections, and a lesion of these corticospinal projections will enhance RC excitability. Lesions interrupting these different pathways at different levels in stroke, spinal cord injury and Strumpell–Lorrain disease (hereditary spastic paraplegia) are sketched by double-headed horizontal arrows. (*b*), (*c*) The size of the reference H reflex (left groups of histograms) and of the H′ test reflex (right groups of histograms), expressed as a percentage of M_{max}, at rest (□) and during soleus tonic contractions of weak (10% of MVC, pale grey columns) and strong (80% of MVC, ■) force in one normal subject (*b*) and one stroke patient with good recovery (*c*). (*d*)–(*f*) The size of H′ (as a percentage of M_{max}) is plotted against the size of H1 (as a percentage of M_{max}) in three different spastic patients to show the different patterns observed. (*d*) 'Bell-shaped' pattern with depression of H′ amplitudes starting with larger H1 reflex amplitude than in normal subjects. (*e*) 'Plateau-like' pattern. (*f*) 'Straight-line' pattern (the dotted oblique line represents the curve which would be recorded if H′ equalled H1). Modified from Katz & Pierrot-Deseilligny (1982) ((*b*), (*c*)) and (1998) ((*d*)–(*f*)), with permission.

Patients with hereditary spastic paraparesis (Strumpell–Lorrain disease)

In all patients tested, H′ could be recorded. Two patients had a 'straight-line' pattern (Fig. 4.11(*f*)), which was not modified by acute injection of L-Ac, possibly due to complete loss of recurrent inhibition coupled with other mechanisms, such as extended susceptibility of motoneurones to Ia excitatory effects (Mazzocchio *et al.,* 1990). In the remaining patients, the soleus H′ response was reduced by acute injection of L-Ac (Mazzocchio *et al.,* 1990), and they fell into two groups (Mazzocchio & Rossi, 1997b). About half had a 'bell-shaped' pattern similar to that observed in normal subjects except that, due to the hyperexcitability of the monosynaptic reflex arc, maximal depression of H′ amplitudes was obtained with significantly larger H1 reflex amplitudes (Fig. 4.11(*d*)). In these patients, the chronic intake of L-Ac reduced the size of H′ and H_{max}, and recurrent inhibition at rest was then considered to be normal. In the second group, H′ had a plateau-like pattern (Fig. 4.11(*e*)) and neither H′ nor H_{max} were modified by chronic intake of L-Ac. Given the absence of effect of L-Ac, the absence of a decay phase in H′ is unlikely to be due to a decrease in the AHP, and this group was considered to have a *reduced* recurrent inhibition at rest.

Conclusions

Only in those patients with slowly progressive paraparesis is there evidence for decreased recurrent inhibition at rest. However, as will be seen below, even when recurrent inhibition appears normal at rest, its control during voluntary movements is disturbed.

Mechanisms underlying changes in recurrent inhibition in spastic patients

Increased recurrent inhibition after corticospinal lesions

Given the corticospinal suppression of recurrent inhibition observed in normal subjects, increased recurrent inhibition at rest in patients after stroke or spinal cord injury implies that the corticospinal inhibition is normally exerted tonically. The descending inhibition may be due to a control exerted directly onto Renshaw cells or indirectly through reticulospinal nuclei (Fig. 4.11(*a*) and its legend). In addition, Renshaw cells have been shown to receive noradrenergic inhibition from the locus coeruleus (Fung, Pompeiano & Barnes, 1987), and supraspinal tonic inhibition via serotonergic pathways (Sastry & Sinclair, 1976). In any case, increased recurrent inhibition after stroke or spinal cord injury implies that Renshaw cells are released from a descending tonic inhibition. This change is the opposite of that required for abnormal recurrent inhibition to play a role in the stretch reflex exaggeration of spasticity.

Hereditary spastic paraparesis

In hereditary spastic paraparesis, the pathology suggests involvement of the dorsal reticulospinal tract with lesser involvement of the corticospinal tract (for references, see Mazzocchio & Rossi, 1997b; Fig. 4.11(*a*)). It is therefore likely that the resulting lesion spares more the descending inhibitory pathways than the descending facilitatory pathways to Renshaw cells and shifts the balance in favour of the former.

Amyotrophic lateral sclerosis

In amyotrophic lateral sclerosis, the increase in recurrent inhibition probably reflects pathology within the spinal cord rather than the loss of corticospinal inputs due to the upper motoneurone lesion.

Changes in homonymous recurrent inhibition during motor tasks in spastic patients

Changes in recurrent inhibition during contraction have been compared in normal subjects and in hemiplegic and paraparetic patients (Katz & Pierrot-Deseilligny, 1982; Mazzocchio & Rossi, 1989), chosen because all had a normal 'bell-shaped'

pattern of H′ at rest and were able to perform tonic voluntary contractions of soleus at different forces (Fig. 4.11(*b*), (*c*)). In normal subjects, an increase in recurrent inhibition during weak contractions is inferred from facilitation of reference H but inhibition of H′, and a decrease in recurrent inhibition during strong contractions is inferred from greater facilitation of H′ than of reference H (p. 174; Fig. 4.11(*b*)). These changes were not seen in the patients, in whom H′ was enhanced during both weak and strong contractions, though to a lesser extent than reference H (as in Fig. 4.11(*c*)). The different task-related modulations of recurrent inhibition seen in healthy subjects (increase during weak contractions of soleus, contractions of tibialis anterior and active stance, but decrease during strong contractions of soleus) were absent in most patients. These abnormalities are probably a consequence of the lesion interrupting the corticospinal pathway conveying the coordinates for the execution of the movement to Renshaw cells. It is probable that the control of Renshaw cells mediating heteronymous recurrent inhibition is similarly impaired, no longer able to oppose unwanted Ia connections. If so this would render muscle synergies less flexible, and could contribute to the involuntary synkinetic movements seen in hemiplegic patients.

Patients with other movement disorders

Patients with a form of cerebral palsy

Recurrent inhibition has been tested in patients who had suffered perinatal brain damage, producing mental retardation, rigidity and inflexible voluntary and/or postural movements, but without pyramidal, extrapyramidal or cerebellar signs. They had a normal 'bell-shaped' pattern of H′, but task-dependent modulations of recurrent inhibition (during weak and strong soleus contractions, tibialis anterior contraction or active stance) were absent. It was suggested that the absence of adaptive changes in recurrent inhibition could partly account for motor difficulties experienced by these patients (Rossi, Decchi & Vecchione, 1992).

Hyperekplexia

In patients with hyperekplexia, a neurological disease with a deficient glycinergic inhibitory system (see Chapter 5, p. 233), recurrent inhibition is preserved (Floeter *et al.*, 1996). Renshaw cells release both GABA and glycine (Schneider & Fyffe, 1992), and it is possible that the release of GABA is sufficient to ensure normal Renshaw cell function.

Parkinson's disease

In patients with Parkinson's disease, homonymous recurrent inhibition of soleus is not modified (Delwaide, 1985; Lalli, Panizza & Hallett, 1991).

Conclusions

Changes in recurrent inhibition in normal motor control

Recurrent inhibition is not a simple negative feedback to motoneurones and, when its functional role is considered, projections to both motoneurones and Ia interneurones must be taken into account. It is also probable that recurrent inhibition serves several functions, that are not exclusive.

During strong flexion–extension movements, homonymous recurrent inhibition to active motoneurones is depressed by a descending (probably corticospinal) inhibitory control. This: (i) ensures a high input–output gain for the motoneurone pool, and (ii) favours a potent depression of antagonistic motoneurones through reciprocal Ia inhibition, thereby preventing unwanted stretch reflex activation of antagonistic muscles. The latter action is supported by facilitation of recurrent inhibition to motoneurones of the antagonistic muscles.

During co-contractions of antagonistic muscles in the lower limb, recurrent inhibition is facilitated or at least not inhibited. Again, this could serve two roles: (i) to ensure the depression of reciprocal Ia inhibition necessary to allow parallel activation of the antagonists, and (ii) to limit the gain of the stretch

reflex so preventing the system from breaking into oscillations.

Because of the parallel distribution of heteronymous recurrent inhibition and heteronymous monosynaptic Ia excitation in the lower limb, recurrent inhibition could limit the extent of Ia excitation. Thus, the descending control of heteronymous recurrent inhibition allows the selection of the appropriate Ia synergism for various postural tasks, by opposing Ia connections that are not required for the chosen task.

Changes in recurrent inhibition and pathophysiology of movement disorders

Only in those patients with slowly progressive spastic paraparesis is there evidence for decreased recurrent inhibition at rest. In most spastic patients with corticospinal lesions (after stroke or spinal cord injury) homonymous recurrent inhibition is normal or increased at rest. However, the ability to modulate recurrent inhibition appropriately for the task being undertaken is lost.

Résumé

Background from animal experiments

Motor axons give off recurrent collaterals, which release the excitatory transmitter acetylcholine, activating interneurones (called Renshaw cells), that in turn inhibit motoneurones. The recurrent IPSP in motoneurones has the short central latency of a disynaptic pathway but a long duration (~40 ms). Recurrent collaterals have been found for axons of motoneurones innervating proximal muscles but not for axons of motoneurones of distal muscles. Independently of excitation produced by the discharge of motoneurones, Renshaw cells receive excitation from peripheral afferents and from a number of higher centres. They are inhibited by cutaneous and group II afferents and by corticospinal volleys. There is a striking overlap between the distribution of heteronymous Renshaw inhibition and monosynaptic Ia excitation. Renshaw cells inhibit Ia interneurones mediating reciprocal Ia inhibition to motoneurones antagonistic to those giving off the recurrent collaterals which excite them. They also inhibit other Renshaw cells and γ motoneurones.

Methodology

Use of antidromic motor volleys to activate homonymous Renshaw cells is invalid in human subjects

Activation of Renshaw cells by an antidromic motor volley must be employed in humans with great care because, when the dorsal roots are intact, the stimulation also produces an orthodromic group I volley, the effects of which interfere with recurrent inhibition, and a complex late afferent discharge in response to the muscle twitch due to the motor volley.

The paired H reflex technique to investigate homonymous recurrent inhibition

Underlying principles, conditioning and test reflexes

Renshaw cells are activated orthodromically by a conditioning reflex discharge, and a collision in motor axons is used to prevent the conditioning reflex from reaching the muscle and producing a twitch-induced afferent discharge. Only motoneurones that discharge in the first (H1) reflex will have their excitability assessed by the subsequent test volley. The test stimulus (SM) is supramaximal for α motor axons and produces an antidromic motor volley in all α motor axons. The H1 conditioning reflex discharge collides with this antidromic motor volley and eliminates the antidromic impulses in the corresponding motor axons so that the test reflex evoked by SM (H′) can appear in these axons. The motoneurones that discharge in H′ will be affected by the post-spike AHP because these motoneurones discharged in the H1 conditioning reflex. At conditioning-test intervals $\geq$10 ms, Ib inhibition evoked by the

conditioning volley cannot contaminate recurrent inhibition.

Evidence for recurrent inhibition

At low conditioning reflex amplitudes H′ remains equal to H1, but further increases in H1 result in a progressive decrease in H′, which is related to the size of the conditioning reflex discharge. This strongly suggests that, in addition to the AHP, the reflex depression is caused by recurrent inhibition set up by the larger conditioning reflex discharge. The time course of the depression of H′ resembles that of recurrent inhibition in animal experiments.

Pharmacological validation

Intravenous injection of a cholinergic agonist (L-acetylcarnitine, L-Ac), that does not alter the size of a control H reflex of similar size, the amount of Ib inhibition or the amplitude of the AHP, potentiates the inhibition of the H′ test reflex. This provides independent evidence for a Renshaw origin of the suppression.

Two conditions must be met to use the paired H reflex technique

The size of the H1 conditioning reflex discharge must be identical in the situations that are compared, and the H1 conditioning discharge must be within the range where an increase results in a progressive decrease in the size of the H′ test reflex expressed as a percentage of M_{max}.

Possible changes in the post-spike AHP

The depression of the test reflex after the H1 discharge also depends on the AHP of the motoneurones discharging in H1. Suppression of H′ will therefore provide an accurate measure of recurrent inhibition, only if the AHP does not change. However, the AHP can vary under certain conditions: activation of descending monoaminergic pathways, and probably when plateau potentials develop in motoneurones.

Comparison with a reference H reflex

The amplitude of the H′ test reflex also depends on any changes in motoneurone excitability in the tested situation. The excitability of the motoneurone pool should be monitored using a control H reflex (reference H) of the same size as H′ in the control situation. Because of changes in membrane conductance during the AHP, motoneurones that have discharged in the H′ test reflex will be less sensitive to PSPs. Thus, there will have been evidence for a change in recurrent inhibition when there is greater change in the H′ test reflex than in the reference H reflex: greater facilitation of H′ reflects decreased recurrent inhibition, and greater inhibition of H′ increased recurrent inhibition.

Conclusions

Although it appears complex, the paired H reflex technique is the only method available to assess *homonymous* recurrent inhibition under physiological and pathological conditions. However, it would be prudent to interpret changes in the size of the H′ test reflex with care, taking into account whether the AHP might have been different in the control and test conditions.

Methods to investigate heteronymous recurrent inhibition

Underlying principle

A conditioning motor discharge, whether a reflex or an antidromic motor volley, is used to activate Renshaw cells, and the resulting recurrent inhibition is assessed in a heteronymous muscle by one of the methods exploring the excitability of the motoneurones: PSTHs of single units, H reflex, and modulation of the on-going EMG or the MEP.

Evidence for recurrent inhibition

Recurrent inhibition is suggested when the depression elicited by the conditioning volley appears and increases with the conditioning motor discharge, is independent of the conditioning stimulus intensity *per se*, has a short central delay, 1–2 ms longer than monosynaptic Ia excitation, and has a long duration, more than 15 ms. In addition the depression is commonly preceded by a peak of monosynaptic Ia excitation. When the conditioning discharge is a monosynaptic reflex, there are cogent arguments against a significant contribution of other pathways to the suppression. When the inhibition is evoked by electrical stimuli above 1 × MT, its Renshaw origin may be more questionable, because the conditioning afferent volley is more complex. However, the findings may be validated by the administration of L-Ac, which increases the long-lasting inhibition produced by the antidromic volley above 1 × MT, without altering early low-threshold group I effects.

Limitations

Ia EPSPs elicited by the conditioning volley can contaminate recurrent inhibition, and the test response is the net result of these opposite matched effects. Recurrent inhibition must therefore be assessed at a long ISI when Ia EPSPs and group I IPSPs evoked by the conditioning stimulus have subsided and the recurrent IPSP is still present.

Conclusion

In clinical studies, the modulation of the on-going EMG is the simplest method.

Organisation and pattern of connections

Homonymous projections to motoneurones

There is evidence for homonymous recurrent inhibition affecting the motor nuclei of all proximal muscles so far tested. The absence of recurrent inhibition in motor nuclei of intrinsic muscles of the hand and foot probably reflects the absence of recurrent collaterals on the corresponding motor axons.

Heteronymous projections to motoneurones

Lower limb

Recurrent connections are much more widely distributed than in the cat hindlimb with, in particular, transjoint connections between quadriceps and all muscles operating at the ankle, and from triceps surae to quadriceps. There is a striking overlap between the distributions of heteronymous recurrent inhibition and of heteronymous monosynaptic Ia excitation. However, some Ia connections are not matched by equivalent recurrent connections and, conversely, some recurrent connections have no Ia equivalent.

Upper limb

Heteronymous transjoint connections are much more restricted in the upper than in the lower limb and do not exist from proximal to distal muscles. An interesting finding is the mutual recurrent inhibition of ECR and FCR motoneurones.

Ia inhibitory interneurones

Ia inhibitory interneurones are inhibited by the recurrent pathway at elbow and ankle levels. Recurrent inhibition of reciprocal inhibition does not exist at wrist level. This finding raises the question of whether the reciprocal inhibition between these muscles is a 'true reciprocal Ia inhibition' (see Chapter 5).

TMS suppresses homonymous and heteronymous recurrent inhibition

This is an effect that occurs only a few milliseconds later than the cortical excitation of motoneurones.

Motor tasks and physiological implications

Recurrent inhibition of motoneurones of a muscle involved in a selective contraction

In the paired H reflex technique, changes in recurrent inhibition can be inferred from differential changes in the H′ test reflex and in a reference H reflex of the same size at rest.

(i) Inhibition of H′ while reference H is facilitated has been observed during weak tonic soleus contractions and at the beginning of ramp contractions. That a similar result may be observed prior to the ramp contraction, i.e. in advance of any contraction-related mechanism, such as motoneurone firing or afferent discharge related to the contraction, provides evidence that the inhibition of H′ is due to descending facilitation of Renshaw cells.

(ii) In contrast, H′ is facilitated significantly more than the reference H during strong tonic contractions and towards the end of a ramp contraction. The greater facilitation of H′ may result from a reduction of recurrent inhibition or of the AHP. The former appears more likely, because a similar result was obtained with heteronymous recurrent inhibition to active motoneurones, i.e. with a method independent of the motoneuronal AHP during contraction. The reduction of recurrent inhibition was shown not to be due to an occlusive mechanism between natural motor and conditioning reflex discharges running through the same recurrent pathway. Inhibition of Renshaw cells is therefore likely, and this inhibition is underestimated because it occurs despite factors that would have reduced H′ facilitation (less sensitivity to excitatory inputs, summation of the AHP, facilitation of Renshaw cells by the strong motor discharge via recurrent collaterals). This inhibition of Renshaw cell activity probably reflects a descending (corticospinal) inhibitory effect exerted directly onto Renshaw cells.

Voluntary contraction of the antagonists

During tonic and ramp contractions of the antagonistic pretibial flexors, there is a facilitation of soleus-coupled Renshaw cells, which is likely to be of supraspinal origin.

Recurrent inhibition during co-contraction of antagonistic muscles

Voluntary contractions of antagonists

During voluntary co-contractions of soleus and the pretibial flexors, whether strong tonic or towards the end of ramp, H′ is inhibited. This contrasts with the greater facilitation of H′ than of reference H observed during voluntary plantar flexion at an equivalent amount of soleus EMG activity. Both the amount of inhibition during strong co-contractions and its time course during ramp contractions suggest a specific control of recurrent inhibition during co-contraction, with descending facilitation of Renshaw cells.

Active stance

During active stance, homonymous recurrent inhibition is increased with respect to that when standing with support. This increase in recurrent inhibition is probably descending, possibly vestibular in origin, and is probably required because the activity of either antagonist may be required to maintain stability.

Heteronymous recurrent inhibition opposing matched Ia excitation

During postural co-contractions of quadriceps with an ankle muscle (e.g. tibialis anterior while leaning backwards) recurrent inhibition from quadriceps to motoneurones of this muscle is decreased, while that to the antagonist (soleus in this example) is unchanged or increased.

Functional implications

Flexion–extension

During strong contractions, the decreased recurrent inhibition to active motoneurones ensures a high input–output gain for the motoneurone pool, and

favours a potent inhibition of antagonist activity through unsuppressed reciprocal Ia inhibition. During weak contractions, the increased recurrent inhibition allows the supraspinal centres to operate over a large part of their working range while causing only small changes in muscle force.

Co-contractions of antagonists

During co-contractions of antagonists recurrent inhibition is either facilitated or not inhibited. This ensures the depression of reciprocal Ia inhibition necessary to allow unimpeded parallel activation of the two antagonistic muscles, and limits the gain of the stretch reflex so preventing the system from breaking into oscillations.

Control of heteronymous projections

Given the heteronymous Ia excitatory projections from one muscle to both antagonistic muscles of a pair operating at another joint, the descending control of heteronymous recurrent inhibition helps the selection of the appropriate Ia synergism for various postural motor tasks.

Studies in patients and clinical implications

Spasticity

So far, only homonymous recurrent inhibition of soleus motoneurones has been investigated, using the paired H reflex technique. In patients with stroke or spinal cord injury, there is evidence for increased homonymous recurrent inhibition. This finding implies that normally there is a supraspinal tonic inhibitory drive on Renshaw cells, and indicates that decreased recurrent inhibition does not contribute to spasticity in these patients. However, task-related changes in recurrent inhibition cannot be demonstrated. Only in patients with progressive paraparesis due to hereditary spastic paraparesis and amyotrophic lateral sclerosis is there evidence for decreased recurrent inhibition at rest.

Other movement disorders

In patients with a form of cerebral palsy, with mental retardation, rigidity and inflexible voluntary and/or postural movements, but without pyramidal, extrapyramidal or cerebellar deficits, there is an absence of task-related modulation of recurrent inhibition. In patients with hyperekplexia, recurrent inhibition is not modified. In patients with Parkinson's disease, recurrent inhibition is not modified either.

REFERENCES

Aymard, C., Chia, L., Katz, R., Lafitte, C. & Pénicaud, A. (1995). Reciprocal inhibition between wrist flexors and extensors in man: a new set of interneurones? *Journal of Physiology (London)*, **487**, 221–35.

Aymard, C., Decchi, B., Katz, R. *et al.* (1997). Recurrent inhibition between motor nuclei innervating opposing wrist muscles in the human upper limb. *Journal of Physiology (London)*, **499**, 267–82.

Baldissera, F., Hultborn, H. & Illert, M. (1981). Integration in spinal neuronal systems. In *Handbook of Physiology*, section I, *The Nervous System*, vol. II, *Motor Control*, ed. V. B. Brooks, pp. 508–95. Bethesda: American Physiological Society.

Barbeau, H., Marchand-Pauvert, V., Meunier, S., Nicolas, G. & Pierrot-Deseilligny, E. (2000). Posture-related changes in heteronymous recurrent inhibition from quadriceps to ankle muscles in humans. *Experimental Brain Research*, **130**, 345–61.

Baret, M., Katz, R., Lamy, J. C., Pénicaud, A. & Wargon, I. (2003). Evidence for recurrent inhibition of reciprocal Ia inhibition from soleus to tibialis anterior. *Experimental Brain Research*, **152**, 133–6.

Binder, M. D., Kroin, J. S., Moore, G. P. & Stuart, D. G. (1977). The response of Golgi tendon organs to single motor unit contractions. *Journal of Physiology (London)*, **271**, 337–49.

Bussel, B. & Pierrot-Deseilligny, E. (1977). Inhibition of human motoneurones, probably of Renshaw origin, elicited by an orthodromic motor discharge. *Journal of Physiology (London)*, **269**, 319–39.

Chaco, J., Blank, A., Ferber, I. & Gonnen, B. (1984). Recurrent inhibition in spastic hemiplegia. *Electromyography and Clinical Neurophysiology*, **24**, 571–6.

Coombs, J. S., Eccles, J. C. & Fatt, P. (1955a). The electrical properties of the motoneurone membrane. *Journal of Physiology (London)*, **130**, 291–325.

(1955b). Excitatory synaptic action in motoneurones. *Journal of Physiology (London)*, **130**, 374–95.

Créange, A., Faist, M., Katz, R. & Pénicaud, A. (1992). Distribution of heteronymous Ia facilitation and recurrent inhibition in the human deltoid muscle. *Experimental Brain Research*, **90**, 620–4.

Cullheim, S. & Kellerth, J. P. (1978). A morphological study of the axons and recurrent axon collaterals of cat α-motoneurones supplying different hind-limb muscles. *Journal of Physiology (London)*, **281**, 285–99.

Delwaide, P. J. (1985). Are there modifications in spinal cord functions of Parkinsonian patients? In *Clinical Neurophysiology in Parkinsonism*, ed. P. J. Delwaide & E. Agnoli, pp. 19–32. Amsterdam: Elsevier.

Eccles, J. C., Fatt, P. & Koketsu, K. (1954). Cholinergic and inhibitory synapses in a pathway from motor-axon collaterals to motoneurones. *Journal of Physiology (London)*, **126**, 524–62.

Eccles, J. C., Eccles, R. M., Iggo, A. & Ito, M. (1961a). Distribution of recurrent inhibition among motoneurones. *Journal of Physiology (London)*, **159**, 479–99.

Eccles, J. C., Eccles, R. M., Iggo, A. & Lundberg, A. (1961b). Electrophysiological investigations of Renshaw cells. *Journal of Physiology (London)*, **159**, 461–78.

Ellaway, P. H. (1971). Recurrent inhibition of fusimotor neurones exhibiting background discharges in the decerebrate and the spinal cat. *Journal of Physiology (London)*, **216**, 419–39.

Ellaway, P. H. & Murphy, P. R. (1980). A comparison of the recurrent inhibition of α- and γ-motoneurones in the cat. *Journal of Physiology (London)*, **115**, 43–58.

Floeter, M. K., Andermann, F., Andermann, E., Nigro, M. & Hallett, M. (1996). Physiological studies of spinal inhibitory pathways in patients with hereditary hyperekplexia. *Neurology*, **46**, 766–72.

Fromm, C., Haase, J. & Wolf, E. (1977). Depression of recurrent inhibition of extensor motoneurones by the action of group II afferents. *Brain Research*, **120**, 459–68.

Fung, S. J., Pompeiano, O. & Barnes, C. D. (1987). Suppression of the recurrent inhibitory pathway in lumbar cord segments during locus coeruleus stimulation in cats. *Brain Research*, **402**, 351–4.

Granit, R. & Renkin, B. (1961). Net depolarization and discharge rate of motoneurones as measured by recurrent inhibition. *Journal of Physiology (London)*, **158**, 461–75.

Granit, R., Pascoe, J. E. & Steg, G. (1957). The behaviour of tonic alpha and gamma motoneurons during stimulation of recurrent collaterals. *Journal of Physiology (London)*, **138**, 381–400.

Gustafsson, B., Katz, R. & Malmsten, J. (1982). Effect of chronic partial deafferentation on the electrical properties of lumbar α-motoneurones in the cat. *Brain Research*, **246**, 23–30.

Hamm, T. M. (1990). Recurrent inhibition to and from motoneurons innervating the flexor digitorum and flexor hallucis longus muscles of the cat. *Journal of Neurophysiology*, **63**, 395–403.

Hörner, M., Illert, M. & Kümmel, H. (1991). Absence of recurrent axon collaterals in motoneurones to extrinsic digit extensor muscles of the cat forelimb. *Neuroscience Letters*, **122**, 183–6.

Hultborn, H. (1989). Overview and critiques of Chapters 22 and 23: Recurrent inhibition – in search of a function. In *Progress in Brain Research*, vol. 80, ed. J. H. J. Allum & M. Hulliger, pp. 269–71. Amsterdam: Elsevier.

Hultborn, H. & Pierrot-Deseilligny, E. (1979a). Changes in recurrent inhibition during voluntary soleus contractions in man studied by an H-reflex technique. *Journal of Physiology (London)*, **297**, 229–51.

(1979b). Input–output relations in the pathway of recurrent inhibition to motoneurones in the cat. *Journal of Physiology (London)*, **297**, 267–87.

Hultborn, H., Jankowska, E. & Lindström, S. (1971a). Recurrent inhibition from motor axon collaterals of transmission in the Ia inhibitory pathway to motoneurones. *Journal of Physiology (London)*, **215**, 591–612.

(1971b). Relative contribution from different nerves to recurrent depression of Ia IPSPs in motoneurones. *Journal of Physiology (London)*, **215**, 637–64.

Hultborn, H., Jankowska, E., Lindström, S. & Roberts, W. (1971c). Neuronal pathway of the recurrent facilitation of motoneurones. *Journal of Physiology (London)*, **218**, 495–614.

Hultborn, H., Lindström, S. & Wigström, H. (1979a). On the function of recurrent inhibition in the spinal cord. *Experimental Brain Research*, **37**, 399–403.

Hultborn, H., Pierrot-Deseilligny, E. & Wigström, H. (1979b). Recurrent inhibition and after-hyperpolarization following motoneuronal discharge in the cat. *Journal of Physiology (London)* **297**, 253–66.

Hultborn, H., Lipski, J., Mackel, R. & Wigström, H. (1988a). Distribution of recurrent inhibition within a motor nucleus. I. Contribution from slow and fast motor units to the excitation of Renshaw cells. *Acta Physiologica Scandinavica*, **134**, 347–61.

Hultborn, H., Katz, R. & Mackel, R. (1988b). Distribution of recurrent inhibition within a motor nucleus. I. Amount of recurrent inhibition in motoneurones to fast and slow units. *Acta Physiologica Scandinavica*, **134**, 363–74.

Hultborn, H., Enriquez Denton, M., Wienecke, J. & Nielsen, J. B. (2003). Variable amplification of synaptic input to cat spinal motoneurones by dendritic persistent inward current. *Journal of Physiology (London)*, **552**, 945–52.

Hultborn, H., Brownstone, R. B., Toth, T. & Gossard, J. P. (2004). Key mechanisms for setting the input–output gain across the motoneuron pool. *Progress in Brain Research*, **143**, 77–95.

Iles, J. F. & Pardoe, J. (1999). Changes in transmission in the pathway of heteronymous spinal recurrent inhibition from soleus to quadriceps motor neurons during movement in man. *Brain*, **122**, 1757–64.

Iles, J. F., Ali, A. & Pardoe, J. (2000). Task-related changes of transmission in the pathway of heteronymous spinal recurrent inhibition from soleus to quadriceps motor neurones in man. *Brain*, **123**, 2264–72.

Illert, M. & Kümmel, H. (1999). Reflex pathways from large muscle spindle afferents and recurrent axon collaterals to motoneurones of wrist and digit muscles: a comparison in cats, monkeys and humans. *Experimental Brain Research*, **128**, 13–19.

Illert, M. & Wietelmann, D. (1989). Distribution of recurrent inhibition in the cat forelimb. In *Progress in Brain Research: Afferent Control of Posture and Locomotion*, vol. 80, ed. J. H. L. Allum & M. Hulliger, pp. 273–81. Amsterdam: Elsevier.

Ito, M. & Oshima, T. (1962). Temporal summation of after-hyperpolarization following a motoneurone spike. *Nature (London)*, **195**, 910–11.

Jankowska, E. & Lindström, S. (1971). Morphological identification of Renshaw cells. *Acta Physiologica Scandinavica*, **81**, 428–30.

Katz, R. & Pierrot-Deseilligny, E. (1982). Recurrent inhibition of motoneurones in patients with upper motor neuron lesions. *Brain*, **105**, 103–24.

(1984). Facilitation of soleus-coupled Renshaw cells during pretibial flexor voluntary contraction in man. *Journal of Physiology (London)*, **355**, 587–603.

(1998). Recurrent inhibition in humans. *Progress in Neurobiology*, **57**, 325–55.

Katz, R., Pierrot-Deseilligny, E. & Hultborn, H. (1982). Recurrent inhibition of motoneurones prior to and during ramp and ballistic movements. *Neuroscience Letters*, **31**, 141–5.

Katz, R., Pénicaud, A. & Rossi, A. (1991). Reciprocal Ia inhibition between elbow flexors and extensors in the human. *Journal of Physiology (London)*, **437**, 269–86.

Katz, R., Mazzocchio, R., Pénicaud, A. & Rossi, A. (1993). Distribution of recurrent inhibition in the human upper limb. *Acta Physiologica Scandinavica*, **149**, 189–98.

Koehler, W., Windhorst, U., Schmidt, J., Meyer-Lhomann, J. & Henatsch, H. D. (1978). Diverging influences on Renshaw cell responses and monosynaptic reflexes from stimulation of capsula interna. *Neuroscience Letters*, **8**, 35–9.

Kudina, L. P. & Pantseva, R. E. (1988). Recurrent inhibition of firing motoneurones in man. *Electroencephalography and Clinical Neurophysiology*, **69**, 179–85.

Lalli, S., Panizza, M. & Hallett, M. (1991). Spinal inhibitory mechanisms in Parkinson's disease. *Neurology*, **41**, 553–6.

Lindsay, A. D. & Binder, M. D. (1991). Distribution of effective synaptic currents underlying recurrent inhibition in cat triceps surae motoneurons. *Journal of Neurophysiology*, **65**, 168–77.

Lipski, J., Fyffe, R. E. W. & Jodkowski, J. (1985). Recurrent inhibition of cat phrenic motoneurons. *Journal of Neuroscience*, **5**, 1545–55.

Löscher, W. N., Cresswell, A. G. & Thorstensson, A. (1996). Recurrent inhibition of soleus α-motoneurons during a sustained submaximal plantar flexion. *Electroencephalography and Clinical Neurophysiology*, **101**, 334–8.

MacLean, J. B. & Leffman, H. (1967). Supraspinal control of Renshaw cells. *Experimental Neurology*, **18**, 94–104.

Mattei, B., Schmied, A. & Vedel, J. P. (2003). Recurrent inhibition of wrist extensor motoneurones: a single unit study on a deafferented patient. *Journal of Physiology (London)*, **549**, 975–84.

Mazzocchio, R. & Rossi, A. (1989). Further evidence for Renshaw inhibition in man: a combined electrophysiological and pharmacological approach. *Neuroscience Letters*, **106**, 131–6.

(1997a). A method for potentiating Renshaw cell activity in humans. *Brain Research Protocols*, **2**, 53–8.

(1997b). Involvement of spinal recurrent inhibition in spasticity. Further insight into the regulation of Renshaw cell activity. *Brain*, **120**, 991–1003.

Mazzocchio, R., Schieppati, M., Scarpini, C. & Rossi, A. (1990). Enhancement of recurrent inhibition by intravenous administration of L-acetylcarnitine in spastic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **53**, 321–6.

Mazzocchio, R., Rossi, A. & Rothwell, J. C. (1994). Depression of Renshaw recurrent inhibition by activation of corticospinal fibres in human upper and lower limb. *Journal of Physiology (London)*, **481**, 487–98.

Meunier, S., Pénicaud, A., Pierrot-Deseilligny, E. & Rossi, A. (1990). Monosynaptic Ia excitation and recurrent

inhibition from quadriceps to ankle flexors and extensors in man. *Journal of Physiology (London)*, **423**, 661–75.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1994). Pattern of heteronymous recurrent inhibition in the human lower limb. *Experimental Brain Research*, **102**, 149–59.

Meunier, S., Mogyoros, I., Kiernan, M. & Burke, D. (1996). Effects of femoral nerve stimulation on the electromyogram and reflex excitability of tibialis anterior and soleus. *Muscle and Nerve*, **19**, 1110–15.

Miles, T. S., Le, T. H. & Türker, K. S. (1989). Biphasic inhibitory responses and their IPSPs evoked by tibial nerve stimulation in human soleus motor neurones. *Experimental Brain Research*, **77**, 637–45.

Morin, C. & Pierrot-Deseilligny, E. (1977). Role of Ia afferents in the soleus motoneurone inhibition during a tibialis anterior voluntary contraction in man. *Experimental Brain Research*, **27**, 509–22.

Nielsen, J. & Pierrot-Deseilligny, E. (1996). Evidence of facilitation of soleus-coupled Renshaw cells during voluntary cocontraction of antagonistic ankle muscles in man. *Journal of Physiology (London)*, **493**, 603–11.

Paillard, J. (1955). *Réflexes et régulations d'origine proprioceptive chez l'Homme*. Thèse de Sciences, 289 pp. Paris: Arnette.

Piercey, M. F. & Goldfarb, J. (1974). Discharge patterns of Renshaw cells evoked by volleys in ipsilateral cutaneous and high threshold muscle afferents and their relationship to reflexes recorded in ventral roots. *Journal of Neurophysiology*, **37**, 294–302.

Pierrot-Deseilligny, E. & Bussel, B. (1975). Evidence for recurrent inhibition by motoneurones in human subjects. *Brain Research*, **88**, 105–8.

Pierrot-Deseilligny, E. & Morin, C. (1980). Evidence for supraspinal influences on Renshaw inhibition during motor activity in man. In *Spinal and Supraspinal Mechanisms of Voluntary Motor Control and Locomotion. Progress in Clinical Neurophysiology*, vol. 8, ed. J. E. Desmedt, pp. 142–69. Basel: Karger.

Pierrot-Deseilligny, E., Bussel, B., Held, J. P. & Katz, R. (1976). Excitability of human motoneurones after discharge in a conditioning reflex. *Electroencephalography and Clinical Neurophysiology*, **40**, 279–87.

Pierrot-Deseilligny, E., Morin, C., Katz, R. & Bussel, B. (1977). Influence of posture and voluntary movement on recurrent inhibition in human subjects. *Brain Research*, **124**, 427–36.

Pierrot-Deseilligny, E., Katz, R. & Morin, C. (1979). Evidence for Ib inhibition in human subjects. *Brain Research*, **166**, 176–9.

Pierrot-Deseilligny, E., Katz, R. & Hultborn, H. (1983). Functional organization of recurrent inhibition: changes in recurrent inhibition preceding and accompanying voluntary movements in man. In *Motor Control Mechanisms in Health and Diseases, Advances in Neurology*, vol. 39, ed. J. E. Desmedt, pp. 443–57. New York: Raven Press.

Raynor, E. M. & Shefner, J. M. (1994). Recurrent inhibition is decreased in patients with amyotrophic lateral sclerosis. *Neurology*, **44**, 2148–53.

Renshaw, B. (1941). Influence of discharge of motoneurones upon excitation of neighboring motoneurons. *Journal of Neurophysiology*, **4**, 167–83.

Rossi, A. & Mazzocchio, R. (1991). Presence of homonymous recurrent inhibition in motoneurones supplying different lower limb muscles in humans. *Experimental Brain Research*, **84**, 367–73.

(1992). Renshaw inhibition to motoneurones innervating proximal and distal muscles of the human upper and lower limbs. In *Muscle Afferents and Spinal Control of Movement*, ed. L. Jami, E. Pierrot-Deseilligny & D. Zytnicki, pp. 313–20. Oxford: Pergamon Press.

Rossi, A., Mazzocchio, R. & Scarpini, C. (1987). Evidence for Renshaw cell–motoneuron decoupling during tonic vestibular stimulation in man. *Experimental Neurology*, **98**, 1–12.

Rossi, A., Decchi, B. & Vecchione, V. (1992). Supraspinal influences on recurrent inhibition in humans. Paralysis of descending control of Renshaw cells in patients with mental retardation. *Electroencephalography and Clinical Neurophysiology*, **85**, 419–24.

Rossi, A., Zalaffi, A. & Decchi, B. (1994). Heteronymous recurrent inhibition from gastrocnemius muscle to soleus motoneurones in humans. *Neuroscience Letters*, **169**, 141–4.

Ryall, R. W. (1970). Renshaw cell mediated inhibition of Renshaw cells: Patterns of excitation and inhibition from impulses in motor axon collaterals. *Journal of Neurophysiology*, **33**, 257–70.

(1981). Patterns of recurrent excitation and mutual inhibition of cat Renshaw cells. *Journal of Physiology (London)*, **316**, 439–52.

Ryall, R. W. & Piercey, M. F. (1971). Excitation and inhibition of Renshaw cells by impulses in peripheral afferent nerve fibers. *Journal of Neurophysiology*, **34**, 242–51.

Sastry, B. S. & Sinclair, J. G. (1976). Tonic inhibitory influence of a supraspinal monoaminergic system on recurrent inhibition of an extensor monosynaptic system. *Brain Research*, **117**, 69–76.

Schieppati, M. & Crenna, P. (1985). Excitability of reciprocal and recurrent inhibitory pathways after voluntary muscle relaxation in man. *Experimental Brain Research*, **59**, 249–56.

Schneider, S. P. & Fyffe, R. E. (1992). Involvement of GABA and glycine in recurrent inhibition of spinal motoneurons. *Journal of Neurophysiology*, **68**, 397–406.

Shefner, J. M., Berman, S. A., Sarkarati, M. & Young, R. R. (1992). Recurrent inhibition is increased in patients with spinal cord injury. *Neurology*, **42**, 2162–8.

Shefner, J. M., Berman, S. A. & Young, R. R. (1993). The effect of nicotine on recurrent inhibition in the spinal cord. *Neurology*, **43,** 2647–51.

Upton, A. R. M., McComas, A. J. & Sica, R. E. P. (1971). Potentiation of 'late' responses evoked in muscles during effort. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 699–711.

Veale, J. L. & Rees, S. (1973). Renshaw cell activity in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 674–83.

Veale, J. L., Rees, S. & Mark, R. F. (1973). Renshaw cell activity in normal and spastic man. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 523–37. Basel: Karger.

Wilson, V. J., Talbot, W. H. & Kato, M. (1964). Inhibitory convergence upon Renshaw cells. *Journal of Neurophysiology*, **27**, 1063–79.

Windhorst, U. (1996). On the role of recurrent inhibitory feedback in motor control. *Progress in Neurobiology*, **49**, 517–87.

5

Reciprocal Ia inhibition

The disynaptic pathway mediating reciprocal Ia inhibition to antagonistic motoneurones through Ia interneurones has been investigated extensively in animal experiments, and is the most thoroughly studied spinal circuit in human subjects. The extensive convergence described on Ia interneurones provided the first example of integration in the spinal cord. It has been suggested that motoneurones and Ia interneurones are controlled in parallel from the brain to produce a co-ordinated contraction of agonists and relaxation of antagonists (Lundberg, 1970). This appealing hypothesis prompted experiments in humans, and the study of changes in reciprocal Ia inhibition from ankle flexors to extensors during voluntary dorsiflexion was the first attempt to investigate changes in transmission in spinal pathways during movement (Tanaka, 1974). Although the results recorded during tonic contractions have long been a matter of dispute, the existence of a parallel control of α motoneurones and corresponding Ia interneurones has now been demonstrated in a number of motor tasks at ankle level. However, it has proved difficult to extrapolate from results obtained at ankle level to wrist flexors and extensors. It has become clear that reciprocal inhibition between flexors and extensors in the forearm is probably mediated by non-reciprocal group I interneurones (so-called Ib inhibitory interneurones), and not by 'true' Ia inhibitory interneurones.

Background from animal experiments

Initial findings

In a decerebrate preparation Sherrington (1897) demonstrated that the contraction of a muscle is accompanied by relaxation of its antagonist(s), and coined the term 'reciprocal inhibition'. Using monosynaptic reflex testing, Lloyd (1946) considered the reciprocal inhibition of the mechanical antagonist acting at the same joint as the counterpart of excitation in a myotatic unit and, because of its very short latency, believed that it was exerted monosynaptically on motoneurones (Lloyd, 1941; hence the term 'direct inhibition'). Later intracellular recordings established that one interneurone is interpolated in the Ia inhibitory pathway (Eccles, Fatt & Landgren, 1956), and demonstrated that activity in this pathway can inhibit the monosynaptic reflex (Araki, Eccles & Ito, 1960; see Chapter 1, pp. 9–10). The interneurone was called 'Ia interneurone', a name which has been kept, despite the demonstration that Ia afferents also produce (although to a much lesser extent) disynaptic inhibition of motoneurones through another pathway (that of non-reciprocal group I inhibition, formerly known as 'Ib inhibition'; see Chapter 6). The Ia interneurone was first viewed as a mechanism for transforming

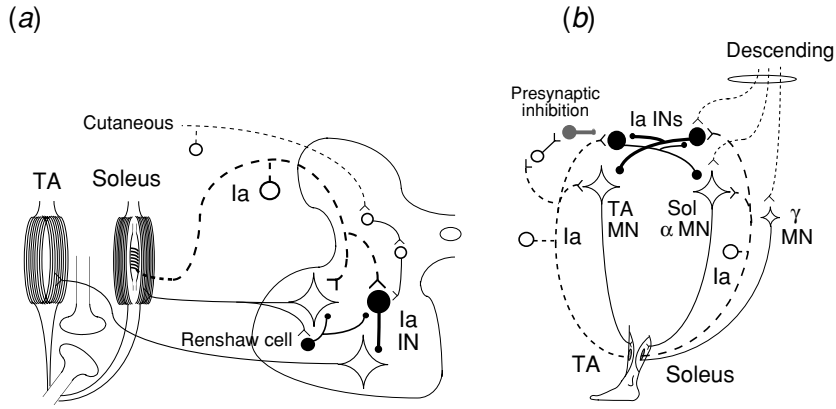


Fig. 5.1. Wiring diagram of the connections of the reciprocal Ia pathway. (*a*), (*b*) In this and subsequent figures, excitatory synapses are represented by Y-shaped bars and inhibitory synapses by small filled circles, excitatory interneurones by open circles and inhibitory interneurones by large filled circles, Ia afferents by thick dashed lines, cutaneous and joint afferents by thin dashed lines. (*a*) Ia afferents originating from muscle spindle primary endings of soleus have monosynaptic excitatory projections to homonymous motoneurones (MN) and activate Ia inhibitory interneurones (IN) inhibiting the MNs of the antagonistic tibialis anterior (TA). Ia INs fed by soleus Ia afferents are inhibited by Renshaw cells activated by recurrent collaterals from soleus motor axons. Ia INs receive short-latency excitation from low-threshold cutaneous afferents. (*b*) Similar influences of descending tracts on α (and γ) MNs and 'corresponding' extensor INs (inhibiting flexor MNs). Extensor-coupled Ia INs inhibit 'opposite' flexor-coupled Ia INs, and vice versa. The pathway of presynaptic inhibition of Ia terminals on tibialis anterior-coupled Ia INs is also represented. Data from Hultborn (1976), and Enriquez-Denton *et al.* (2000).

the excitatory action of primary afferents into an inhibitory action. However, it was soon realised that it might also act as a simple 'integrative centre' (R. M. Eccles & Lundberg, 1958). A striking convergence of segmental and supraspinal inputs was then found on α motoneurones and corresponding Ia interneurones (i.e. those with the same Ia excitatory input, see Lundberg, 1970; Hultborn, 1976).

General features

Identification

Ia inhibitory interneurones have three characteristic features allowing their identification: (i) monosynaptic input from Ia afferents, (ii) projection to motoneurones antagonistic to the muscle(s) from which the Ia input arises, and (iii) disynaptic recurrent inhibition from those motoneurones that receive the same monosynaptic Ia excitation (see below; Fig. 5.1(*a*)).

Location and morphology

Ia inhibitory interneurones are located in the ventral part of lamina VII, just outside the motor nuclei receiving the same Ia input (Jankowska & Lindström, 1972). The trajectory of their axons, via the lateral or ventral funiculi, depends on the location of their target motoneurones, and they can reach motoneurones several segments away.

Pharmacology

The transmitter released from terminals of Ia inhibitory interneurones is glycine (see Curtis, 1959). This provides a unique opportunity to investigate changes in reciprocal Ia inhibition in patients with a selective deficiency of the glycinergic inhibitory

system, producing, among other deficits, defective transmission of reciprocal Ia inhibition (see p. 233). Much less is known about the pharmacology of their excitation, but they are activated readily by L-glutamate (Jankowska & Roberts, 1972).

Mode of action

Individual Ia inhibitory interneurones may inhibit a considerable proportion of α motoneurones of a given nucleus (up to 20%), but each interneurone produces fairly small IPSPs in motoneurones, and it has been estimated that 70 interneurones on average are required to inhibit individual motoneurones (Jankowska & Roberts, 1972). Ia interneurones make synaptic contacts predominantly on the soma and proximal parts of the dendrites (R. E. Burke, Fedina & Lundberg, 1971).

Electrophysiology

Ia inhibitory interneurones respond with a single spike to a synchronous volley in Ia afferents. They are, however, able to discharge in bursts following stimulation of other afferents (e.g. FRA). They have tonic background activity, which is particularly high in non-anaesthetised decerebrate preparations (see Jankowska, 1992).

Projections from Ia interneurones

Projections to motoneurones

The pathway of reciprocal Ia inhibition is very simple. In general, Ia interneurones inhibit direct antagonistic motoneurones in the way initially described (Lloyd, 1946; Laporte & Lloyd, 1952). However, there are many exceptions to this rule. (i) Intracellular recordings have revealed a more extensive distribution (e.g. there is inhibition from the pure knee extensor vasto-crureus to motoneurones of the hip flexors; R. M. Eccles & Lundberg, 1958). (ii) In contrast, reciprocal Ia inhibition is not found between adductors and abductors (R. M. Eccles & Lundberg, 1958) or expiratory and inspiratory intercostal muscles of the same segment (Sears, 1964). (iii) It is also worth noting that in the hindlimb of the anaesthetised and spinalised cat, maximal Ia IPSPs are much larger in flexor than in extensor motoneurones (R. M. Eccles & Lundberg, 1958). Ia interneurones have no projections to γ motoneurones (Eccles, Eccles & Lundberg, 1960).

Projections to opposite Ia interneurones

The only interneurones affected by Ia inhibitory interneurones are the 'opposite' Ia interneurones (Hultborn, Illert & Santini, 1976a). Thus, as illustrated in Fig. 5.1(*b*), Ia interneurones activated from flexor Ia afferents inhibit Ia interneurones activated from extensor Ia afferents, and vice versa.

Input to Ia interneurones

Ia afferents provide the main segmental input to Ia interneurones

When Ia afferents from different synergists evoke disynaptic inhibition in an antagonistic motor nucleus, the convergence occurs onto common Ia interneurones, not at the motoneurones themselves (Hultborn & Udo, 1972b).

Other segmental inputs

Flexion reflex afferents (FRA)

Volleys in ipsilateral and contralateral flexion reflex afferents (FRA) evoke a mixture of polysynaptic excitation and inhibition in Ia inhibitory interneurones. However, interneurones excited monosynaptically from flexor nerves receive stronger net excitation from the ipsilateral FRA than do extensor-coupled interneurones, while the opposite pattern is seen from the contralateral FRA. These patterns are similar to those found in flexor and extensor motoneurones, respectively. In the acute spinal cat, FRA pathways thus evoke parallel effects in α motoneurones and 'corresponding' Ia interneurones (see Hultborn, 1976).

Low-threshold cutaneous afferents

These may also activate Ia interneurones through a short-latency 'private' pathway (Fedina & Hultborn, 1972).

Recurrent inhibition

Renshaw cells inhibit Ia inhibitory interneurones (see Hultborn, Jankowska & Lindström, 1971a; Fig. 5.1(*a*)). If one excepts Renshaw cells themselves, Ia interneurones are the only spinal interneurones to receive recurrent inhibition, and this constitutes a unique way of identifying them. α motoneurones and 'corresponding' Ia interneurones receive recurrent inhibition in a strictly parallel fashion. This inhibition of Ia interneurones is responsible for 'recurrent facilitation', which is due to inhibition of tonically active Ia interneurones (see Hultborn *et al.*, 1971b; Chapter 4, p. 154).

Descending inputs

There is a striking parallel between the descending input to motoneurones and that to corresponding Ia interneurones.

Corticospinal input

Corticospinal volleys facilitate transmission in Ia interneurones to motoneurones of the cat hindlimb (Lundberg & Voorhoeve, 1962), and the corticospinal inhibition of feline motoneurones appears to be mediated to a large extent by Ia inhibitory interneurones (Hultborn & Udo, 1972a). An even more direct coupling between corticospinal fibres and Ia interneurones has been found in forelimb segments of the cat (disynaptic, via propriospinal neurones; Illert & Tanaka, 1978) and in the hindlimb of primates (monosynaptic; Jankowska, Padel & Tanaka, 1976). Studies in the monkey have shown that those corticospinal cells with a 'reciprocal Ia inhibition pattern' (facilitation of agonist, inhibition of antagonist) are vigorously active during flexion-extension movements, but may fail to discharge during a power grip involving co-contraction of wrist flexors and extensors (Fetz & Cheney, 1987).

Rubrospinal input

Rubrospinal volleys evoke di- and polysynaptic EPSPs in Ia interneurones, mixed with some inhibition.

Vestibulospinal input

Vestibulospinal volleys evoke mono- and disynaptic EPSPs in extensor-coupled Ia interneurones, and disynaptic IPSPs in flexor-coupled Ia interneurones (Hultborn, Illert & Santini, 1976b). Here again, these effects are similar to the vestibulospinal effects on the corresponding motoneurones.

Tonic descending inhibition

In the anaesthetised baboon, reciprocal Ia inhibition is detectable only after spinal transection. This has been interpreted as due to a descending system tonically inhibiting Ia interneurones in the anaesthetised state. The existence of descending control 'may reflect the increasing need of primates to use the Ia-system in movements other than flexion–extension, either in lateral movements or in co-contraction of flexors and extensors' (Hongo *et al.*, 1984), i.e. in movements in which Ia excitation is not paralleled by Ia inhibition of the antagonists.

Presynaptic inhibition

Conditioning stimulation of ankle flexor, but not extensor, group I afferents evokes presynaptic inhibition of Ia terminals projecting to Ia interneurones. A parallel control of presynaptic inhibition of Ia afferent terminals on Ia interneurones and motoneurones is likely. In addition, conditioning stimuli to flexor and extensor nerves and cutaneous nerves elicit a long-lasting increase in excitability of the terminals of Ia inhibitory interneurones, possibly

due to presynaptic inhibition of the terminals of the interneurones themselves (Enriquez-Denton *et al.*, 2000).

Conclusions

The general principle has emerged that all peripheral and descending neuronal systems which influence motoneurones have similar projections on Ia inhibitory interneurones. This coupling of motoneurones and corresponding Ia inhibitory interneurones may serve to link reciprocal inhibition of antagonists with excitation of agonists in flexion-extension movements ('α-γ linkage in the reciprocal Ia inhibition'; Lundberg, 1970; Jankowska & Lundberg, 1981).

Methodology

Underlying principles

Inhibition mediated through the pathway of reciprocal Ia inhibition between antagonistic flexors and extensors can be assessed in motoneurones using group I volleys to modulate the H reflex, the ongoing EMG or the PSTHs of single units. Several features suggest that the resulting inhibition is due to the activation of Ia inhibitory interneurones: (i) elicitation by a pure Ia volley, (ii) central delay consistent with a disynaptic transmission, (iii) inhibition by recurrent inhibition, and (iv) distribution restricted to motoneurones of strict antagonists.

Inhibition of various responses

Monosynaptic test reflex

Exploration of the spinal circuitry of human subjects started with the description of the low-threshold, short-latency inhibition of the soleus H reflex following conditioning stimulation to the common peroneal nerve (Kots & Zhukov, 1971; Mizuno, Tanaka & Yanagisawa, 1971). Because the conditioning volley originated from the antagonistic muscle, this was interpreted as due to reciprocal Ia inhibition of soleus motoneurones by Ia volleys from the pretibial flexors. At ankle level, testing usually involves peroneal inhibition of the soleus H reflex. A deep peroneal nerve volley at 1 × MT usually inhibits the soleus H reflex of normal subjects at rest. The inhibition has an onset at the 1-ms ISI when the conditioning stimulus is delivered ~6 cm more distally than the test, reaches a maximum 1–2 ms later, and has a brief overall duration, ~2–3 ms (Fig. 5.2(*b*); Crone *et al.*, 1987). In those subjects, in whom it is possible to evoke an H reflex in tibialis anterior, reciprocal inhibition can be demonstrated consistently at rest. Because the conditioning volley is applied more proximally than the test volley, synchronous arrival of the two volleys at spinal level occurs when the conditioning volley is delivered *after* the test volley (at negative intervals). Here also, it reaches a maximum 1 ms later and has a brief duration (Fig. 5.2(*b*); Tanaka, 1974; Pierrot-Deseilligny *et al.*, 1981; Crone *et al.*, 1987). At wrist level, a short-latency low-threshold radial-induced inhibition of the FCR H reflex and a median-induced inhibition of the ECR H reflex have been described (Fig. 5.4(*b*); Day *et al.*, 1981, 1984; Baldissera, Campadelli & Cavallari, 1983). The extent to which this inhibition truly represents reciprocal Ia inhibition is discussed on pp. 211–14. Because it is rarely possible to record an H reflex of significant size at rest in the biceps and triceps brachii, reciprocal inhibition between elbow flexors and extensors has been investigated using the tendon jerk, conditioned by an electrical volley to the nerve innervating the antagonistic muscle (triceps or musculo-cutaneous nerve, respectively) in the upper part of the arm (on its posterior or anterior aspect, respectively). Because of the mechanical delay introduced by the tendon tap, the simultaneous arrival of the conditioning and test volleys at spinal level occurs when the conditioning stimulus is delivered *after* the test volley (hence the negative intervals on the abscissa in Fig. 5.3(*b*); Katz, Pénicaud & Rossi, 1991). Here again, the inhibition reaches a maximum 1–1.5 ms after its onset and has a brief duration (3 ms).

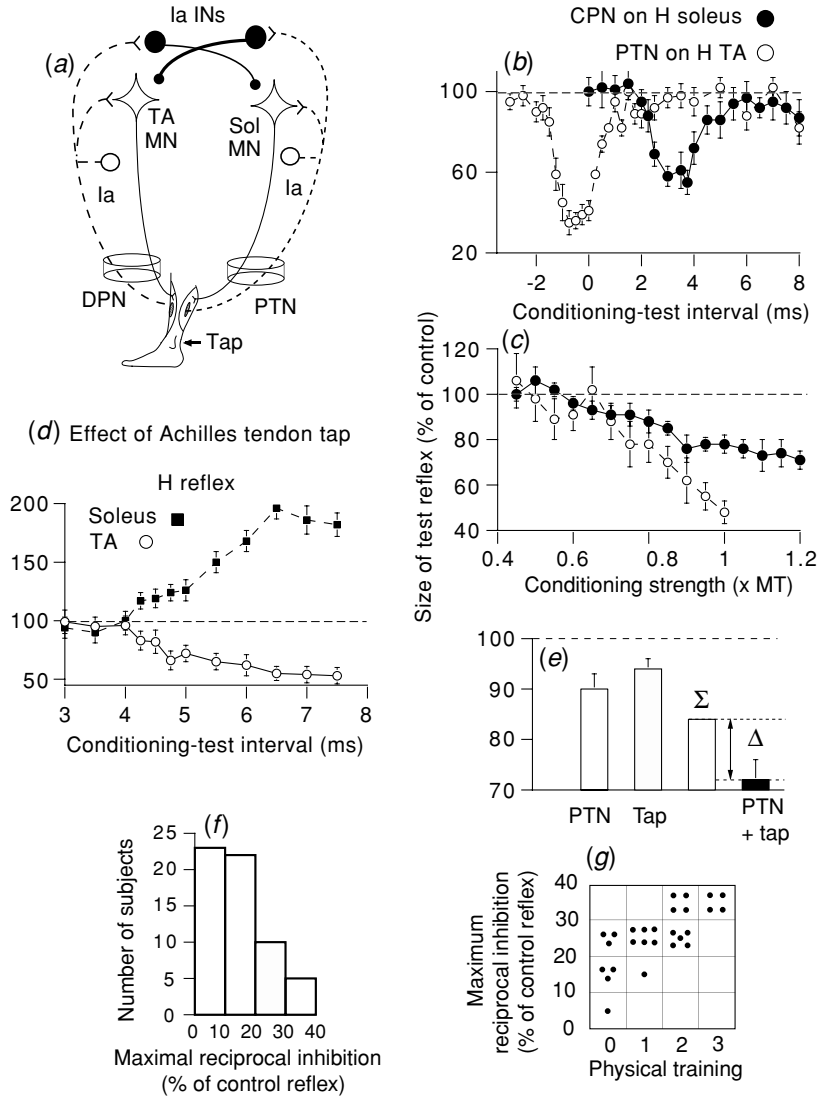


Fig. 5.2. Reciprocal Ia inhibition between ankle muscles. (*a*) Sketch of the pathway of reciprocal Ia inhibition from the deep peroneal nerve (DPN) to soleus (Sol), and from the posterior tibial nerve (PTN) to tibialis anterior (TA) motoneurones (MN). (*b*)–(*d*) Changes in the amplitude of the H reflex (as a percentage of its unconditioned value, each symbol mean of 20–80 measurements, vertical bars ±1 SEM). (*b*), (*c*) The amplitude of the DPN-induced modulation of the Sol (●) and of the PTN-induced modulation of the TA (○) H reflexes is plotted against the interstimulus interval (ISI) ((*b*), conditioning stimulus 1 × MT), and the conditioning stimulus strength ((*c*) ISI giving the strongest inhibition). (*d*) Time course of the effects of an Achilles tendon tap (0.95 × tendon jerk threshold) on the H reflexes of Sol (■) and TA (○). Given that the stimulating electrode eliciting the TA H reflex was 6 cm more distal (i.e., closer to the Achilles tendon) than that eliciting the Sol H reflex, the same tap-test ISI for the onset of the two effects is consistent with a 1 ms longer central delay for the effect in TA MNs. (*e*) Inhibition of the TA H reflex by separate stimuli (PTN, 0.65 × MT, –0.5 ms ISI, first column; Achilles tap, 0.4 × reflex threshold, 6 ms ISI, second column) and combined stimulation (black column). The interrupted horizontal line at 100% represents control reflex size. Σ represents the sum of the inhibitions produced by PTN and Tap delivered separately, the double-headed vertical arrows (Δ) indicate the extra inhibition on combined stimulation. (*f*) Extent of reciprocal inhibition of the soleus H reflex (% of control reflex) evoked by a DPN stimulation at 1 × MT and measured at the optimal ISI for each subject in 60 subjects. (*g*) Comparison of the maximal reciprocal inhibition of the soleus H reflex (ordinate, % of control reflex) and the amount of regular weekly physical exercise (abscissa: 0, no physical exercise; 1, less than 2 hours; 2, between 2 and 5 hours; 3, more than 5 hours), each dot representing one subject. Modified from Crone *et al.* (1987) ((*b*)–(*f*)) and Crone, Hultborn & Jespersen (1985) (*g*), with permission.

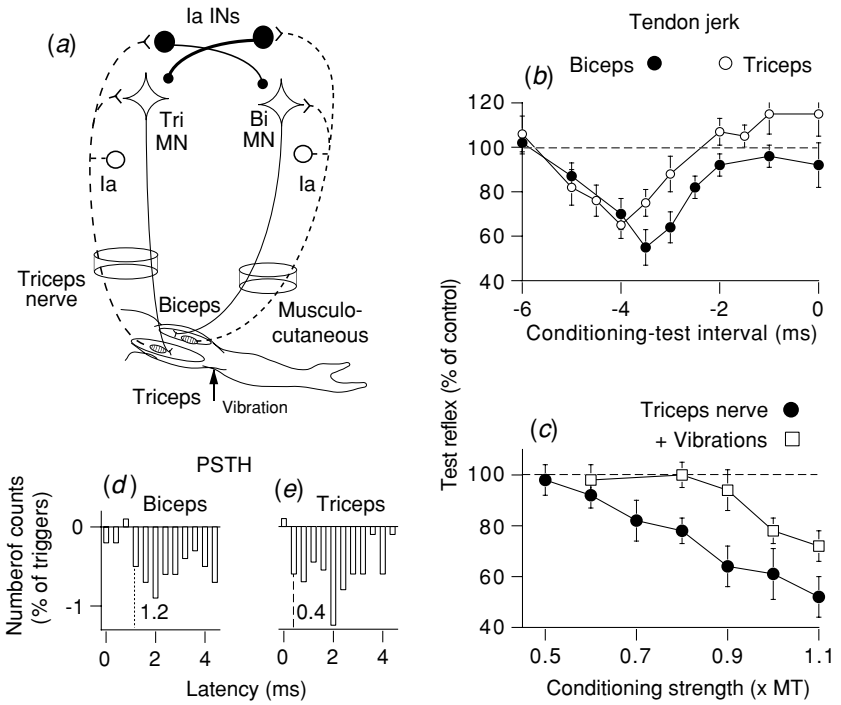


Fig. 5.3. Reciprocal Ia inhibition between elbow muscles. (*a*) Sketch of the pathway of reciprocal Ia inhibition from the musculo-cutaneous nerve to triceps brachii (Tri) and from the triceps nerve to biceps brachii (Bi) motoneurones (MN). (*b*), (*c*) Changes in the amplitude of tendon jerk, expressed as a percentage of its unconditioned value (each symbol is the mean of 60 measurements in (*b*) and 20 in (*c*), vertical bars, ±1 SEM). (*b*) Time course of the Tri-induced modulation of the Bi tendon jerk (●) and of the musculo-cutaneous-induced modulation of the Tri tendon jerk (○) (conditioning stimulus 1 × MT). (*c*) The amplitude of the Bi tendon jerk is plotted against the intensity of the Tri nerve conditioning stimulus (−3 ms ISI, when the inhibition is maximal, see (*b*)) in a control situation (●) and after a long-lasting vibration to the Tri tendon (166 Hz for 25 minutes, □). (*d*), (*e*) PSTHs (after subtraction of the background firing, 0.4-ms bin width) of a Bi unit after Tri nerve stimulation ((*d*), 1 × MT) and of a Tri unit after musculo-cutaneous stimulation ((*e*), 1 × MT). The zero of the abscissa represents the latency of the peak of homonymous monosynaptic Ia excitation. The vertical dotted (*d*) and dashed (*e*) lines indicate the onset of the inhibitions, with their latencies. The difference (Δ) between the latencies of the reciprocal suppression and of the homonymous peak in the Bi-Tri pair depends on the peripheral afferent conduction time for the Bi (Bi.aff) and Tri (Tri.aff) and on the supplementary central delay (D) of the inhibition with respect to that of the monosynaptic Ia excitation. Thus, in the same subject with the same stimulation sites, one has:

(*d*) Δ biceps (1.2 ms) = (Tri.aff + D) – Bi.aff = Tri.aff – Bi.aff + D
(*e*) Δ triceps (0.4 ms) = (Bi.aff + D) – Tri.aff = Bi.aff – Tri.aff + D

Adding these equations gives: 1.2 + 0.4 = 2D, i.e., D = 1.6/2 = 0.8 ms.
Modified from Katz, Pénicaud & Rossi (1991), with permission.

Modulation of the on-going EMG

Modulation of the on-going EMG by a conditioning volley from the antagonistic muscle may be used to assess reciprocal Ia inhibition (Capaday, Cody & Stein, 1990). The resulting common peroneal nerve-induced inhibition of the soleus EMG is more profound and has a longer duration than that of the soleus H reflex recorded under the same conditions (10 ms vs. 3 ms; Fig. 1.11 (b), (c)). The reasons

for this are discussed in Chapter 1 (pp. 26–7). The inhibition can be demonstrated despite the depression of reciprocal Ia inhibition directed to voluntarily activated motoneurones (Petersen, Morita & Nielsen, 1998; p. 223), and this is a suitable method for comparing the amount of reciprocal Ia inhibition in two motor tasks, at equivalent level of background EMG activity (e.g. gait and voluntary contraction, see pp. 227–9).

PSTHs of single units

A group I volley suppresses the discharge of voluntarily activated units of the antagonistic muscle. The method was introduced by Peter Ashby to document reciprocal Ia inhibition between ankle flexors and extensors (Ashby & Labelle, 1977; Ashby & Zilm, 1978), and has also been used to document reciprocal inhibition from quadriceps to biceps femoris (Kudina, 1980), and between flexors and extensors of the elbow (Katz, Pénicaud & Rossi, 1991) and the wrist (Aymard *et al.*, 1995). Here also and for the same reasons as the EMG suppression (Chapter 1, pp. 26–7), the duration of the trough in the PSTH is longer than that of the H reflex inhibition (e.g. see the femoral induced-inhibition of a biceps femoris unit in Fig. 5.6(*b*)). Again, the inhibition can be detected despite the weak contraction of the target muscle necessary for the PSTH technique.

Evidence for reciprocal Ia inhibition

Evidence that the inhibition is elicited by Ia afferents

Low electrical threshold

The electrical threshold for the reciprocal Ia inhibition to soleus and tibialis anterior motoneurones is low (~0.6 × MT, Fig. 5.2(*c*); Crone *et al.*, 1987), i.e. close to that of monosynaptic Ia excitation in the PSTHs of single units (0.5 × MT; Chapter 2, p. 75). The finding that the threshold for the inhibition is slightly higher than for monosynaptic Ia excitation in a firing motoneurone is to be expected because the interneurones mediating the inhibition must be brought to threshold whereas the facilitation can be detected as a subthreshold event. However, the threshold for the inhibition is remarkably low: reciprocal Ia inhibition of tibialis anterior motoneurones may be evoked by stimuli subthreshold for the compound soleus H reflex (Mao *et al.*, 1984) or tendon jerk (Crone *et al.*, 1987).

Absence of effects from cutaneous afferents

A possible role for cutaneous afferents in the inhibition has been excluded, because cutaneous stimulation mimicking the sensation evoked by the mixed nerve volley does not produce a similar inhibition either at ankle or elbow level (Pierrot-Deseilligny *et al.*, 1981; Crone *et al.*, 1987; Katz, Pénicaud & Rossi, 1991).

Tendon tap

The low electrical threshold for the reciprocal inhibition implicates group I fibres, but does not identify muscle spindle Ia afferents as responsible. However, the same inhibition can be evoked by tendon taps which, at rest, preferentially activate muscle spindle primary endings and Ia fibres (cf. Chapter 2, p. 67). Thus, an Achilles tendon tap, just below threshold for the soleus tendon jerk, produces both homonymous monosynaptic Ia facilitation of the soleus H reflex and reciprocal Ia inhibition of the tibialis anterior H reflex (Crone *et al.*, 1987; Fig. 5.2(*d*)). Moreover, when an Achilles tendon tap is combined with a soleus Ia afferent volley produced by electrical stimulation of the posterior tibial nerve, the resulting inhibition of the tibialis anterior H reflex is more marked than the sum of the effects of separate stimuli (Crone *et al.*, 1987; Fig. 5.2(*e*)). This indicates spatial and/or temporal summation in common interneurones (see Chapter 1, p. 47), and provides further evidence that the inhibitions elicited by the mechanical and electrical volleys are mediated through the same pathway.

Effects of long-lasting tendon vibration

The effects of long-lasting high-frequency vibration of the tendon of the 'conditioning' muscle have confirmed that reciprocal inhibition between elbow flexors and extensors is probably due to Ia afferents. The vibration raises the electrical threshold of Ia afferents (cf. Chapter 2, p. 76) and, as a result, the threshold for the inhibition from triceps to biceps brachii was increased and its extent decreased (Katz, Pénicaud & Rossi, 1991; Fig. 5.3(*c*)).

Evidence for disynaptic transmission

Modulation of the H reflex

The deep peroneal-induced inhibition of the soleus H reflex starts to manifest itself at an ISI of 1–1.5 ms. Given that the conditioning volley was elicited 6–8 cm more distally than the test volley (see Tanaka, 1974; Crone *et al.*, 1987), the central delay of the presumably oligosynaptic effect would be almost zero. This is explicable because the time course of the changes in the H reflex underestimates the central delay of conditioning effects (cf. Chapter 1, pp. 9–10). An ingenious method has been proposed to estimate the central delay of reciprocal inhibition of the H reflex (Day & Rothwell, 1983; Day *et al.*, 1984) when reciprocal inhibition between flexors and extensors operating at the same joint can be tested in the same subject in both directions. This is possible at the wrist and ankle levels. The method is independent of peripheral conduction distances or velocities because the test Ia volley for one reflex is the conditioning volley for the other and vice versa. The underlying assumptions are that: (i) the same afferents are responsible for the H reflex and the short-latency inhibition of the antagonistic H reflex; (ii) the central organisation (and delay) is equal in both directions; (iii) maximal inhibition of the H reflex occurs when the excitatory signal (test) from homonymous afferents and the inhibitory signal from antagonist afferents (conditioning) arrive simultaneously at the motoneurone pool. The additional time for impulses to reach the antagonistic motoneurones, in excess of that required to reach homonymous motoneurones, is then obtained by dividing by 2 the sum of the ISIs at which the reciprocal inhibition of the flexor and extensor H reflex is maximal in the same subject. This gives a central delay of 0.9 ms for 'reciprocal' inhibition at the wrist (cf. Fig. 5.4(*b*) and its legend; Day *et al.*, 1984), and 0.9–1 ms for reciprocal inhibition at the ankle (Crone *et al.*, 1987). The technique relies on one additional assumption (iv) that the latencies to the maximal inhibition are not affected by superimposed facilitatory or inhibitory inputs from other afferent species, i.e. that the measurement point reflects only Ia inhibition, and does so at least as well as the onset of the inhibition.

PSTHs of single units

A similar method, independent of assumptions concerning the peripheral conduction distances or velocities, has been proposed to estimate the central delay of reciprocal Ia inhibition assessed in motor units belonging to a pair of antagonistic muscles operating at the same joint. The delay is obtained by relating the latencies to the respective homonymous monosynaptic Ia latencies, summing the differences and dividing by 2 (cf. Fig. 5.3(*d*), (*e*), where the appropriate calculations are detailed in the legend). Thus, there are central delays of ~0.8 ms at elbow and wrist (Katz, Pénicaud & Rossi, 1991; Aymard *et al.*, 1995).

Recurrent inhibition of the relevant interneurones

In the cat Ia inhibitory interneurones are inhibited by Renshaw cells (cf. p. 200), and this provides a unique means of identification, allowing, in particular, the distinction between reciprocal Ia and non-reciprocal group I inhibition (see Jankowska, 1992). It is therefore crucial to know whether transmission in the pathway of disynaptic reciprocal inhibition is depressed by recurrent inhibition.

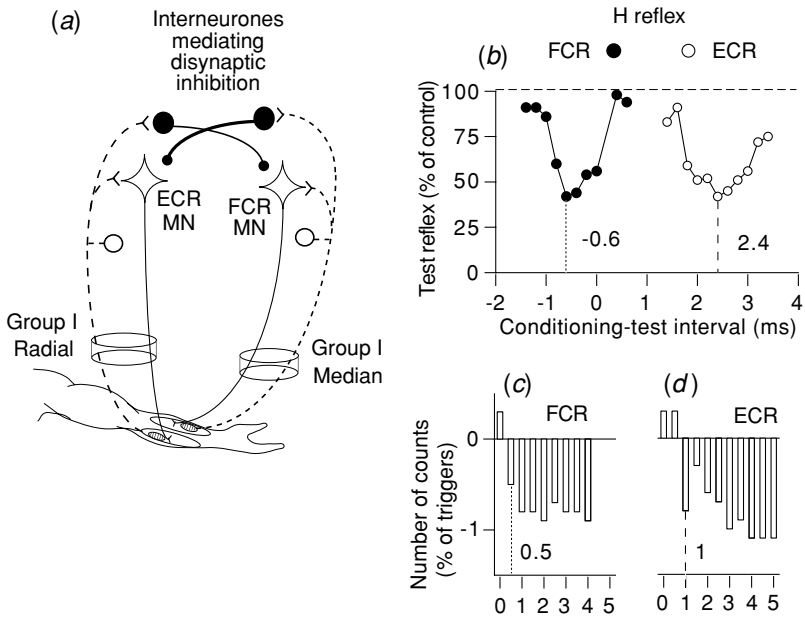


Fig. 5.4. Disynaptic non-reciprocal group I inhibition between wrist muscles. (*a*) Sketch of the pathway of the disynaptic non-reciprocal group I inhibition from the radial nerve to FCR and from the median nerve to ECR motoneurones (MN). (*b*) Time course of the radial-induced modulation of the FCR H reflex (●) and of the median-induced modulation of the ECR H reflex (○) (conditioning stimulus 1 × MT, vertical dotted and dashed lines indicate the peaks of the inhibitions, with their latencies). Each point is the average of 10 trials. The additional time for impulses to reach the antagonist motoneurones, in excess of that required to reach homonymous motoneurones, is obtained by dividing by 2 the sum of the ISIs at which the inhibition of the FCR and ECR H reflex is maximal in the same subject (for details of the calculation, see Day *et al.*, 1984): $(-0.6 + 2.4)/2 = 1.8/2 = 0.9$ ms. (*c*), (*d*) PSTHs (after subtraction of the background firing, 0.5 ms bin width) for a FCR unit after radial nerve stimulation ((*c*), 1 × MT) and of a ECR unit after median nerve stimulation ((*d*), 1 × MT). The zero of the abscissa represents the latency of the peak of homonymous monosynaptic Ia excitation, and the vertical dotted (*c*) and dashed (*d*) lines indicate the onset of the inhibitions, with their latencies. Modified from Day *et al.* (1984) (*b*), and from Aymard *et al.* (1995) ((*c*), (*d*)), with permission.

Evidence for recurrent depression of reciprocal Ia inhibition from ankle extensors to tibialis anterior

Reciprocal inhibition of the tibialis anterior H reflex was produced by an electrical stimulus to the posterior tibial nerve. To produce recurrent inhibition of Ia inhibitory interneurones, these stimuli were conditioned by a preceding soleus H reflex discharge (cf. the sketch in Fig. 5.5(*a*)) evoked by a S1 stimulus. The soleus motor discharge suppressed the reciprocal Ia inhibition, with a short central delay and a long duration, i.e. a time course closely resembling that of recurrent inhibition of motoneurones (Fig. 5.5(*b*), ●; cf. Chapter 4, p. 152). There was no suppression of reciprocal inhibition when the S1 conditioning stimulus was just subthreshold for the H reflex, and thus did not activate Renshaw cells (□, although it would have produced similar post-activation depression at the synapse of the Ia fibre and the Ia interneurone). These findings indicate that soleus-coupled Renshaw cells, activated by the conditioning soleus H reflex discharge, depress Ia interneurones mediating reciprocal Ia inhibition from soleus to tibialis anterior (Baret *et al.*, 2003).

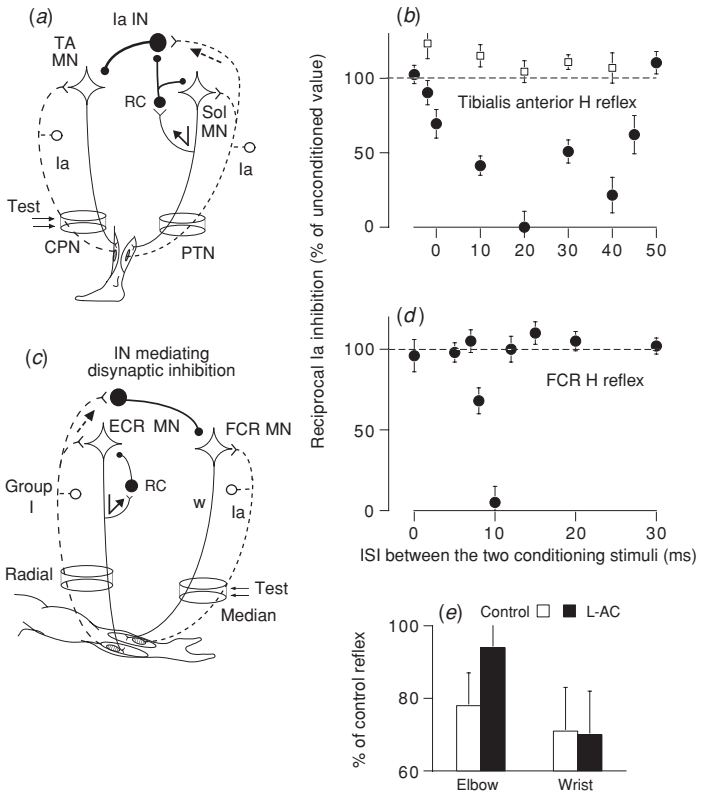


Fig. 5.5. Recurrent projections onto interneurones mediating disynaptic reciprocal inhibition at ankle, elbow and wrist. (*a*), (*c*) Sketches of the presumed pathways. Continuous arrows, conditioning reflex discharges activating Renshaw cells (RC) evoked by a S1 conditioning stimulus. Dashed arrows, Ia volley in the posterior tibial nerve (PTN, (*a*)) and group I volley in the radial nerve (*c*) activating interneurones (INs) mediating disynaptic reciprocal Ia inhibition from soleus (Sol) to tibialis anterior (TA) motoneurones (MN) (*a*), and radial-induced non-reciprocal group I inhibition to FCR MNs (*c*). The former INs are inhibited by RCs (*a*), but the latter are not (*c*). (*b*), (*d*) Results in different subjects. Each symbol mean of 20 measurements; vertical bars ±1 SEM. The test response is the reciprocal inhibition of the H reflex of TA ((*b*) conditioning volley to the PTN, 0.7 × MT, 0 ms ISI) and the FCR ((*d*) conditioning volley to the radial nerve, 0.95 × MT, 0 ms ISI). Reciprocal inhibition (●, expressed as a percentage of its unconditioned value), when conditioned by a soleus H reflex (*b*) and a ECR tendon jerk (*d*), is plotted against the ISI between the conditioning stimulus activating RCs and that activating INs mediating reciprocal inhibition. □ in (*b*) results obtained with a Ia volley just subthreshold for the soleus H reflex. (*d*) There is transient depression of the inhibition due to refractoriness of ECR Ia afferents following the tap-elicited volley. Because of the mechanical delay introduced by the tap and the distal location of the tendon, the tap-induced Ia volley passes beneath the electrode in the spiral groove 8–10 ms after the tap. This depression confirms that both stimuli excited Ia afferents from ECR. (*e*) The amount of triceps-induced reciprocal Ia inhibition of the biceps tendon jerk (left) and of radial-induced inhibition of the FCR H reflex (right) (as a percentage of control reflex) is compared in the 10 minutes before (□) and after (■) intravenous administration of 2 g L-AC. Mean results obtained in four subjects. Modified from Baret *et al.* (2003) (*b*), Aymard *et al.* (1995) (*d*), Rossi *et al.* (1995) (*e*), with permission.

Elbow

A similar depression of reciprocal Ia inhibition by recurrent inhibition has been found in both directions between flexors and extensors of the elbow (see Katz, Pénicaud & Rossi, 1991; Chapter 4, p. 171; Fig. 4.7(*b*)).

Different results have been obtained for the flexors and extensors of the wrist

Unlike what has been observed at elbow and ankle, radial-induced disynaptic group I inhibition of the FCR H reflex was not depressed by the tendon jerk discharge from the 'conditioning' ECR muscle. There was only a transient depression of the inhibition at ISIs of 8–10 ms due to refractoriness of ECR Ia afferents following the tap-elicited volley (Aymard *et al.*, 1995; Fig. 5.5(*c*), (*d*) and its legend).

Pharmacological validation

Intravenous administration of a cholinergic agonist (L-acetylcarnitine, L-Ac) specifically increases recurrent inhibition (cf. Chapter 4, pp. 159–60), and this provides an independent method for investigating the effects of recurrent inhibition on reciprocal Ia inhibition between different antagonistic pairs. Reciprocal Ia inhibition from tibialis anterior to soleus motoneurones is depressed by L-Ac (Schieppati, Gritti & Romano, 1991) whereas disynaptic non-reciprocal group I inhibition from gastrocnemius to soleus is not modified (Rossi, Zalaffi & Decchi, 1994). Triceps-induced reciprocal Ia inhibition of the biceps tendon jerk and disynaptic group I radial-induced inhibition of the FCR H reflex have been measured before and after intravenous administration of L-Ac (Rossi *et al.*, 1995; Fig. 5.5(*e*)). Reciprocal inhibition was potently reduced at elbow level, whereas the radial-induced inhibition was not modified at wrist level. Thus, the increase in Renshaw cell activity induced by L-Ac depresses reciprocal inhibition between antagonistic muscles of the elbow, but not between those of the wrist. This confirms that interneurones mediating reciprocal inhibition between flexors and extensors of the wrist are not inhibited by Renshaw cells, and are therefore not 'true Ia interneurones' (as will be discussed further on pp. 211–14).

Critique of the tests to study reciprocal Ia inhibition

At ankle and elbow, interneurones mediating disynaptic reciprocal inhibition are probably analogous to the Ia inhibitory interneurones mediating reciprocal Ia inhibition studied in the cat and the monkey (see pp. 198–201), because the inhibition: (i) is between strictly antagonistic muscles operating at the same joint, (ii) can be evoked by pure Ia volleys, and (iii) is depressed by recurrent inhibition. However, even at these hinge joints, methodological precautions are required to avoid misinterpretations.

Estimate of the central delay

An essential criterion of reciprocal Ia inhibition is that it is disynaptic. This can be approached by calculating the central delay of the inhibition from estimates of the peripheral conduction times or, more precisely, by using the method developed by Day & Rothwell (1983) and described on p. 205. Data mentioning only a 'short-latency' inhibition without measurement of its central delay (e.g. the femoral-induced inhibition of hamstring units; Kudina, 1980; Bayoumi & Ashby, 1989) are not conclusive.

Intensity of the conditioning volley

Reciprocal inhibition induced by stimuli $<1 \times$ MT is often very small, particularly the common peroneal inhibition of soleus, the most frequently investigated paradigm. It is therefore tempting to use stimuli $>1 \times$ MT which elicit more profound inhibition. This should be avoided because: (i) when the volley is applied to the deep peroneal nerve, there is greater risk of encroaching upon superficial peroneal Ia afferents (cf. below); (ii) the stronger the stimulus intensity, the greater the risk that the reciprocal Ia

inhibition is contaminated by Ib or group II excitation, which can become a problem when exploring the modulation of the ongoing EMG because temporal resolution is then poor; and (iii) the activation of Renshaw cells by the resulting antidromic motor volley can depress transmission in Ia interneurones. The latter could explain why the amount of reciprocal Ia inhibition stops increasing at conditioning stimulus intensities above 1.2 × MT (see Crone *et al.*, 1987, their Fig. 1(*b*)), while the Ia volley is then far from maximal (see Chapter 2, pp. 77–8).

Superimposition of longer-latency inhibition

A longer-latency inhibition is superimposed on reciprocal Ia inhibition of soleus motoneurones 1 ms after its onset during active dorsiflexion (Crone *et al.*, 1987). There are reasons to believe that it is mediated through lumbar propriospinal neurones (see Chapter 10, pp. 497–8). Discrepancies between the results obtained by different groups during tonic dorsiflexion of the foot are presumably due in part to a confusion between changes in this longer latency inhibition and in the early reciprocal Ia inhibition (see p. 219).

Necessity for selective activation of the deep peroneal nerve

Conflicting results have been reported concerning the amount (or even the existence) of reciprocal Ia inhibition of the soleus H reflex at rest in normal subjects (see below). Part of the discrepancy between the results obtained by different groups may be explained by the potent Ia monosynaptic excitatory projections from peroneal muscles to soleus motoneurones (see Meunier, Pierrot-Deseilligny & Simonetta, 1993; Chapter 2, p. 73; Fig. 2.4(*c*)). Stimulation of Ia afferents in the superficial peroneal nerve may obscure reciprocal inhibition from pretibial flexors onto soleus. This could explain why Mao *et al.* (1984) failed to find evidence for common peroneal-induced inhibition of soleus units, and the excitation preceding the inhibition observed in the modulation of the H reflex (Kots & Zhukov, 1971) or of the ongoing EMG (Capaday, Cody & Stein, 1990; Capaday, 1997). Selective activation of the deep peroneal nerve by the conditioning stimulus is therefore required. This is usually possible when the electrodes are placed distal to the head of the fibula and just ventral to, or around, the neck of the fibula, and it should be verified by palpation of the tendons that the threshold of the direct motor response in the tibialis anterior is well below that for activation of peroneal muscles.

Elbow level

Because the triceps brachii nerve is stimulated close to other upper limb nerves (and in particular the branches of the deep radial nerve to forearm extensors), it is crucial to ensure that the conditioning stimulus does not encroach upon these nerves. On the other hand, since the electrodes stimulating biceps and triceps brachii afferents are located over the belly of the muscle, it is important to ensure that increasing the stimulation above 1 × MT results in a steep increase in the motor response involving the whole muscle and not just a limited part of it (corresponding to activation of a branch of the muscle nerve).

Organisation and pattern of connections

Pattern and strength of reciprocal Ia inhibition at rest at hinge joints

Reciprocal Ia inhibition between flexors and extensors of the ankle

Reciprocal inhibition between ankle flexors and extensors can be considered true reciprocal Ia inhibition, because: (i) the muscles are antagonists, (ii) the inhibition can be evoked by a pure Ia volley (cf. pp. 204–5; Fig. 5.2(*d*), (*e*)), and (iii) the inhibition is depressed by recurrent inhibition (cf. pp. 205–8; Fig. 5.5(*b*)).

Peroneal-induced inhibition of soleus motoneurones

Conflicting results have been obtained at rest. Several investigations have found the disynaptic peroneal-induced Ia inhibition of the soleus H reflex to be rare or absent at rest and, when present, to be weak (with a maximal decrease of ~10% of the unconditioned test reflex) (Mizuno, Tanaka & Yanagisawa, 1971; Tanaka, 1974; Pierrot-Deseilligny *et al.*, 1981; Shindo *et al.*, 1984; Baret *et al.*, 2003). In contrast, others have been able to demonstrate reciprocal Ia inhibition consistently (Kots & Zhukov, 1971; Crone, Hultborn & Jespersen, 1985; Iles, 1986; Crone *et al.*, 1987; Sato *et al.*, 1999; Perez, Field-Fote & Floeter, 2003). As discussed above, the discrepancy may be attributed in part to monosynaptic excitation elicited by inadvertent stimulation of Ia afferents in the superficial peroneal nerve. However, even when great care is taken to prevent the conditioning stimulus from encroaching on the superficial peroneal nerve, the amount of peroneal-induced reciprocal Ia inhibition of the soleus H reflex varies between normal subjects. In the large population investigated by Crone *et al.* (1987), the soleus H reflex was reduced by 0 to 40% of its control value in different subjects (Fig. 5.2(*f*)). This population was dominated by young students and, as shown in Fig. 5.2(*g*), there is a positive correlation between the strength of the inhibition and the degree of physical training, estimated as the amount of regular weekly exercise (Crone, Hultborn & Jespersen, 1985). This correlation could be due to plasticity in the pathway of reciprocal Ia inhibition, much as has been described in normal and spastic subjects (see pp. 232–3).

Reciprocal Ia inhibition of tibialis anterior motoneurones

Reciprocal Ia inhibition can be demonstrated consistently at rest in those subjects, in whom it is possible to evoke an H reflex in the tibialis anterior (Tanaka, 1974; Pierrot-Deseilligny *et al.*, 1981; Crone *et al.*, 1987; Baret *et al.*, 2003). Similarly, posterior tibial-induced reciprocal Ia inhibition was observed in the PSTHs of all tibialis anterior units investigated by Mao *et al.* (1984). Tibialis anterior H reflexes are inhibited from the posterior tibial nerve to a greater extent than soleus H reflexes from the deep peroneal nerve (Crone *et al.*, 1987; Fig. 5.2(*b*), (*c*)), and reciprocal Ia inhibition of the tibialis anterior may be revealed when the conditioning stimulus is applied to afferents of only one head of the triceps surae (inferior soleus or gastrocnemius medialis nerve, Pierrot-Deseilligny *et al.*, 1981; Fig. 6.2(*g*)). The quantitative difference between reciprocal inhibition of ankle flexors and extensors is reminiscent of the similar difference in the cat hindlimb (see p. 199).

Reciprocal Ia inhibition between flexors and extensors of the elbow

At the elbow, another hinge joint, the three criteria for true reciprocal inhibition between flexors and extensors have been met: strictly antagonistic muscles; elicitation by pure Ia volleys (Fig. 5.3(*c*)); and depression by recurrent inhibition (Fig. 4.7(*b*)). However, at this joint, the amount of reciprocal inhibition of the tendon jerk is similar at its peak in biceps and triceps brachii (Katz, Pénicaud & Rossi, 1991; Fig. 5.3(*b*)).

Reciprocal Ia inhibition between flexors and extensors of the knee

Data on reciprocal Ia inhibition between flexors and extensors of the knee are sparse and more difficult to interpret. Short-latency low-threshold femoral-induced inhibition has been described in the PSTHs of single units from hamstrings (Kudina, 1980; Bayoumi & Ashby, 1989; Fig. 5.6(*b*)). However, there was no confirmation that the inhibition was disynaptic, evoked by a pure Ia volley, or depressed by recurrent inhibition, and the reciprocal Ia origin of this inhibition cannot be affirmed. Low-threshold short-latency inhibition was found only exceptionally in the PSTHs of quadriceps units after stimulation of the nerves of the hamstrings (Bayoumi & Ashby, 1989). This does not necessarily reflect an asymmetry of reciprocal inhibition in favour of flexors, because it is almost impossible to prevent a conditioning stimulus to the sciatic nerve or its

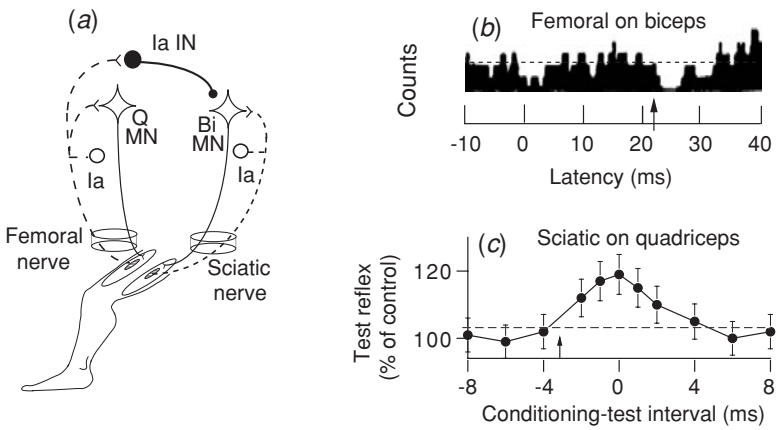


Fig. 5.6. Reciprocal inhibition between flexors and extensors of the knee. (*a*) Sketch of the presumed pathway of reciprocal inhibition from quadriceps (Q) to biceps femoris (Bi) motoneurones (MN) through Ia inhibitory interneurones (IN). (*b*) Peristimulus time histogram (0.4 ms bin width) of a biceps femoris unit after stimulation of the femoral nerve (0.71 × MT). Zero indicates the time of the stimulation, and the inhibition occurs at 22 ms (arrow). (*c*) The amplitude of the Q H reflex (expressed as a percentage of its unconditioned value) after stimulation of the sciatic nerve at the gluteal fold is plotted against the ISI. The arrow indicates the expected time of arrival of the conditioning volley at the segmental level of Q MNs. Any reciprocal inhibition is obscured by facilitation at monosynaptic latency, probably due to the activation of Ia afferents from leg and foot muscles contained in the sciatic nerve. These afferents have monosynaptic excitatory projections to quadriceps motoneurones (cf. Chapter 2, Table 2.1). Adapted from Bayoumi & Ashby (1989) (*b*); and Valls-Solé, Hallett & Brasil-Neto (1998) (*c*), with permission.

hamstring branches from encroaching upon the afferents from ankle extensors and plantar muscles. The resulting excitation of quadriceps motoneurones (cf. Table 2.1) could obscure any reciprocal inhibition from hamstrings (see Fig. 5.6(*c*) and its legend; Valls-Solé, Hallett & Brasil-Neto, 1998).

Conclusions

So far, reciprocal Ia inhibition has been established unequivocally in human subjects only at the ankle and elbow levels. Data for knee muscles are uncertain, while the strong inhibition between flexors and extensors in the forearm appears to be a non-reciprocal group I inhibition, and is discussed below.

Absence of 'true' reciprocal Ia inhibition at wrist level

Some features of the low-threshold disynaptic inhibition between muscles innervated by the median and the radial nerves are not compatible with those of the reciprocal Ia inhibition.

Inhibition at wrist level does not fulfil the criteria for reciprocal Ia inhibition

Two essential criteria for a 'true reciprocal Ia inhibition' are missing: (i) there is no evidence that the reciprocal inhibition between flexors and extensors in the forearm can be evoked by *pure* Ia volleys (see below), and (ii) the inhibition is not depressed by Renshaw cell activation (Aymard *et al.*, 1995; p. 208; Fig. 5.5(*d*)). In addition, it cannot be taken for granted that this inhibition is between strictly antagonistic muscles: (i) FCR and ECR operate as synergistic muscles in wrist abduction movements and, accordingly, there is recurrent inhibition between them (see Chapter 4, p. 171); (ii) inhibition of ECR by group I volleys in the median nerve cannot be equated to inhibition between antagonists, since the median nerve also innervates the flexors of

the fingers, which are synergists of wrist extensors in clenching and grasping (see Livingston *et al.*, 1951).

Convergence of group I afferents from several different muscles

Group I afferents from elbow muscles

Convergence of group I afferents from elbow muscles on interneurones mediating disynaptic reciprocal inhibition to FCR motoneurones has been observed in the PSTHs of single FCR units (Aymard *et al.*, 1995). Using spatial facilitation (Chapter 1, p. 47), it was shown that stimuli to the radial and the triceps brachii nerves, adjusted to be without effect by themselves, produced inhibition on combined stimulation (Fig. 5.7(*b*), (*c*)). A similar effect was seen consistently when radial and musculocutaneous volleys were combined. This indicates that interneurones mediating radial-induced disynaptic group I inhibition of FCR motoneurones receive excitatory input from elbow muscle group I afferents.

Group I afferents contained in the median and radial nerves

These afferents also converge onto common interneurones mediating disynaptic reciprocal inhibition of FCR motoneurones (Wargon *et al.*, 2005). Indeed, stimulation of the radial nerve, adjusted to produce weak inhibition in the PSTH of a FCR unit by itself, evoked a much greater suppression of the peak of homonymous monosynaptic Ia excitation when combined with a median volley (Fig. 5.7(*d*)–(*g*) and its legend). The extra suppression on combined stimulation is presumably due to convergence of median and radial group I volleys onto common interneurones. It spared the first 0.6 ms of the median group I excitation, and this is consistent with disynaptic inhibition elicited by the homonymous group I test volley and is reminiscent of the Ib inhibition elicited by such volleys (see Chapter 1, pp. 14–16; Chapter 6, pp. 265–7).

Non-reciprocal group I inhibition?

The only group I input to Ia interneurones mediating 'true' reciprocal Ia inhibition is Ia activity from the antagonistic muscle (p. 199). The convergence described above does not by itself rule out the possibility that part of the reciprocal inhibition between wrist muscles is reciprocal Ia inhibition. However, the finding that interneurones mediating group I reciprocal inhibition of wrist motoneurones receive excitation from group I afferents contained in other nerves, including the homonymous nerve, indicate that part of this inhibition is mediated through interneurones other than 'true' inhibitory Ia interneurones. In this respect, interneurones mediating non-reciprocal group I inhibition are good candidates (see Chapter 6, pp. 257–8). A contribution of Ib afferents to the activation of interneurones mediating the radial-induced inhibition of the FCR H reflex is further supported by experiments in which the electrical threshold of ECR Ia afferents was raised by long-lasting high-frequency vibration applied to the ECR tendon (Wargon *et al.*, 2005). Contrary to what is observed at elbow level (p. 205; Fig. 5.3(*c*)), the vibration only slightly increased the threshold and reduced the extent of the radial-induced inhibition of the FCR H reflex, thus implying that other afferents contribute to this disynaptic inhibition. These afferents are presumably Ib afferents, given the latency of the inhibition. Some Ib afferents respond to vibration of relaxed muscles (Chapter 3, pp. 130–1), and this could explain the slight increase in the threshold of the inhibition after vibration, but convergence of Ia and Ib afferents onto the relevant interneurones would be an equally satisfactory alternative explanation.

Other features of the inhibition are consistent with non-reciprocal group I inhibition

Post-activation depression

The absence of increased peroneal-induced reciprocal Ia inhibition of the soleus H reflex during tonic voluntary ankle dorsiflexion may be attributed to post-activation depression at the synapse of the Ia

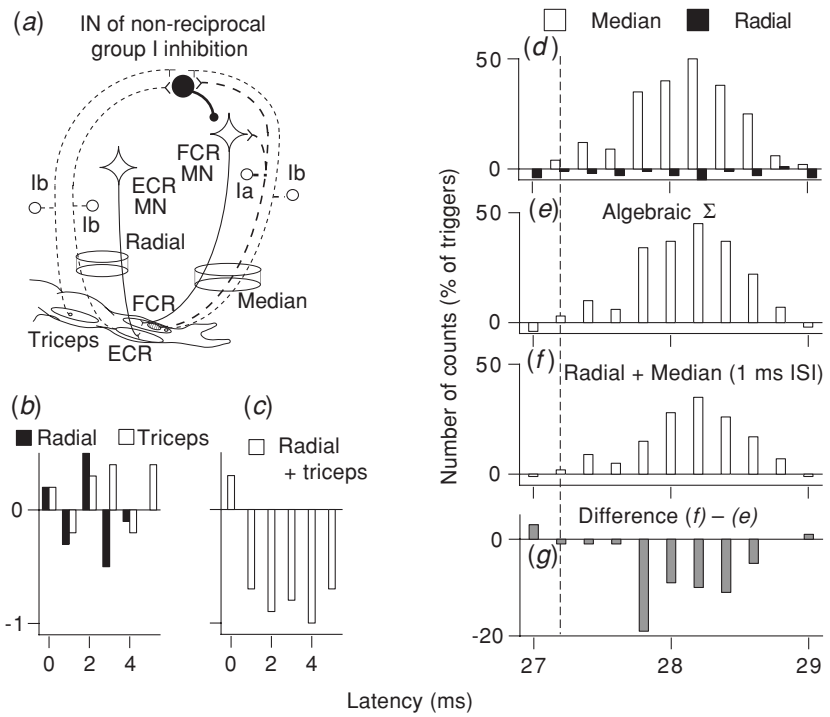


Fig. 5.7. Convergence of group I afferents from different muscles onto interneurones mediating the radial-induced inhibition of the FCR. (*a*) Sketch of the presumed pathways showing the convergence onto interneurones (IN) mediating disynaptic radial-induced non-reciprocal group I inhibition of FCR motoneurones (MN) by Ib afferents in the triceps nerve and by Ia and Ib afferents in the median nerve. (*b*), (*c*) PSTHs of the discharge of a single FCR unit (after subtraction of the background firing, 1 ms bin width) with stimulation (0.6 × MT) of the radial innervation of forearm extensors ((*b*), ■) and of the triceps brachii nerve ((*b*), □) and of both nerves together (*c*), the two volleys being timed to arrive synchronously at spinal level. Zero on the abscissa indicates the expected time of arrival of the volleys at MN level. While separate stimulation of each nerve has little effect (*b*), inhibition appears on combined stimulation. (*d*)–(*g*) PSTHs of the discharge of another FCR unit (after subtraction of the background firing, 0.2 ms bin width). (*d*) Facilitation (□) and inhibition (■) produced by separate stimulation (0.75 × MT) of the median and radial nerves, respectively (abscissa, time after median nerve stimulation even when radial stimulation is given 1 ms earlier, by itself). (*e*) Algebraic sum (Σ) of the effects of separate stimulation of the median and radial nerves. (*f*) Combined stimulation of the median and radial nerves, the radial preceding the median stimulation by 1 ms. (*g*) The suppression of the median group I excitation, calculated as ((*f*)–(*e*)). The dashed vertical line indicates the onset of the peak of homonymous Ia excitation. Note the lack of suppression in the initial bins of the median group I excitation. Modified from Aymard *et al.* (1995) ((*b*), (*c*)), Wargon *et al.* (2005) ((*d*)–(*g*)), with permission.

fibre on the Ia interneurone (Nielsen *et al.*, 1995; p. 221). This phenomenon is analogous to the post-activation depression at the synapse of the Ia fibre on the motoneurone (Chapter 2, pp. 96–9). Accordingly, increasing the frequency of stimulation drastically decreases the amount of reciprocal Ia inhibition of the tibialis anterior H reflex (even when the amplitude of the test reflex is the same as in the control situation). In contrast, at wrist level, the amount of radial-induced inhibition of the FCR H reflex is not modified when the frequency of the stimulation is increased (Lamy *et al.*, 2005). This in keeping with

the finding that post-activation depression has been found to be marginal in interneurones of the feline intermediate zone fed by group I afferents (Hammar, Slawinska & Jankowska, 2002).

Mutual inhibition

Radial-induced reciprocal inhibition of the FCR H reflex is depressed by a preceding group I volley to the median nerve (Baldissera *et al.*, 1987), and the time course and threshold of this disinhibition are similar to that of the median-induced inhibition of the ECR H reflex. Symmetrically, the median-induced inhibition of the ECR H reflex is depressed by a preceding radial Ia volley. This was interpreted, not unreasonably at the time, as due to the mutual inhibition between opposite Ia interneurones described in the cat (see p. 199). However, it could equally reflect the mutual inhibition of interneurones mediating non-reciprocal ('Ib') group I inhibition (see Chapter 6, p. 246). This would not be inconsistent with the spatial facilitation of radial and median group I inputs in 'Ib' interneurones described above, because the threshold for the trisynaptic inhibition of these interneurones would be expected to be higher than their disynaptic excitation by the convergent peripheral volleys.

Results obtained in patients with hyperekplexia

In hyperekplexia, a disease with a deficient glycinergic inhibitory system (cf. p. 233), reciprocal Ia inhibition at ankle level is completely abolished whereas radial-induced reciprocal inhibition of the FCR is preserved, although weak and somewhat delayed (J. B. Nielsen personal communication). Again, this is reminiscent of the findings for non-reciprocal group I inhibition, which is not significantly modified in these patients (Floeter *et al.*, 1996; Chapter 6, p. 276).

Conclusions

The absence of recurrent inhibition of the interneurones mediating the inhibition between flexors and extensors in the forearm innervated by the median and radial nerve argues against mediation via 'true' Ia inhibitory interneurones. In addition, several features suggest that a major part of this inhibition might be mediated through the interneurones of non-reciprocal group I inhibition. Accordingly, it may have been appropriate to treat this disynaptic non-reciprocal group I inhibition in Chapter 6 (Ib pathways). However, because it is more profound, more constant and therefore much easier to investigate than at other joints, a considerable amount of literature (in particular, in patients) has been devoted to this inhibition between wrist muscles, erroneously attributed (including by one of the authors of this book) to reciprocal Ia pathways. This is the reason for its inclusion in the present chapter. However, because the organisation of the spinal circuitry at this ball joint is unique in many aspects, changes in transmission in the pathway of non-reciprocal group I inhibition during wrist movements are considered in Chapter 11 (pp. 524–6).

Cutaneous facilitation of reciprocal Ia inhibition

Ia inhibitory interneurones are facilitated by low-threshold cutaneous afferents in the cat (cf. p. 200), and the effects of cutaneous stimuli on the reciprocal Ia inhibition from ankle flexors to extensors have therefore been investigated (Rossi & Mazzocchio, 1988). A cutaneous stimulus to the superficial peroneal nerve at the ankle, without effect on the soleus H reflex by itself, was shown to increase the deep peroneal-induced reciprocal Ia inhibition of the reflex (Fig. 5.8(*b*)). The central delay of this effect was estimated at 1–3 ms. The smaller the extent of reciprocal Ia inhibition in the control situation, the greater the cutaneous-induced increase in the inhibition (Fig. 5.8(*c*)). The disappearance of the cutaneous-induced facilitation when the reciprocal Ia inhibition is profound could be due to occlusion in Ia interneurones and is further evidence for convergence of Ia and cutaneous inputs on Ia interneurones. The functional significance of this

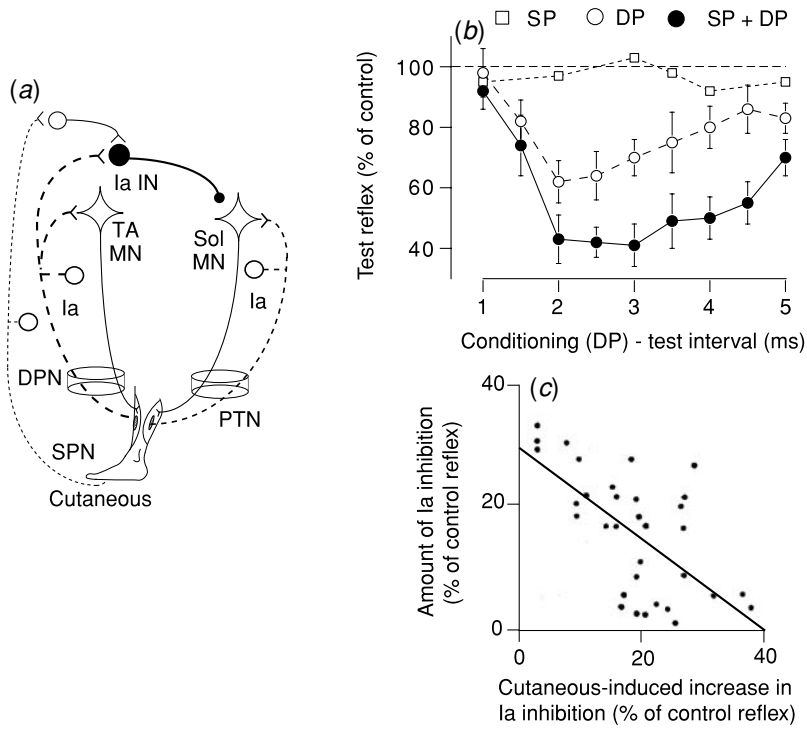


Fig. 5.8. Cutaneous facilitation of peroneal-induced reciprocal Ia inhibition of the soleus H reflex. (*a*) Sketch of the presumed pathways showing the convergence onto interneurones (INs) mediating the deep peroneal (DPN)-induced reciprocal Ia inhibition of soleus (Sol) motoneurones (MN) of cutaneous afferents from the foot contained in the superficial peroneal nerve (SPN). (*b*) Time course of the reciprocal Ia inhibition of the Sol H reflex evoked by DPN stimulation (0.9 × MT) in the absence (○) and in the presence (●) of cutaneous stimulation (2 × PT) to the SPN at the ankle, preceding the DPN stimulation by 10 ms. The cutaneous volley by itself did not modify the test reflex (□). Each symbol is the mean of 40 measurements. Vertical bars ±1 SEM. Data from a single subject. (*c*) The amount of Ia inhibition of the reflex in the control situation (ordinate, expressed as a percentage of the control reflex, the conditioning stimulus strength to CPN being varied) is plotted against the cutaneous-induced increase in the Ia inhibition (i.e. the difference between the amount of inhibition on combined stimulation and the sum of effects of separate stimuli, abscissa, expressed as a percentage of control reflex) (DPN-test ISI 3 ms, SPN-DPN ISI 10 ms). Modified from Rossi & Mazzocchio (1988) ((*b*), (*c*)), with permission.

cutaneous-induced facilitation, without local sign (it is evoked from all foot skin fields), could be to provide automatic correction when the forward movement of the foot is unexpectedly obstructed in the transition from the stance phase to the swing phase of gait. Reciprocal Ia inhibition of soleus motoneurones is increased with respect to rest in this phase of gait (Petersen, Morita & Nielsen, 1999; pp. 227–9; Fig. 5.13(*b*)), and the cutaneous facilitation would favour the contraction of ankle flexors necessary to move the foot away from the obstacle (see Chapter 11, p. 549).

Descending facilitation of reciprocal Ia inhibition

In animal experiments, corticospinal and vestibulospinal volleys facilitate Ia interneurones mediating reciprocal Ia inhibition (cf. p. 200).

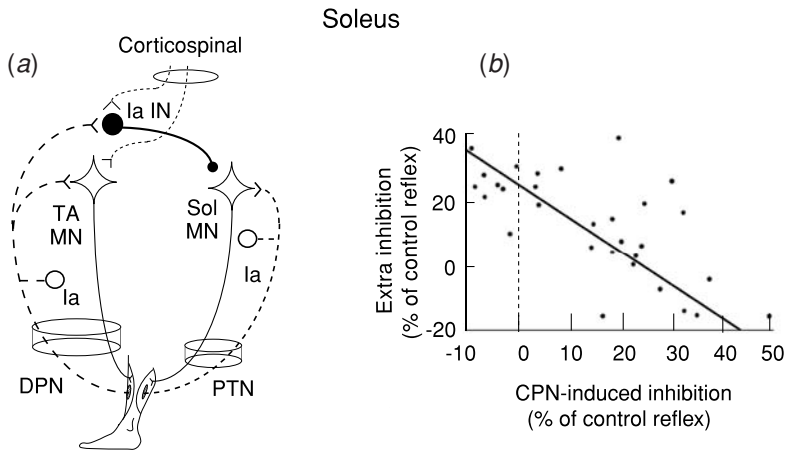


Fig. 5.9. Corticospinal facilitation of reciprocal Ia inhibition. (*a*) Sketch of the presumed pathways showing the corticospinal facilitation of interneurones (IN) mediating the deep peroneal (DPN)-induced reciprocal Ia inhibition of soleus (Sol) motoneurones (MN). (*b*) The amount of extra inhibition on combined stimulation of the DPN (2.5 ms ISI) and of the motor cortex (electrical stimulation, –0.5 ms ISI). The extra inhibition on combined stimulation (i.e. the difference between the amount of inhibition on combined stimulation and the sum of effects of separate stimuli, ordinate, expressed as a percentage of control reflex) is plotted against the amount of peroneal-induced inhibition in the control situation (abscissa, expressed as a percentage of the control reflex). Data from two subjects, in whom the conditioning stimulus strength to CPN was varied from 0.6 to 2 × MT. Modified from Iles & Pisini (1992b) (*b*), with permission.

Corticospinal facilitation of reciprocal Ia inhibition

The effects of TMS on the deep-peroneal-induced reciprocal inhibition of the soleus H reflex have been investigated by Kudina, Ashby & Downes (1993). Provided that the conditioning stimuli did not modify the H reflex when delivered separately, the dominant effect on combined stimulation was extra inhibition over and above that expected from the sum of the two separate responses. Further evidence for corticospinal facilitation of tibialis anterior-coupled Ia interneurones has been provided by Nielsen *et al.* (1993), who showed that corticospinal inhibition of the soleus H reflex: (i) is mediated by tibialis anterior-coupled Ia interneurones, (ii) is potently facilitated during voluntary ankle dorsiflexion and, accordingly, (iii) has a similar threshold as the short-latency (presumably monosynaptic) corticospinal facilitation of tibialis anterior motoneurones. Here again, the greater the amount of reciprocal Ia inhibition in the control situation, the smaller the extra inhibition on combined stimulation. This probably results from occlusion between the two inputs at the Ia interneurones (Fig. 5.9(*b*); Iles & Pisini, 1992b). The finding that occlusion occurs at weak levels of reciprocal Ia inhibition (reducing the control reflex by ~20%) implies that the population of Ia interneurones is rapidly saturated. This may be relevant to the modest amount of reciprocal Ia inhibition to soleus motoneurones often found in healthy subjects (see p. 210).

Vestibulospinal facilitation of reciprocal Ia inhibition

Stimulation of the vestibular apparatus produces facilitation of reciprocal Ia inhibition from tibialis anterior to soleus in two situations: (i) static backward tilt (from 80 to 40°) of the subject fixed to a tilting chair (Rossi, Mazzocchio & Scarpini, 1988), and (ii) galvanic stimulation of vestibular afferents, producing a forward sway (Iles & Pisini, 1992a). This has

been interpreted as resulting from disinhibition of the relevant flexor-coupled Ia interneurones (Iles & Pisini, 1992a).

Motor tasks and physiological implications

Data on the effects of movement on true reciprocal Ia inhibition are available only for ankle movement, given that the studies performed at wrist level probably examined non-reciprocal group I inhibition and are considered in Chapter 11 (pp. 524–6).

Voluntary contraction of the antagonistic muscle

Depression of the unconditioned soleus H reflex during voluntary ankle dorsiflexion

Voluntary dorsiflexion of the ankle strongly depresses the soleus H reflex (Hoffmann, 1918; Kots, 1969). During a ramp-and-hold contraction, there is a close correspondence between agonist activity (the force of ankle dorsiflexion) and the inhibition of the antagonistic soleus H reflex (Crone *et al.*, 1987). The inhibition progressively increases throughout the ramp phase, reaches a maximum at the end of the ramp (where the test reflex is reduced to 10–20% of its rest value) and then remains constant during the holding phase. Several mechanisms contribute to this depression (sometimes referred to as 'natural reciprocal inhibition').

Central and peripheral factors

The time course of the depression during a brief contraction is illustrated in Fig. 5.10(*b*). It occurs 50 ms prior to the onset of the tibialis anterior contraction (Kots, 1969; Pierrot-Deseilligny, Lacert & Cathala, 1971; Crone & Nielsen, 1989a), suggesting a descending control from the brain. The inhibition, however, increases greatly 50–100 ms into the movement (Morin & Pierrot-Deseilligny, 1977; Kagamihara & Tanaka, 1985), when the contraction-induced afferent feedback is arriving at the spinal cord. This secondary reinforcement of the inhibition is markedly reduced during ischaemic blockade of group I afferents from the leg, confirming that it is of peripheral origin (Morin & Pierrot-Deseilligny, 1977). Notwithstanding, when the peripheral input is blocked by ischaemia, a significant inhibition of the soleus H reflex persists 100 ms after the onset of contraction (Fig. 5.10(*b*)). It also persists during fictive dorsiflexion following complete block of the peroneal nerve using lidocaine (Nielsen *et al.*, 1995). These findings suggest that descending inputs contribute to the 'natural' reciprocal inhibition of the soleus H reflex.

Neuronal pathways

Four mechanisms could contribute to the above depression of the soleus H reflex (see the sketch in Fig. 5.10(*a*)): (i) reciprocal Ia inhibition, (ii) interneurones transmitting the longer-latency (propriospinally mediated) inhibition (see Crone & Nielsen, 1989a; Chapter 10, pp. 497–8), (iii) presynaptic inhibition on Ia terminals on soleus motoneurones (see Chapter 8, pp. 360–1), and (iv) a stretch-evoked Ia discharge from soleus, with post-activation depression of the afferent terminals on soleus motoneurones (Crone & Nielsen, 1989b). There will be descending (probably corticospinal) facilitation of reciprocal Ia inhibition (see Crone *et al.*, 1987) and of presynaptic inhibition on soleus Ia terminals (Meunier & Morin, 1989; Nielsen & Kagamihara, 1993) before any contraction-associated group I discharge reaches the spinal level. Both reciprocal Ia inhibition and presynaptic inhibition on Ia soleus terminals are fed by the group I discharge from the contracting pretibial flexors and will contribute to the secondary reinforcement of the reflex inhibition. The longer-latency propriospinally mediated inhibition correlates well with the changes in the soleus H reflex throughout a voluntary dorsiflexion (Crone & Nielsen, 1989a). It cannot be demonstrated at rest, and this therefore implies that the descending drive provides a sufficient facilitation of the relevant propriospinal interneurones to discharge

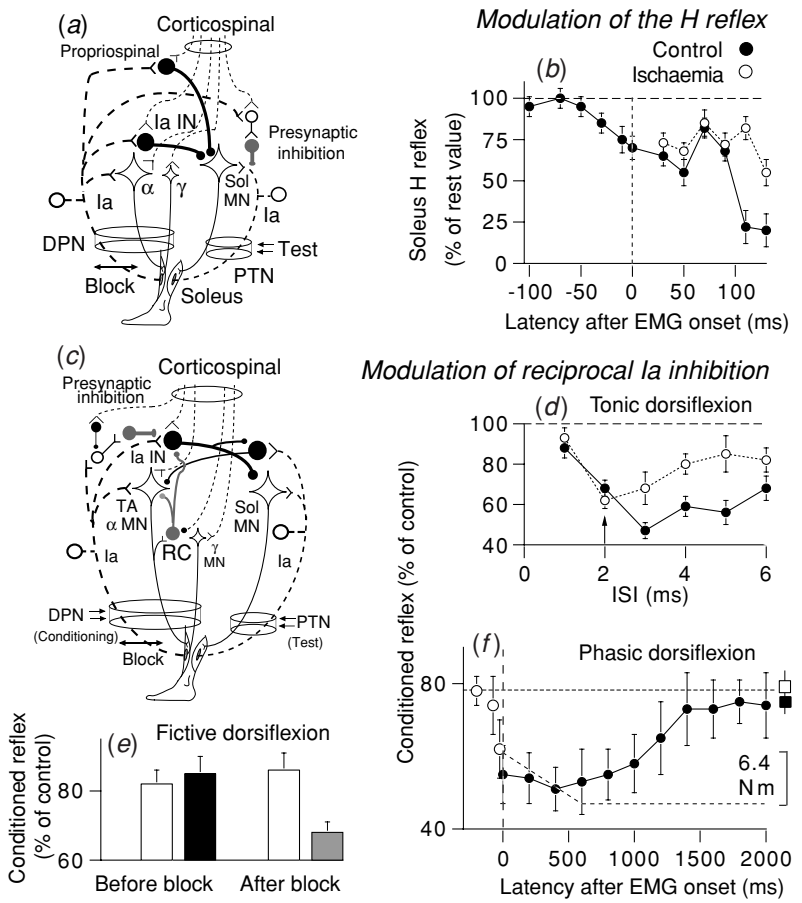


Fig. 5.10. Changes in peroneal-induced reciprocal Ia inhibition during voluntary dorsiflexion. (*a*), (*b*) Modulation of the soleus (Sol) H reflex during tibialis anterior (TA) voluntary contraction. (*a*) Sketch of three of the four mechanisms contributing to the Sol H reflex inhibition during TA contraction: (i) reciprocal Ia inhibition with Ia interneurones (INs) activated by direct corticospinal drive and via the γ loop; (ii) propriospinally mediated inhibition; (iii) presynaptic inhibition on soleus Ia terminals. (*b*) Time course of the changes in the Sol H reflex (% of rest value) prior to and after the onset of TA EMG activity in the control situation (●) and after ischaemic blockade of group I afferents in the leg (○). Vertical dashed line in (*b*), (*f*), onset of the TA EMG activity. (*c*)–(*f*) Modulation of peroneal-induced reciprocal Ia inhibition of the Sol H reflex (0.95 × MT). (*c*) Sketch of the mechanisms modulating the excitability of Ia INs (Ia discharge via the γ loop, recurrent inhibition, presynaptic inhibition of Ia terminals on Ia INs, corticospinal activation). (*d*) Time course of the peroneal-induced reciprocal inhibition of the Sol H reflex at rest (○) and during tonic TA contraction (●) (the arrow indicates the 2 ms ISI, when reciprocal Ia inhibition is not yet contaminated by propriospinally mediated inhibition). (*e*) Peroneal-induced (2 ms ISI, 0.95 × MT) inhibition of the soleus H reflex (as a percentage of control reflex) is compared at rest (□), during tonic dorsiflexion before block (■) and during fictive dorsiflexion after block (grey column). (*f*) Time course of the changes in reciprocal Ia inhibition prior to (○) and during (●) a ramp-and-hold dorsiflexion (600 ms ramp phase, as shown by the thin dashed line indicating the torque). The big open and filled squares on the right indicate the level of reciprocal inhibition at rest and during tonic dorsiflexion, respectively. (*d*), (*f*) Conditioned reflex expressed as a percentage of control reflex, vertical bars ±1 SEM. Modified from Pierrot-Deseilligny, Lacert & Cathala (1971) and Morin & Pierrot-Deseilligny (1977) (*b*), Crone & Nielsen (1989a) (*d*), Nielsen *et al.* (1995) (*e*), and Crone *et al.* (1987) (*f*), with permission.

them during voluntary dorsiflexion (see Chapter 10, pp. 497–8; Chapter 11, pp. 519–20).

Peroneal-induced inhibition of the soleus H reflex during tonic voluntary dorsiflexion

In the cat, there is a striking similarity in the segmental and supraspinal convergence onto α motoneurones and the Ia interneurones inhibiting the motoneurones of the antagonistic muscle ('corresponding' Ia interneurones, see p. 201). This led Lundberg (1970) to suggest that α (and γ) motoneurones and corresponding Ia interneurones are controlled in parallel from the brain during movement in order to achieve a coordinated contraction of agonists and relaxation of antagonists ('α-γ linkage in the reciprocal Ia inhibition', see the sketches in Fig. 5.10(*a*), (*c*)). This hypothesis has been extensively tested in human subjects at ankle level (see below).

Conflicting results

In the original report by Tanaka (1974), peroneal-induced inhibition of the soleus H reflex was absent at rest despite the use of a conditioning train of three shocks to the common peroneal nerve. It appeared during tonic voluntary dorsiflexion, and was maximal 1.7 ms after the last shock of the train. Increased reciprocal inhibition of the soleus H reflex during tonic dorsiflexion was confirmed by Iles (1983, however, see Iles, 1986), Shindo *et al.* (1984, 1995) and Sato *et al.* (1999), but not in repeated experiments performed on a large number of subjects in The Panum Institute in Copenhagen (Crone, Hultborn & Jespersen, 1985; Crone *et al.*, 1987; Crone & Nielsen, 1989a, 1994; Nielsen *et al.*, 1992, 1995).

Methodological considerations might account for part of these discrepancies

(i) Normalisation to control reflexes of different size (see Chapter 1, p. 16) would cause the inhibition to appear greater when expressed as a percentage of the unconditioned test reflex, which is strongly depressed during voluntary dorsiflexion (see above). Thus, Crone, Hultborn & Jespersen (1985) emphasised the importance of maintaining a constant reflex size by 'boosting' the test reflex during dorsiflexion to be of the same size as at rest. (Note, however, that while this correction would eliminate differences in the size-related sensitivity of the test reflex as a factor, it has an unwanted consequence: the afferent volley is not the same under the two conditions, see Chapter 1, p. 18). (ii) At rest, the maximal peroneal inhibition of the soleus H reflex is reached at the 2 ms ISI and, during dorsiflexion, there is no increase in this value, which represents the 'true' reciprocal Ia inhibition (vertical arrow in Fig. 5.10(*d*); Crone & Nielsen, 1989a). In contrast, at later ISIs, inhibition is markedly increased during dorsiflexion, because of the appearance during contraction of the longer-latency propriospinally mediated inhibition, which can be recorded consistently in subjects (Crone & Nielsen, 1989a; Chapter 10, pp. 497–8). Because Tanaka (1974) always and Shindo *et al.* (1984) sometimes used a conditioning train, their test stimulus was delivered 4–9 ms after the first conditioning shock, and the responses could have been contaminated by the long-latency inhibition.

Individual variations

However, Shindo *et al.* (1995) complied with all conditions necessary to demonstrate 'true' reciprocal Ia inhibition (single deep peroneal shock, 2 ms ISI, same size of the test reflex in the two situations), and confirmed that reciprocal inhibition of the soleus H reflex is increased during tonic dorsiflexion with respect to rest. Furthermore, they were able to demonstrate the increase in reciprocal Ia inhibition in single motor units using the unitary H reflex (as described in Chapter 1, pp. 37–9), though this occurred only with very weak tonic dorsiflexion of <2% MVC and not with slightly stronger contractions of 3–8%. Because these results were obtained in only six subjects, inter-individual variations might be another cause of the discrepancy. Indeed, several subjects in the large population investigated

by Crone *et al.* (1987) did have some increase in reciprocal Ia inhibition during tonic dorsiflexion, even though there was no mean difference between rest and contraction for all 40 subjects. There is therefore a risk that the small sample of subjects might have been unrepresentative.

Conclusions

The issue remains unresolved. However, it is probably of little importance, because facilitation of Ia interneurones does exist, but cannot manifest itself fully during tonic contractions (see below).

Increased reciprocal inhibition after blocking conduction in Ia afferents

The difficulty in proving increased reciprocal Ia inhibition during tonic dorsiflexion contractions contrasts with the ease with which it can be demonstrated at the onset of dynamic contractions (see below). The possibility then arises that afferent activity from the contracting pretibial flexors decreases the efficacy of the peroneal conditioning volley in activating Ia interneurones during tonic contractions. This was tested by blocking the group I afferent feedback from the leg by ischaemia (Nielsen *et al.*, 1992) and by a complete block of conduction in the common peroneal nerve by local injection of lidocaine (Nielsen *et al.*, 1995), the blocks being distal to the conditioning peroneal nerve stimulation. Reciprocal Ia inhibition was not modified by 'normal' tonic voluntary dorsiflexion, but was significantly increased during the nerve blocks (Fig. 5.10(*e*)). These results indicate that, during voluntary dorsiflexion, increased reciprocal Ia inhibition of soleus motoneurones can manifest itself, provided that the feedback from the contracting pretibial flexors is blocked.

Mechanisms underlying the reduced efficacy of the conditioning volley

Several mechanisms dependent on the natural group I discharge during tonic dorsiflexion could contribute to the decreased efficacy of the conditioning volley in activating Ia interneurones.

Occlusion in Ia interneurones

During voluntary dorsiflexion, Ia interneurones receive strong excitation from descending centres and through the γ loop such that further input from the conditioning volley could result in occlusion. However, the role of occlusion is probably only marginal: Crone *et al.* (1987) and Nielsen *et al.* (1992) failed to demonstrate an increase in reciprocal Ia inhibition during tonic dorsiflexion when they reduced the intensity of the conditioning stimulus and/or the strength of the contraction. Furthermore, as illustrated in Fig. 5.10(*f*), there is a significant increase in reciprocal inhibition during the dynamic phase of a ramp-and-hold dorsiflexion. This is difficult to reconcile with occlusion, because (i) both corticospinal activation of neurones (see Fetz, 1992) and γ-induced Ia feedback (see p. 135) are greater during the dynamic phase of an isometric contraction, and (ii) at the onset of contraction, presynaptic inhibition on Ia terminals mediating the conditioning volley is decreased, effectively increasing the Ia volley from tibialis anterior (see below).

Presynaptic inhibition

Presynaptic inhibition on Ia terminals directed to Ia interneurones could be enhanced by the natural feedback from the contracting muscle (see Enriquez-Denton *et al.*, 2000; pp. 200–1), with resulting reduction of the activation of Ia interneurones by the conditioning volley. However, when the increase in Ia discharge from the contracting muscle is interrupted by a nerve block using ischaemia or lidocaine, presynaptic inhibition on Ia terminals from quadriceps to soleus motoneurones is not significantly reduced (Nielsen *et al.*, 1992, 1995). If this applies to Ia afferents on tibialis anterior motoneurones and Ia interneurones, presynaptic inhibition would not be a major factor in the decreased efficacy of the peroneal conditioning volley on Ia interneurones during tonic dorsiflexion.

Post-activation depression

A further possibility is that the contraction-induced Ia discharge produces post-activation depression at the synapse between the Ia afferent and the Ia interneurone. Activity in Ia afferents results in post-activation depression at the Ia afferent-motoneurone synapse (see Chapter 2, pp. 96–9), and it is likely that similar depression occurs at the Ia afferent terminals which synapse with Ia interneurones in humans (see Lamy *et al.*, 2005). Thus, because of the enhanced Ia discharge from tibialis anterior during tonic voluntary dorsiflexion (see Chapter 3, pp. 133–5), the amount of transmitter released by the conditioning peroneal volley would be smaller than at rest, and this could mask the effects of this volley. However, when the background activity of peroneal afferents is blocked by ischaemia or lidocaine injection, there should be no post-activation depression and the amount of transmitter released by the conditioning volley at rest and during contraction would be the same. As a result, a descending drive to Ia interneurones during attempted voluntary tonic dorsiflexion would increase reciprocal inhibition. This has been shown to be the case (Nielsen *et al.*, 1992, 1995).

Conclusions

All three mechanisms discussed above could contribute to the absence of increased reciprocal Ia inhibition of soleus motoneurones evoked by a peroneal group I volley during 'normal' voluntary tonic dorsiflexion. However, the contribution from the post-activation depression at the Ia afferent-Ia interneurone synapse is likely to be the most important, and there are arguments against major roles for the other two.

Increased reciprocal Ia inhibition during dynamic contractions

In contrast, increased peroneal-induced reciprocal Ia inhibition is easily and consistently demonstrated 50 ms prior to, at the onset of and during the dynamic phase of voluntary dorsiflexion of the ankle (Kots & Zhukov, 1971; Simoyama & Tanaka, 1974; Crone *et al.*, 1987; Fig. 5.10(*f*)). The finding that this increase occurs before the Ia input has reached the spinal level implicates a descending mechanism, independent of the Ia discharge.

Mechanisms underlying changes in the efficacy of the conditioning peroneal volley

Changes in reciprocal inhibition elicited by the artificially synchronised electrical volley used to activate pretibial flexor-coupled Ia interneurones are the result of several mechanisms, which are discussed in this section (see the sketch in Fig. 5.10(*c*)):

Descending drive on Ia interneurones

The increased reciprocal Ia inhibition observed during voluntary tonic dorsiflexion when the γ-induced Ia discharge is blocked by ischaemia or lidocaine indicates the existence of a descending tonic excitatory drive on Ia inhibitory interneurones. It could be argued that the increased descending drive observed in such experiments results from an adaptive strategy to compensate for the interruption of spindle feedback. However, corticospinal inhibition of the soleus H reflex is largely mediated by reciprocal Ia inhibitory interneurones, and is strongly increased during 'normal' tonic dorsiflexion (Nielsen *et al.*, 1993). This finding supports the view of a descending facilitation of the Ia interneurones even when Ia feedback is intact. The simplest explanation for the increased peroneal-induced reciprocal Ia inhibition at the onset of contraction is that the inhibitory interneurones are facilitated by supraspinal pathways in parallel with activated α motoneurones, and facilitation is visible here because the post-activation depression has not yet manifested itself, and/or is compensated for by a decrease in presynaptic inhibition on Ia terminals on Ia interneurones (see below).

Effects due to the 'natural' Ia discharge

The Ia discharge associated with an isometric contraction is maximal at the onset of the contraction

and decreases by ~30% when the contraction is maintained (cf. Chapter 3, p. 135; Fig. 3.7(*b*), (*c*)). The increased Ia discharge would produce both increased excitability of Ia interneurones and post-activation depression, and the change in the peroneal-induced inhibition of the H reflex would be the net result of these two opposing effects and of the level of presynaptic inhibition on Ia terminals (cf. below).

Presynaptic inhibition of Ia terminals on Ia interneurones

If data obtained in soleus and quadriceps can be transposed to tibialis anterior, there would be a tonic level of presynaptic inhibition at rest and, despite the increased group I afferent input from pretibial flexors, there could be a considerable decrease in presynaptic inhibition of Ia terminals on tibialis anterior motoneurones and corresponding Ia interneurones during the first part of the tibialis anterior ramp contraction (see Chapter 8, pp. 355–9). This could cause the conditioning Ia volley to be more effective in firing Ia interneurones, and could be sufficient to explain the increased peroneal-induced reciprocal Ia inhibition at the onset of contraction.

Recurrent inhibition

Recurrent inhibition activated orthodromically via recurrent collaterals by the motor discharge from pretibial flexors could inhibit Ia inhibitory interneurones (cf. p. 200). However, if the data obtained for soleus (see Chapter 4, p. 179) can be transposed to tibialis anterior, recurrent inhibition to active motoneurones should be depressed during strong tonic contractions in order to leave reciprocal Ia interneurones to exert their inhibitory action fully.

Functional implications

Effective reciprocal inhibition of the antagonistic muscle is required during phasic flexion–extension movements

This is discussed below with regard to flexion of the ankle, but the principles apply equally to flexion-extension movements of all hinge joints. Contraction of the agonist (tibialis anterior) produces a stretch-induced Ia discharge from the antagonistic muscle (soleus), which is larger during phasic than tonic contractions. This Ia discharge will produce two undesirable effects: excitation of antagonistic motoneurones (and this could evoke a soleus stretch reflex) and excitation of 'corresponding' soleus-coupled Ia interneurones inhibiting tibialis anterior motoneurones. The contributions of different spinal mechanisms (presynaptic inhibition of Ia terminals on soleus motoneurones, reciprocal Ia inhibition, longer-latency propriospinally mediated inhibition) to the relaxation of the antagonist are addressed in Chapter 11 (pp. 519–21). The present discussion focuses on reciprocal Ia inhibition, which opposes not only the activation of antagonistic motoneurones but is also the sole mechanism opposing the activation of opposite 'soleus-coupled' Ia interneurones (see Fig. 5.10(*c*)).

Mechanisms underlying an increase in natural reciprocal Ia inhibition during voluntary contraction

These mechanisms can be inferred from the changes in reciprocal Ia inhibition produced by an artificial volley discussed above. When fusimotor drive increases the Ia discharge from a contracting muscle, the efficacy of this discharge will be enhanced at the onset of the contraction by decreased presynaptic gating. The discharge may well be able to activate Ia interneurones, especially if they are depolarised by a descending drive and not inhibited by recurrent inhibition (see the sketch in Fig. 5.10(*c*)). However, post-activation depression will help maintain the synaptic efficacy of the Ia fibre-Ia interneurone synapse at a relatively low level during slow or tonic voluntary movements. In addition, muscle shortening in a 'concentric' contraction will unload spindle endings (cf. Chapter 3, p. 135), and an increase in Ia discharge will then occur only in slow contractions or when the contracting muscle is working against a load. Thus, during a rapid phasic shortening contraction, i.e. the type of contraction with the greatest potential to

trigger a stretch-induced Ia discharge from the antagonist, it is likely that many muscle spindle endings in the contracting muscle will be silenced. Unwanted activation of soleus motoneurones and extensor-coupled Ia interneurones would then require that tibialis anterior-coupled Ia interneurones receive a descending drive that is sufficient to fire them, i.e. that tibialis anterior motoneurones and corresponding Ia interneurones receive a parallel descending excitation, as postulated by Lundberg (1970) and demonstrated in experiments performed after blocking the Ia afferent feedback (see p. 220).

Reciprocal Ia inhibition directed to motoneurones of the active muscle

Decreased reciprocal Ia inhibition of the soleus H reflex during soleus contractions

In contrast with the conflicting results described during dorsiflexion, there is general agreement that peroneal-induced reciprocal Ia inhibition of the soleus H reflex is reduced below its resting value during tonic voluntary contractions of soleus (Tanaka, 1974; Shindo *et al.*, 1984; Iles, 1986; Crone *et al.*, 1987; Fig. 5.11(*b*)). The stronger the soleus contraction, the more marked the depression of reciprocal Ia inhibition (Petersen, Morita & Nielsen, 1998; Fig. 5.11(*d*)). Similarly, the posterior tibial-induced reciprocal Ia inhibition of the tibialis anterior H reflex is significantly depressed during a tonic voluntary contraction involving tibialis anterior motoneurones (Crone *et al.*, 1987).

Reciprocal Ia inhibition of the on-going soleus EMG activity

Evidence for EMG suppression

Figure 5.11(*c*) shows the inhibition appearing as a depression of the rectified on-going voluntary EMG activity of soleus elicited by stimulation of the deep peroneal nerve (Petersen, Morita & Nielsen, 1998). Given the latency of the H reflex and the difference in afferent conduction times for the peroneal and posterior tibial Ia volleys, the latency of the inhibition is consistent with disynaptic reciprocal Ia inhibition. Other pathways may also contribute to the depression: (i) the longer-latency propriospinally mediated inhibition (cf. above), and even (ii) the peroneal-induced presynaptic inhibition of soleus Ia terminals, which could participate in the late part of the EMG suppression through suppression of the Ia drive set up via the γ loop.

Influence of the conditioning stimulus strength

With a conditioning stimulus to the deep peroneal nerve at 1.1 × MT, reciprocal Ia inhibition of both the H reflex and the on-going soleus EMG can be demonstrated during weak plantar flexion but disappears almost totally during strong plantar flexion. With a conditioning stimulus at 1.5 × MT, the inhibition of the H reflex and of the on-going EMG is depressed to a similar extent during weak and strong tonic plantar flexion (Fig. 5.11(*d*)–(*g*)). However, high-intensity stimuli activate many fibres other than deep peroneal Ia afferents (see pp. 208–9), and the resulting inhibition of soleus motoneurones may then be due to spinal mechanisms other than reciprocal Ia inhibition (see Petersen, Morita & Nielsen, 1998).

Conclusions

Reciprocal Ia inhibition to active motoneurones may be compared during various motor tasks by assessing changes in suppression of the on-going EMG activity elicited by a Ia volley from the antagonistic muscle. However, the comparison is only valid when conditioning stimuli are weak and activate only group I afferents contained in the deep peroneal nerve. Then, the stronger the voluntary contraction of the target muscle, the smaller reciprocal Ia inhibition so assessed.

Spinal mechanisms underlying the decreased reciprocal Ia inhibition

Mutual inhibition of 'opposite' Ia interneurones

Mutual inhibition from increased descending facilitation of soleus-coupled Ia interneurones is the

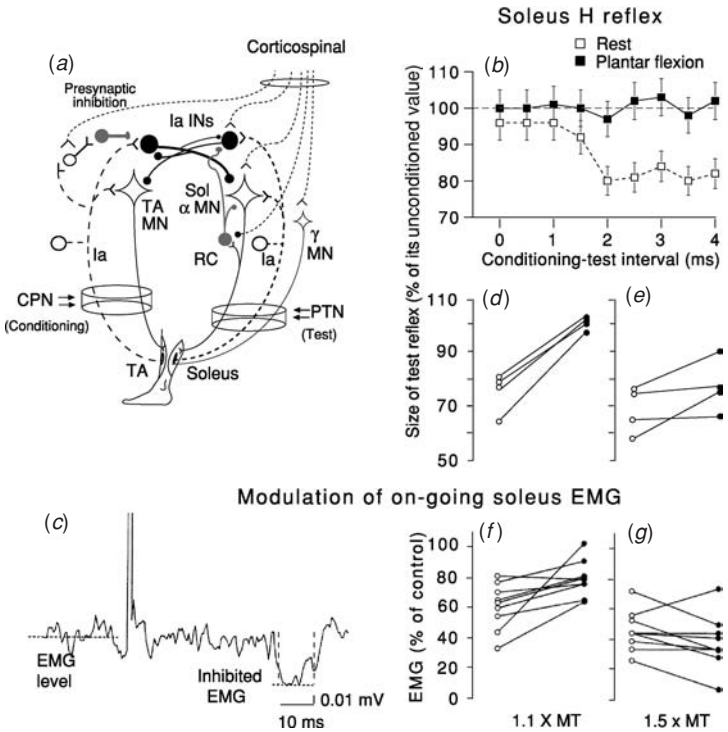


Fig. 5.11. Changes in peroneal-induced reciprocal Ia inhibition during voluntary plantar flexion. (*a*) Sketch of the different mechanisms contributing to the depression of the reciprocal inhibition from tibialis anterior (TA) to soleus (Sol) during voluntary ankle plantar flexion: (i) facilitation of 'opposite' Sol-coupled Ia interneurones (INs) (via Ia discharge through the γ loop, corticospinal activation, disinhibition from Renshaw cells [RC]), (ii) facilitation of presynaptic inhibition of Ia terminals on TA-coupled Ia INs. (*b*) Time course of the peroneal-induced (1 × MT) reciprocal Ia inhibition of the Sol H reflex at rest (❍) and during tonic ankle plantar flexion (●). Data from one subject. Each symbol is the mean of 20 measurements; vertical bars ±1 SEM. (*c*) Modulation of the on-going soleus EMG activity by a peroneal volley during a voluntary plantar flexion (5% MVC) in one subject. (*d*)–(*g*) The H reflex ((*d*), (*e*) 2 ms ISI) and the on-going soleus EMG ((*f*), (*g*), assessed during the 10 ms between the vertical dashed lines in (*c*)) conditioned by a peroneal volley at 1.1 ((*d*), (*f*)) and 1.5 ((*e*), (*g*)) × MT during weak (5% MVC, ❍) and strong (40% MVC, ●) plantar flexion. Each symbol represents one subject. With weak conditioning volleys, the reciprocal Ia inhibition of both the H reflex (*d*) and the on-going EMG (*f*) is still detectable during weak plantar flexion (❍), but largely disappears during strong plantar flexion (●). Modified from Shindo *et al.* (1984) (*b*) and from Petersen, Morita & Nielsen (1998) ((*c*)–(*g*)), with permission.

mechanism generally put forward to explain the decreased reciprocal Ia inhibition directed to active soleus motoneurones (see p. 199 and the sketch in Fig. 5.11(*a*)). Parallel activation of soleus α motoneurones and the corresponding Ia interneurones can explain why the depression of reciprocal Ia inhibition increases with the strength of plantar flexion. Ia interneurones are activated directly by descending tracts, and indirectly through increased fusimotor drive to the contracting muscle. The ease with which the depression of reciprocal Ia inhibition to soleus motoneurones can be demonstrated during tonic plantar flexion is due to the fact that the conditioning peroneal Ia volley and the fusimotor-driven Ia discharge from the contracting soleus do not traverse the same afferents (and synapses).

Inhibition of soleus-coupled Renshaw cells

Mutual inhibition of Ia interneurones is also favoured by the inhibition of soleus-coupled Renshaw cells, as occurs during strong tonic contractions and towards the end of ramp plantar flexion (see Chapter 4, p. 179; Fig. 5.11(*a*)). This would leave soleus-coupled Ia interneurones to exert their inhibitory action fully on opposite Ia interneurones (Pierrot-Deseilligny, Katz & Hultborn, 1983).

Facilitation of presynaptic inhibition

Facilitation of presynaptic inhibition of Ia terminals on motoneurones antagonistic to the active muscle and on corresponding Ia interneurones might also reduce the efficacy of the peroneal Ia volley in activating Ia interneurones. Indeed, if data obtained for soleus during voluntary contraction of the antagonistic muscle can be transposed to tibialis anterior, soleus contractions should be accompanied by facilitation of PAD interneurones mediating presynaptic inhibition of tibialis anterior Ia afferents (see the sketch in Fig. 5.11(*a*)), though this effect is moderate (Chapter 8, pp. 360–1).

Functional implications

The depression of the reciprocal Ia inhibition to motoneurones activated in a movement of flexion-extension prevents the Ia discharge elicited by the stretch of the antagonistic muscles from inhibiting agonist motoneurones and corresponding Ia interneurones (Fig. 5.11(*a*)).

Reciprocal Ia inhibition during co-contraction of antagonistic muscles

Methodology

A balanced co-contraction (i.e. one with equal activity in the antagonistic muscles) can be produced by asking the subject to perform a specified level of plantar flexion, and then to bring the torque exerted on the foot plate back to zero, while maintaining a constant EMG level in the soleus (Fig. 5.12(*f*)–(*i*)).

Decreased reciprocal Ia inhibition during co-contraction

Reciprocal Ia inhibition of the soleus H reflex has been compared during isolated dorsi- and plantar flexion contractions at a level of EMG activity equivalent to that recorded during co-contraction (Nielsen & Kagamihara, 1992; Fig. 5.12(*b*)–(*e*)). Reciprocal inhibition during co-contraction was strongly depressed. It was always smaller than the sum of the effects evoked by separate dorsi- and plantar flexion contractions, suggesting a control mechanism specific to co-contraction. There was similar depression of reciprocal Ia inhibition from ankle extensors to ankle flexors in those subjects in whom it was possible to evoke a tibialis anterior H reflex during plantar flexion and co-contraction. Finally, to ensure that the depression of reciprocal Ia inhibition observed during co-contraction was not the consequence of a change in the recruitment gain of the reflex (see Chapter 1, pp. 18–20), reciprocal Ia inhibition of a tibialis anterior motor unit and a soleus unit was compared during separate activation of the target unit and during co-contraction of the two units. Here again, reciprocal Ia inhibition was significantly reduced during co-contraction of the units belonging to the two antagonistic muscles. Reciprocal Ia inhibition was still depressed during co-contraction (i) when peripheral feedback from the contracting muscle(s) was blocked, and (ii) at the very onset of a dynamic co-contraction, when the conditioning-test stimulus pair was triggered by the first voluntary EMG potential, i.e. before any contraction-induced peripheral afferent feedback had reached the spinal cord.

Mechanisms underlying the decreased reciprocal Ia inhibition during co-contraction

Reciprocal Ia inhibition is maximally depressed even at low co-contraction levels, and there is no modulation as the strength of co-contraction increases.

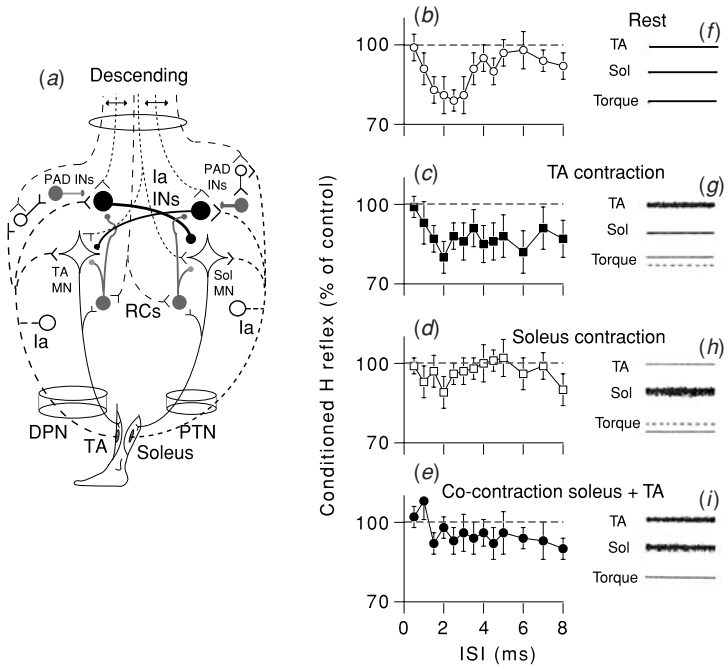


Fig. 5.12. Changes in peroneal-induced reciprocal Ia inhibition during voluntary co-contraction of dorsi- and plantar flexors of the ankle. (*a*) Sketch of the different mechanisms contributing to the depression of the reciprocal inhibition of the soleus (Sol) H reflex during co-contraction: (i) the descending drive to α motoneurones (MN) is not accompanied by a parallel drive to Ia interneurones (INs) (decoupling: horizontal double-headed arrows), (ii) there is descending facilitation of both Renshaw cells (RCs) and PAD INs mediating presynaptic inhibition of Ia terminals on Ia INs. (*b*)–(*e*) Time course of the peroneal-induced (1 × MT) changes in reciprocal Ia inhibition of the Sol H reflex. The control H reflex was 15% of M_{max} and the size of the conditioned H reflex is expressed as a percentage of its unconditioned value. Vertical bars ±1 SEM. (*f*)–(*i*) The corresponding rectified integrated EMG of the tibialis anterior (TA) and Sol, and the torque exerted at the foot plate (the horizontal dashed line in (*g*), (*h*) indicates zero). Results at rest ((*b*), (*f*)), during tonic dorsiflexion (torque at 4 Nm, (*c*), (*g*)), tonic plantar flexion (torque at 4 Nm, ((*d*), (*h*)), and simultaneous co-contraction of both ankle flexors and extensors ((*e*), (*i*)). Reciprocal inhibition peaks at 2–2.5 ms at rest (*b*), changes little during tonic dorsiflexion but a longer-latency propriospinally mediated inhibition appears at 4–5 ms (*c*), is less pronounced than at rest during tonic plantar flexion where only a small peak of inhibition may be discerned at 2 ms (*d*), and disappears during tonic co-contraction of ankle flexors and extensors (*e*). Modified from Nielsen & Kagamihara (1992), with permission.

These findings indicate a decoupling of the descending control of motoneurones and Ia interneurones, in contrast with the linkage seen during simple flexion–extension movements. This decoupling is reminiscent of studies in the monkey suggesting that the descending control of the spinal motor system is conveyed by different descending pathways during co-contraction and flexion–extension movements (Fetz & Cheney, 1987; p. 200; Chapter 11, p. 533). The observation that reciprocal Ia inhibition is depressed during co-contraction with respect to rest further suggests that the pathway mediating reciprocal Ia inhibition is actively inhibited during such contractions. Two spinal candidates probably contribute to this depression of the transmission in the reciprocal Ia pathway. (i) Presynaptic inhibition on Ia terminals from both antagonistic muscles is markedly increased during

co-contraction (cf. Chapter 8, p. 361). An important functional role of this increased presynaptic inhibition could be to decrease the Ia input to Ia interneurones to allow the parallel activation of the two antagonistic muscles (see Chapter 11, p. 532; Fig. 5.12(*a*)). (ii) Recurrent inhibition is increased during co-contraction, and the resulting depression of the transmission in the Ia inhibitory pathway would contribute to the parallel activation of the two antagonistic muscles (see Chapter 4, p. 181; Fig. 5.12(*a*)).

Functional implications

There was no significant difference in the amount of reciprocal Ia inhibition between ankle muscles when standing up at rest with support and when sitting down at rest. However, there was a decrease in reciprocal Ia inhibition when the subjects were forced to make a co-contraction of dorsi- and plantar flexors in order to maintain balance, e.g. when they were standing on one leg or on an unstable platform (Nielsen & Kagamihara, 1992). Functionally the decrease in reciprocal Ia inhibition ensures unopposed activation of antagonistic motoneurone pools during co-contractions.

Depression of reciprocal Ia inhibition during contraction of remote muscles

A depression of peroneal-induced reciprocal Ia inhibition of the soleus H reflex has also been described during voluntary teeth clenching (Takada *et al.*, 2000). The manoeuvre produces reflex reinforcement, akin to the classical Jendrassik manoeuvre, and the H reflex is facilitated in both the soleus and the tibialis anterior, in proportion to biting force. Under these circumstances, the question arises about whether depression of reciprocal Ia inhibition is merely the result of a subliminal co-contraction of ankle flexors and extensors or is related to the mechanisms responsible for the generalised reflex reinforcement (cf. Chapter 3, p. 133).

Changes in reciprocal Ia inhibition during postural activity

With the initiation of a fast stepping movement by one leg, there is an automatic postural reaction in the supporting leg, with a burst of EMG activity in the tibialis anterior and a silent period in the tonic EMG activity of soleus (Komiyama & Kasai, 1997). The soleus H reflex is depressed prior to and during the tibialis anterior EMG activity, while the tibialis anterior H reflex is greatly facilitated. Peroneal-induced (1 × MT, 2 ms ISI) reciprocal Ia inhibition of the soleus H reflex is enhanced with a time course similar to that of the soleus H reflex depression. In contrast, the D1 presynaptic inhibition was found to be only marginally and inconsistently increased. This suggests that the silent period in the soleus is due to increased disynaptic reciprocal Ia inhibition. The similar time courses of both the increased reciprocal Ia inhibition of the soleus H reflex and the tibialis anterior H reflex facilitation would then provide an example of parallel control of α motoneurones and corresponding Ia interneurones in an automatic postural task.

Changes in reciprocal Ia inhibition during gait

The amount of reciprocal Ia inhibition between ankle flexors and extensors is modulated during walking, albeit by less than during voluntary contractions at equivalent levels of EMG activity (Petersen, Morita & Nielsen, 1999; Fig. 5.13).

Methodology

In some subjects, it has been possible to investigate the changes in reciprocal inhibition of the soleus H reflex throughout the step cycle. In addition, the modulation of reciprocal inhibition seen in the ongoing rectified EMG of the soleus and tibialis anterior was explored during the stance and swing phases of walking, respectively, after stimulation of the nerve

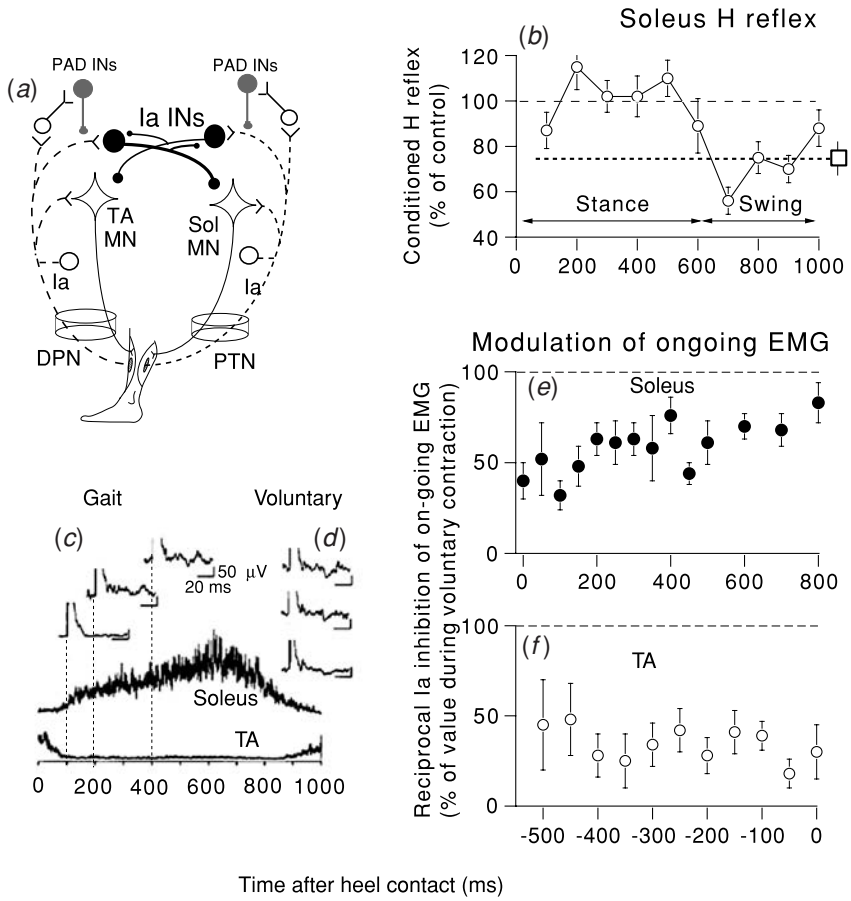


Fig. 5.13. Changes in reciprocal Ia inhibition of ankle muscles during walking. (*a*) Sketch of the presumed pathways with reciprocal Ia inhibition of soleus (Sol) and tibialis anterior (TA) motoneurones (MN) and opposite Ia interneurones (INs) and PAD INs mediating presynaptic inhibition of Ia terminals on Ia INs. (*b*) Time course of the changes in peroneal-induced (1.1 × MT, 2 ms ISI) reciprocal Ia inhibition of the Sol H reflex throughout the step cycle. The amplitude of the conditioned H reflex (as a percentage of its unconditioned value) is plotted against the time after heel contact. Data from a single subject. The intensity of the posterior tibial nerve (PTN) stimulation was adjusted to maintain the control H reflex at ~5% of M_{max}. Vertical bars ±1 SEM. (*c*)–(*f*) Modulation of reciprocal inhibition of the on-going rectified and stimulus-averaged EMG of Sol ((*c*)–(*e*)) and TA (*f*). (*c*), (*d*) Inhibition of the Sol EMG activity induced by stimulation of the deep peroneal nerve (DPN, 1.1 × MT). (*c*) The traces show the stimulus-triggered averaged (75 sweeps) and rectified Sol EMG activity at different times during the stance phase of walking after heel strike (100, 200, 400 ms); vertical calibration bars 50 μV; horizontal bars 20 ms; the latter also indicates the baseline level for the EMG. The lower part of (*c*) shows the Sol and TA EMG activity (average of 30 sweeps); abscissa time after heel contact. (*d*) Similar measurements as in (*c*), but at increasing levels of isometric plantar flexion when standing, from bottom to top, matching the level of EMG during walking. (*e*), (*f*) Group data (14 and 10 subjects). The amount of reciprocal inhibition of Sol EMG during the stance phase (*e*) and of TA EMG during the swing phase (*f*) (expressed as a percentage of the amount of inhibition observed during a voluntary contraction at equivalent EMG) is plotted against the time after heel contact. Vertical bars ±1 SEM. Modified from Petersen, Morita & Nielsen (1999), with permission.

supplying the antagonistic muscle. The resulting inhibition was assessed within its first 10 ms (cf. Fig. 5.11(*c*)), and expressed as a percentage of that obtained during a voluntary contraction of the corresponding muscle at an equivalent amount of EMG activity.

Modulation of reciprocal Ia inhibition

In the subject illustrated in Fig. 5.13(*b*), there was significant peroneal-induced reciprocal Ia inhibition of the reflex at rest, but this disappeared during the stance phase. Around the onset of the swing phase, reciprocal inhibition became greater than at rest, and then progressively decreased. This suggests that transmission in the pathway of reciprocal Ia inhibition to ankle plantar flexors is depressed during the stance phase, and facilitated during the swing phase. Peroneal-induced inhibition of the on-going soleus EMG was much smaller at heel strike than during tonic plantar flexion when standing. It progressively increased through the stance phase, though always smaller than during the voluntary contraction (Fig. 5.13(*c*)–(*e*)). Reciprocal inhibition of the on-going tibialis anterior EMG during the swing phase was similarly much smaller than during voluntary dorsiflexion (Fig. 5.13(*f*)).

Mechanisms underlying the changes in reciprocal Ia inhibition

(i) Presynaptic inhibition of Ia terminals on soleus motoneurones is decreased during dynamic voluntary contractions of soleus but strongly increased throughout the stance phase of walking (Chapter 8, pp. 365–7). Given the probable parallel control of presynaptic inhibition on Ia terminals on motoneurones and on Ia interneurones (see pp. 200–1), increased presynaptic inhibition that reduces the Ia input to Ia interneurones could contribute to the lesser reciprocal Ia inhibition during walking than during voluntary contraction.

(ii) Mutual inhibition of opposite Ia interneurones would be consistent with the small inhibition from plantar flexors to dorsiflexors during the swing phase (Fig. 5.13(*f*)), when inhibition from dorsiflexors to plantar flexors is large (Fig. 5.13(*b*)). Regardless of the spinal mechanism, peroneal-induced inhibition of the on-going soleus EMG activity is modulated similarly when conduction in large diameter afferents is blocked by ischaemia. This suggests that the pattern of afferent feedback cannot explain the observed modulation.

Functional implications

Reciprocal Ia inhibition from dorsiflexors to plantar flexors is large in the swing phase and small in the stance phase of gait, and that from plantar flexors to dorsiflexors is small in swing. This modulation would help ensure that antagonistic motoneurones are not activated inappropriately during the walking cycle. However, the modulation is less marked than during voluntary movements, a finding that could reflect a need to stabilise the ankle during the stance phase of walking (see Chapter 11, p. 546).

Studies in patients and clinical implications

Methodology

So far, changes in transmission in the pathway of 'true' reciprocal Ia inhibition have been investigated in patients only at ankle level. Because it is unusual for a sizeable H reflex to be recordable in tibialis anterior, peroneal-induced reciprocal Ia inhibition of the soleus H reflex is usually explored (however, see p. 232). Care is necessary to ensure that the conditioning stimulus activates only the deep peroneal nerve (see p. 209), and the conditioning stimuli should not be above 1 × MT.

Spasticity

Peroneal-induced reciprocal Ia inhibition of soleus motoneurones

Conflicting results have been obtained in patients with different lesions, and even within a population

of patients with apparently the same type and location of lesion. Methodological reasons, in particular inadvertent stimulation of the superficial peroneal nerve, may account for some discrepant findings (see p. 209).

Stroke patients

Results obtained in stroke patients by different authors illustrate well the variability of the changes in reciprocal Ia inhibition in patients. Yanagisawa, Tanaka & Ito (1976) found that a train of three shocks to the peroneal nerve had no effect in 6 of 11 patients with hemiplegia, but produced an early inhibition in two patients and an early facilitation in the other three. However, these results are difficult to interpret because the authors were unable to record reciprocal Ia inhibition at rest in normal subjects. Delwaide (1985) mentioned an early peroneal-induced facilitation in a few spastic patients, but gave no details about the nature of the spasticity. In all six patients explored by Crone *et al.* (2003), the early peroneal-induced inhibition was replaced by facilitation, which developed in parallel with hyperactive Achilles tendon jerks on the spastic side, and was not observed on the 'unaffected' side. The absence of reciprocal inhibition on the unaffected side represents further evidence that spinal mechanisms are not normal on the clinically unaffected side of hemiparetic patients (see Chapter 12, pp. 577–9). In 16 patients at various stages after a stroke, Okuma & Lee (1996) found that reciprocal Ia inhibition of the soleus H reflex was increased in patients who showed good recovery of function with mild spasticity, but was unchanged or diminished, in patients who had made a poor recovery and had more marked extensor spasticity. In patients in whom serial recordings were obtained there was an increase in Ia inhibition during the recovery period following stroke, a finding not confirmed by Crone *et al.* (2003).

Patients with traumatic spinal cord injury

Here again, variable results have been obtained. Boorman *et al.* (1991) reported that reciprocal Ia inhibition of the soleus H reflex was more profound in patients with incomplete spinal cord injury who had recovered sufficient function to walk with some assistance than in healthy subjects. However, many other authors have reported that reciprocal Ia inhibition is reduced with respect to normal subjects.

(i) In patients with asymmetrical spinal spasticity the inhibition was found to be pronounced in the leg with good recovery and less spasticity, but small or absent in the more spastic leg (Okuma, Mizuno & Lee, 2002).

(ii) An early facilitation replacing the early inhibition was seen in two of four patients with incomplete spinal cord injury and four of the seven patients with a complete spinal lesion reported by Crone *et al.* (2003).

(iii) In patients with incomplete spinal cord injury, Perez & Field-Fote (2003) reported that, reciprocal inhibition tested at the 3-ms ISI was slightly decreased.

Multiple sclerosis

Crone *et al.* (1994) studied 39 patients and 74 healthy control subjects. Average data from the two populations show that the clear reciprocal Ia inhibition observed in normal subjects was absent in the patients (Fig. 5.14(*b*)). This is also illustrated in the histograms of Fig. 5.14(*c*). A further study by the same group (Ørsnes *et al.*, 2000) confirmed that deep peroneal stimulation produces very little or no reciprocal Ia inhibition of the soleus H reflex in patients, a finding that was not modified by oral or intrathecal baclofen.

The early facilitation that often replaces the early inhibition could be due to Ib excitation

It is possible that this facilitation in spastic patients could be due to the fact that a normal Ib excitation is more easily disclosed because of the decreased reciprocal Ia inhibition. However, Crone *et al.* (2003) have argued in favour of increased (facilitated) Ib excitation (see Chapter 6, pp. 277–8).

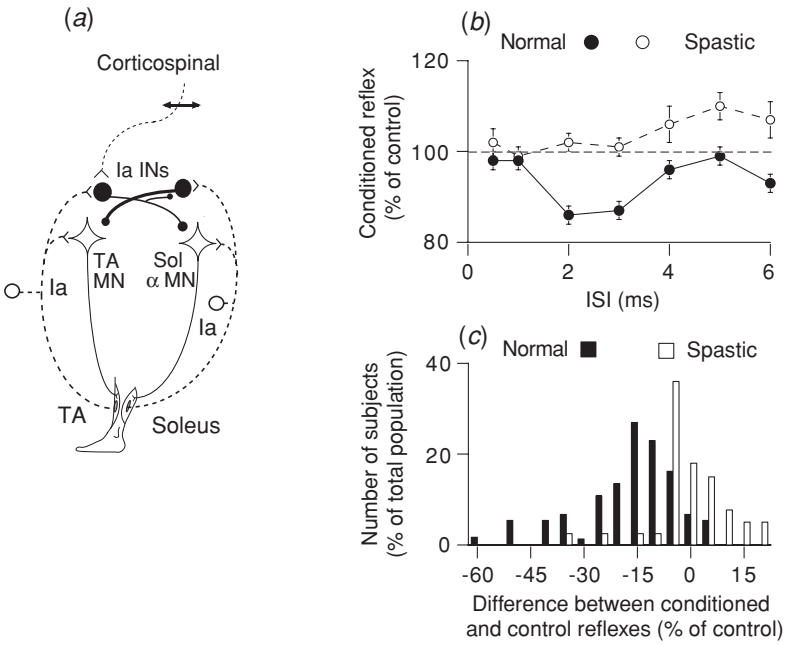


Fig. 5.14. Changes in reciprocal Ia inhibition of ankle muscles in patients with spasticity due to multiple sclerosis. (*a*) Sketch of the presumed pathway of reciprocal Ia inhibition between ankle flexors and extensors. The tonic corticospinal facilitation of tibialis anterior (TA)-coupled Ia interneurones (INs) is presumably interrupted in spastic patients (horizontal double-headed arrow). This produces both a reduction of the reciprocal Ia inhibition to soleus (Sol) motoneurones (MN), and a disinhibition of opposite soleus-coupled INs mediating reciprocal Ia inhibition to TA MNs. (*b*) Time course of the changes in peroneal-induced (1 × MT) reciprocal Ia inhibition of the Sol H reflex. The size of the conditioned H reflex (expressed as a percentage of its unconditioned value) is plotted against the interstimulus interval (ISI). Average data from 74 normal subjects (●) and 39 patients with multiple sclerosis (○). Vertical bars ±1 SEM. (*c*) The amount of reciprocal Ia inhibition assessed at the 2 ms ISI (DPN stimulation at 1 × MT) in normal subjects (■) and patients (□). The number of subjects (expressed as a percentage of the total number of subjects in each population) is plotted against the difference between the size of the conditioned and control reflexes (expressed as a percentage of the control reflex size; negative values: inhibition, positive values: facilitation, at the 2 ms ISI). Modified from Crone *et al.* (1994), with permission.

Changes during voluntary contraction

Changes in reciprocal Ia inhibition during voluntary contractions have been explored only in patients with multiple sclerosis (Morita *et al.*, 2001). The main abnormality in the patients was an absence of the increase in peroneal-induced reciprocal Ia inhibition of the soleus H reflex at the onset of dorsiflexion, though this is seen consistently in healthy subjects (cf. p. 221). With the absence of modulation of presynaptic inhibition of Ia terminals on soleus motoneurones (see Chapter 8, p. 370), this may explain why the soleus H reflex is not depressed at the onset of voluntary dorsiflexion in spastic patients (Pierrot-Deseilligny & Lacert, 1973). However, in functional terms, given the relatively weak sensitivity of the stretch reflex to presynaptic inhibition of Ia terminals (see Chapter 8, pp. 354–5), the absence of increased reciprocal Ia inhibition directed to motoneurones of the antagonistic soleus could be a major factor in the unwanted stretch reflex activity triggered by the dynamic contraction of

tibialis anterior in spastic patients (see Chapter 12, pp. 574–5). This might explain some of the functional disabilities of patients with spasticity (Chapter 12, pp. 559).

Conclusions

The results are, in general, too variable to allow a unifying statement. However, putting aside the results of Boorman *et al.* (1991), it seems that, in patients with focal lesions (whether cerebral or spinal), the better the recovery the greater the reciprocal Ia inhibition of the soleus H reflex. By contrast, with the diffuse lesions typical of multiple sclerosis, there is no correlation between degree of reciprocal Ia inhibition of soleus and the disability of patients. The disfacilitation of Ia interneurones to ankle extensor motoneurones by the corticospinal lesion removes a tonic inhibition on these motoneurones, and this could contribute to their hyperexcitability (see Chapter 12, p. 570). However, this is not a major factor causing spasticity at rest, since normalisation of reciprocal inhibition after frequent peroneal stimulation is not accompanied by significant changes in spasticity (see below).

Reciprocal Ia inhibition from ankle extensors to flexors

In contrast to data on reciprocal Ia inhibition of ankle extensors, it is a consistent finding that posterior tibial-induced reciprocal Ia inhibition of tibialis anterior motoneurones is increased in hemiplegic patients (Yanagisawa *et al.*, 1976), and this is particularly so in patients with poor recovery and severe extensor spasticity (Okuma & Lee, 1996). In investigations using PSTHs, reciprocal inhibition was also greater in patients with incomplete spinal cord injury than in normal subjects (Ashby & Wiens, 1989). The stimulus intensity at which soleus motoneurones and the corresponding Ia interneurones can be brought to threshold provides an estimate of the relative excitability of these two neuronal populations. In patients with spinal cord injury the reflex effects of Ia inhibitory interneurones were obtained at lower threshold than the soleus H reflex, whereas in normal subjects the excitabilities are similar (see p. 204).

Mechanisms underlying changes in reciprocal Ia inhibition in spasticity

In normal subjects, the dominant excitatory effect of corticospinal volleys on ankle muscles is directed to tibialis anterior (Brouwer & Ashby, 1991). One could reasonably expect the dominant corticospinal input to be to the corresponding Ia interneurones (i.e. those inhibiting soleus motoneurones). Through mutual inhibition of Ia interneurones, this would produce tonic inhibition of the 'opposite' Ia interneurones directed to tibialis anterior motoneurones. If there was normally a tonic corticospinal drive to tibialis anterior-coupled Ia inhibitory interneurones, as exists in the baboon (Hongo *et al.*, 1984, p. 200), corticospinal lesions would: (i) reduce the reciprocal Ia inhibition of ankle extensors, particularly in those patients with a focal lesion and significant motor impairment, and (ii) explain the increased reciprocal Ia inhibition from ankle extensors to tibialis anterior motoneurones (see the sketch in Fig. 5.14(*a*) and its legend). Interruption of the corticospinal facilitation of the relevant Ia interneurones by corticospinal lesions probably accounts for why reciprocal Ia inhibition is not increased at the onset of voluntary dorsiflexion in multiple sclerosis patients.

Plasticity in the pathway of reciprocal Ia inhibition

Evidence for plasticity in the pathway of reciprocal Ia inhibition

Evidence for plasticity has been found in normal subjects (Perez, Field-Fote & Floeter, 2003). Reciprocal Ia inhibition was increased for a least 5 min after the end of 'patterned' stimulation intended to mimic the group I discharge from pretibial flexors during the swing phase of walking. This was attributed to potentiation of the glycinergic synapse of Ia interneurones, and/or recruitment of subliminal interneurones, as has been described in the goldfish (Oda *et al.*, 1995).

Plasticity induced by peroneal nerve stimulation

In four multiple sclerosis patients receiving frequent peroneal nerve stimulation ('functional electrical stimulation' using an external peroneal stimulator to assist walking), reciprocal Ia inhibition was as pronounced as in normal subjects. The patients did not differ from the other patients in their degree of spasticity or other clinical features. This suggests that regular peroneal nerve activation can maintain activity in the spinal pathway of reciprocal Ia inhibition (Crone *et al.*, 1994).

Plasticity after training

Plastic changes occur in spinal monosynaptic reflexes after long-term manipulation of motor systems using operant conditioning (Wolpaw & Lee, 1989). It is therefore conceivable that plastic changes occur in the pathway of reciprocal Ia inhibition after training and, if so, this might account for some of the conflicting reports from different groups. Thus, the hemiplegic patients of Okuma & Lee (1996) and the spinal cord-injured patients of Okuma, Mizuno & Lee (2002) with preserved reciprocal Ia inhibition to soleus were undergoing intensive physiotherapy and were leading an active life. It is conceivable that intensive physiotherapy, with repeated attempts to produce ankle dorsiflexion, would increase activity in the Ia inhibitory pathway following the injury. If so, this has important implications for rehabilitation programs.

Patients with cerebral palsy

The first evidence for reciprocal Ia inhibition from ankle flexors to soleus in humans was provided in patients with athetosis (Mizuno, Tanaka & Yanagisawa, 1971), in whom the inhibition was profound, whereas it could not be demonstrated by these authors in normal subjects at rest. Using PSTHs, Berbrayer & Ashby (1990) showed that reciprocal Ia inhibition from ankle extensors to tibialis anterior is also increased in patients with cerebral palsy, whether they have mainly athetosis or spasticity. The increased reciprocal Ia inhibition is in keeping with the pattern of corticospinal projections to corresponding motoneurones as revealed by TMS. Unlike normal subjects, in whom there is a strong facilitation of tibialis anterior motoneurones but little or no facilitation of soleus motoneurones, there is equal facilitation of tibialis anterior and soleus motoneurones in patients with cerebral palsy (Brouwer & Smits, 1996). The reciprocal Ia excitation elicited in similar patients, at the latency of the monosynaptic reflex, by a tap to the antagonistic tendon has been interpreted as a persistent neonatal pattern of connectivity (see Gottlieb & Myklebust, 1993). However, reservations have been expressed in Chapter 2 (p. 86) about whether this finding was really due to spread of the mechanical stimulus to excite spindles in the antagonist.

Patients with hyperekplexia

Reciprocal Ia inhibition is presumed to be mediated by glycine, and has been examined in patients with hereditary hyperekplexia (Crone *et al.*, 2001; Nielsen *et al.*, 2002). Reciprocal Ia inhibition from ankle flexors to extensors was not recordable in patients with the major form (who have a defined mutation in the glycine receptor), whereas it could be recorded in the patients with the minor form (who have no such mutation in the glycine receptor). By contrast, radial-induced inhibition of the FCR H reflex has been found not to be abolished (see p. 214), and this provides further confirmation that the inhibition at wrist level is not 'true' reciprocal Ia inhibition.

Patients with Parkinson's disease

At rest

Reciprocal Ia inhibition from ankle flexors to soleus motoneurones has been reported to be increased significantly in parkinsonian patients with respect to age-matched controls. This abnormality was interpreted as an abnormal reticulospinal activation of Ia interneurones (Delwaide, Pepin & Maertens de Noordhout, 1993), but it could also be due to increased Ia feedback from ankle flexors, perhaps

associated with incomplete relaxation of those muscles (Chapter 12, pp. 587–8).

Onset of voluntary contraction

At the onset of voluntary ankle dorsiflexion, the normal inhibition of the soleus H reflex is reduced, and even reversed to facilitation in parkinsonian patients (Hayashi *et al.*, 1988), a finding attributed to abnormal corticospinal control of Ia inhibitory interneurones during movement. This view is supported by the finding that at the onset of voluntary plantar flexion, the normal facilitation of the soleus H reflex produced by TMS is reduced and, in some cases, reversed to inhibition (cf. Morita *et al.*, 2002; Chapter 12, pp. 590–1). The latter abnormality was correlated with the motor part of the unified Parkinson's disease rating scale, and was improved by pallidotomy.

Changes in non-reciprocal group I inhibition at wrist level

Interneurones mediating the radial-induced inhibition of the FCR H reflex are almost certainly those of non-reciprocal group I inhibition (see pp. 211–14). However, the literature devoted to abnormalities in the pathway of radial-induced inhibition of the FCR H reflex refers to abnormalities in 'reciprocal Ia inhibition', and such changes are therefore considered in this Chapter rather than in Chapter 6.

Stroke patients

In stroke patients, the early phase of radial-induced inhibition of the FCR H reflex is consistently decreased in those with spasticity (Nakashima *et al.*, 1989; Artieda, Quesada & Obeso, 1991), but not in patients with normal muscle tone or flaccid hemiplegia (Nakashima *et al.*, 1989).

Parkinsonian patients

In parkinsonian patients, conflicting results have been found at rest. The early phase of radial-induced inhibition of the FCR H reflex was reported to be decreased by Lelli, Panizza & Hallett (1991), but normal by others (Nakashima *et al.*, 1994; Tsai, Chen & Lu, 1997; Meunier *et al.*, 2000), or even probably increased (Obeso *et al.*, 1985) (cf. Chapter 12, p. 587).

Dystonia

Radial-induced disynaptic inhibition of the FCR H reflex is unchanged (Nakashima *et al.*, 1989) or decreased (Panizza, Hallett & Cohen, 1987; Chen, Tsai & Lu, 1995) in patients with writer's cramp. Interestingly, similar changes have been reported in the unaffected normal arms of patients with writer's cramp (Chen, Tsai & Lu, 1995). This is in keeping with the finding that abnormalities of the hand representation in sensory cortex are more obvious in the hemisphere driving the non-dystonic limb (see Chapter 8, p. 372).

Conclusions

Reciprocal Ia inhibition is mediated through a simple disynaptic pathway fed by Ia afferents, and has a simple function: to link the inhibition of the antagonist and the contraction of the agonist during flexion–extension movements. True reciprocal Ia inhibition between antagonistic flexors and extensors has so far been demonstrated with certainty only at ankle and elbow levels in human subjects. The radial-induced inhibition of the FCR H reflex is probably mediated through the disynaptic pathway of non-reciprocal group I inhibition.

Role of reciprocal Ia inhibition in motor tasks

During voluntary flexion-extension movements, reciprocal Ia inhibition to antagonistic ankle muscle(s) is facilitated. Together with facilitation of interneurones mediating (i) longer-latency propriospinally mediated inhibition, and (ii) facilitation of PAD interneurones mediating presynaptic

inhibition on Ia terminals to antagonistic motoneurones, this helps prevent a stretch reflex in the antagonistic muscle. In addition, a specific role for increased reciprocal Ia inhibition is to oppose the activation of opposite Ia interneurones, activated by the stretch-induced Ia discharge in the antagonist muscle, because this would otherwise inhibit agonist motoneurones.

During co-contractions of antagonists, reciprocal Ia inhibition is markedly depressed, thus ensuring the unopposed activation of antagonistic motoneurone pools. This indicates that the coupling of motoneurones and Ia interneurones is flexible, dependent on the motor task.

During walking, reciprocal Ia inhibition between ankle flexors and extensors is modulated to inhibit the antagonist of the active muscle, but this modulation is less marked than during voluntary contractions, possibly to help stabilisation of the ankle during the stance phase.

Changes in reciprocal Ia inhibition and pathophysiology of movement disorders

Most studies have investigated spastic patients. Those in patients with focal lesions (either cerebral or spinal) have generally demonstrated reduced reciprocal Ia inhibition of the soleus H reflex at rest, and the better the recovery the less marked this reduction. With the diffuse lesions typical of multiple sclerosis, reciprocal inhibition of soleus is also reduced, but there is no correlation between degree of reciprocal Ia inhibition of soleus and the disability of patients. In contrast, reciprocal Ia inhibition directed to pretibial flexors is consistently increased.

Résumé

Background from animal experiments

Ia interneurones receive monosynaptic input from Ia afferents and project, through a glycinergic synapse, onto motoneurones antagonistic to those innervating the muscle from which the Ia input originates. The dominant feature is the striking similarity in the segmental and supraspinal convergence onto α motoneurones and the 'corresponding' Ia interneurones (i.e. those receiving the same Ia input). Thus, they: (i) receive the same inputs from descending tracts, (ii) are similarly inhibited by opposite Ia interneurones (i.e. Ia interneurones activated from flexor Ia afferents are inhibited by Ia interneurones activated from extensor Ia afferents, and *vice versa*), and (iii) are inhibited by Renshaw cells activated by collaterals from those motoneurones which receive the monosynaptic Ia excitation. This provides a unique means of identification. It has therefore been suggested that α and γ motoneurones, and Ia interneurones are controlled in parallel from the brain in order to achieve a coordinated contraction of agonists and relaxation of antagonists ('α-γ linkage in reciprocal Ia inhibition'). There is probably a parallel control of presynaptic inhibition of Ia afferent terminals on Ia interneurones and motoneurones.

Methodology

Underlying principle

Reciprocal Ia inhibition is a disynaptic inhibition, elicited by a Ia volley originating from the antagonistic muscle, and is depressed by recurrent inhibition. It can be assessed using the monosynaptic reflex, the on-going EMG or PSTHs of single motor units.

Evidence for reciprocal Ia inhibition

Elicitation by Ia volleys

The low electrical threshold of the inhibition and the absence of a comparable effect from cutaneous

volleys indicate that it is of group I origin. There is good evidence that the inhibition is due to Ia volleys when it can be evoked by weak tendon taps and/or when prolonged vibration of the 'conditioning' tendon causes the threshold for the inhibition to increase.

Disynaptic transmission

A disynaptic pathway is suggested if the central delay of the inhibition of the H reflex is ~1 ms, taking account of the peripheral afferent conduction times for the conditioning and test Ia pathways. A precise method, independent of peripheral conduction distances and conduction velocities, can be used when reciprocal inhibition between flexors and extensors operating at the same joint are tested in the same subject in both directions. The method rests on the assumptions that the same afferents are responsible for the H reflex (or the peak of homonymous Ia excitation in the PSTH) and the short-latency inhibition of the H reflex (or the PSTH) in the antagonist, and the central organisation (and delay) is equal in both directions.

Recurrent inhibition of Ia interneurones

Suppression of reciprocal Ia inhibition by activation of recurrent inhibitory pathways provides a unique method of confirming that the pathway is truly that of reciprocal Ia inhibition. This has been observed at elbow and ankle level, but not at wrist level.

Critique of the tests to study reciprocal Ia inhibition

(i) The conditioning stimulus intensity must not be too high, in order to avoid recurrent inhibition of Ia interneurones by an antidromic motor volley, contamination by group II effects (especially when studying the modulation of the on-going EMG), inadvertent stimulation of Ia afferents in the superficial peroneal nerve (see below).

(ii) During voluntary ankle dorsiflexion, a longer-latency, presumably propriospinally mediated inhibition is superimposed on the early reciprocal Ia inhibition at ISIs ≥3 ms.

(iii) When investigating the reciprocal Ia inhibition of soleus, great care must be taken to stimulate only the deep peroneal nerve and to avoid activation of Ia afferents in the superficial peroneal nerve because they have monosynaptic Ia projections onto soleus motoneurones.

Organisation and pattern of connections

Pattern and strength of reciprocal Ia inhibition at rest at different joints

Hinge joints

While the criteria for true reciprocal Ia inhibition (inhibition between strict antagonists, elicitation by a pure Ia volley, depression by recurrent inhibition) are fulfilled at ankle and elbow levels, the data are not yet conclusive at knee level. At ankle level, monosynaptic excitation due to stimulation of superficial peroneal afferents could have obscured the deep peroneal-induced inhibition in some studies. There are also important variations between different individuals, and a positive correlation between the strength of the inhibition and the degree of physical training has been reported. In contrast, in those subjects, in whom it is possible to evoke an H reflex in the tibialis anterior, reciprocal inhibition can be demonstrated consistently at rest. This asymmetry in favour of flexors is reminiscent of data in the cat. At elbow level, there is evidence for a profound and symmetrical reciprocal Ia inhibition between flexors and extensors.

Wrist level

Disynaptic inhibition between flexors and extensors in the forearm does not fulfil the essential criteria for 'true' reciprocal Ia inhibition, because: Ib afferents contribute to the inhibition, and may be solely responsible for it; it is not inhibited by recurrent inhibition; it does not link true antagonistic muscles; and it is not abolished in patients with a mutation in the glycine receptor manifesting as hyperekplexia. Interneurones responsible for the disynaptic

inhibition between wrist muscles are activated by group I afferents from a variety of muscles, not only the antagonist but also the target muscle and muscles operating at the elbow. This widespread convergence is consistent with mediation through interneurones of non-reciprocal group I inhibition.

Various conditioning stimuli facilitate transmission in the pathway of reciprocal Ia inhibition of soleus motoneurones

Facilitation-occlusion curves for soleus, reflecting convergence of the two conditioning volleys onto common Ia interneurones, reveal facilitation of Ia interneurones only when the peroneal volley is weak. Thus, Ia interneurones are facilitated by (i) low-threshold cutaneous afferents from the foot, (ii) corticospinal volleys, and (iii) stimulation of the vestibular apparatus.

Motor tasks and physiological implications

Voluntary contraction of the antagonistic muscle

A depression of the soleus H reflex precedes and accompanies a voluntary ankle dorsiflexion, due to changes in at least three mechanisms: reciprocal Ia inhibition, presynaptic inhibition of soleus Ia terminals, and longer-latency propriospinally mediated inhibition. In this chapter, only the changes in reciprocal Ia inhibition are considered.

(i) During tonic ankle dorsiflexion, conflicting results have been obtained. However, when conduction in Ia afferents is interrupted by ischaemia or block of the peroneal nerve using lidocaine, peroneal-induced reciprocal Ia inhibition of the soleus H reflex is consistently increased. This finding indicates that, during dorsiflexion, the natural Ia discharge decreases the efficacy of the peroneal volley in activating Ia interneurones. Post-activation depression, which occurs at the synapse between the Ia fibre and the Ia interneurone, is the most likely mechanism responsible for the absence of increased reciprocal Ia inhibition during tonic contractions: it reduces the efficacy of the artificial conditioning volley in discharging Ia interneurones, and prevents the central facilitation of Ia interneurones from manifesting itself.

(ii) In contrast, peroneal-induced reciprocal Ia inhibition is consistently increased before the Ia input has reached the spinal level, and this implicates a descending mechanism, independent of Ia feedback.

(iii) Origin and function: Increased peroneal-induced reciprocal Ia inhibition may be due to a descending drive onto Ia interneurones and/or descending inhibition of PAD interneurones mediating presynaptic inhibition of Ia terminals on Ia interneurones. In flexion–extension movements, the stretch-induced Ia discharge triggered in the antagonist (soleus) by a contraction of the agonist (tibialis anterior) provides Ia excitation both to antagonistic motoneurones and 'corresponding' extensor-coupled Ia interneurones. This can produce two undesirable effects: a stretch reflex in the antagonistic soleus muscle, and inhibition of agonist tibialis anterior motoneurones through extensor-coupled Ia interneurones. The unwanted stretch reflex may be minimised by several mechanisms (addressed in Chapter 11), and the activation of extensor-coupled Ia interneurones can be prevented by the discharge of tibialis anterior-coupled Ia interneurones. During the dynamic phase of rapid shortening (concentric) contractions, spindle endings in the contracting muscle will be unloaded and may be silenced, and activation of agonist-coupled Ia interneurones would therefore require that they receive a descending drive that is potent enough to fire them.

Voluntary activation of the agonistic muscle

Reciprocal Ia inhibition directed to active motoneurones is depressed during voluntary contractions of the corresponding muscle, and the stronger the contraction, the more marked the depression. Parallel descending activation of active motoneurones and coupled Ia interneurones produces, through

mutual inhibition of Ia interneurones, inhibition of the opposite Ia interneurones directed to the active motoneurones. This provides a further example of the depression of reciprocal Ia inhibition to motoneurones activated in a movement of flexion-extension in order to prevent their undesirable inhibition by the stretch-induced antagonistic Ia discharge.

Co-contractions

During co-contractions of dorsi- and plantar flexors of the ankle, reciprocal inhibition is depressed with respect to rest, and always smaller than the sum of the effects evoked by isolated dorsi- and plantar flexion. This indicates the existence of a descending control specific to co-contraction. Reciprocal Ia inhibition is maximally depressed even at low co-contraction levels, indicating a decoupling of the descending control of motoneurones and Ia interneurones. The pathway mediating reciprocal Ia inhibition is actively inhibited during such contractions, through increased presynaptic inhibition on Ia terminals and increased recurrent inhibition. Functionally the decrease in reciprocal Ia inhibition ensures unopposed activation of antagonistic motoneurone pools during co-contractions.

Postural activity

At the initiation of a fast stepping movement by one leg, there is an automatic postural reaction in the supporting leg with a burst of EMG activity in tibialis anterior and a silent period in the tonic EMG activity of soleus due to increased reciprocal Ia inhibition to soleus motoneurones. This reveals a coupling of α motoneurones and corresponding Ia interneurones during automatic postural adjustments.

Walking

The amount of reciprocal Ia inhibition between ankle flexors and extensors is modulated, with prominent inhibition from dorsiflexors to plantar flexors during the swing phase, whereas inhibition from plantar flexors to dorsiflexors is probably enhanced during the stance phase. This modulation helps ensure that antagonistic motoneurones are kept inactive during appropriate phases of the walking cycle. This modulation is, however, less marked than during voluntary contractions at equivalent levels of EMG activity.

Studies in patients and clinical implications

Methodology

So far, changes in transmission in the pathway of reciprocal Ia inhibition have been investigated in patients only at ankle level, mainly from the peroneal nerve to ankle extensors. Care must be taken to apply the conditioning stimulus selectively to the deep peroneal nerve, using conditioning stimuli that are not above $1 \times$ MT.

Spasticity

Resting conditions

Different studies have reported quite variable findings. In patients with focal lesions (either cerebral or spinal) there is evidence that the poorer the recovery the smaller the reciprocal Ia inhibition of the soleus. Reciprocal Ia inhibition in the other direction, i.e. to pretibial flexors, is increased, particularly in patients with poor recovery and severe extensor spasticity. With the diffuse lesions typical of multiple sclerosis, reciprocal inhibition of soleus is also reduced, but there is no correlation between degree of reciprocal Ia inhibition of soleus and the disability of patients. Thus, corticospinal lesions reduce reciprocal Ia inhibition of ankle extensors and release reciprocal Ia inhibition from ankle extensors to flexors, probably through mutual inhibition of opposite Ia interneurones.

During voluntary dorsiflexion

The normal increase in reciprocal Ia inhibition observed at the onset of the movement has not been

found. This could account for the occurrence of an unwanted stretch reflex of the triceps surae in these patients during dynamic contractions of the antagonist.

Plasticity

Regular peroneal stimulation has been shown to restore reciprocal Ia inhibition to a normal level in some spastic patients. Plastic changes occurring in the pathway of reciprocal Ia inhibition after training could be a factor in the apparently conflicting results observed in patients by different groups.

Other motor disorders

(i) In patients with cerebral palsy, reciprocal inhibition is increased in both directions.

(ii) In Parkinson's disease, reciprocal Ia inhibition of the soleus H reflex is increased with respect to healthy subjects.

(iii) In patients with hyperekplexia, the deficit in glycine results in a loss of reciprocal Ia inhibition at ankle level, but not at wrist level, in line with the idea that the inhibition between wrist muscles is not 'true' reciprocal Ia inhibition.

Inhibition between extensors and flexors of the wrist

This is considered separately (see Chapter 12), because the pathway mediating this inhibition is probably not that of reciprocal Ia inhibition.

REFERENCES

Araki, T., Eccles, J. C. & Ito, M. (1960). Correlation of the inhibitory post-synaptic potential of motoneurones with the latency and time course of inhibition of monosynaptic reflexes. *Journal of Physiology (London)*, **154**, 354–77.

Artieda, J., Queseda, P. & Obeso, J. A. (1991). Reciprocal inhibition between forearm muscles in spastic hemiplegia. *Neurology*, **41**, 286–9.

Ashby, P. & Labelle, K. (1977). Effects of extensor and flexor group I afferent volleys on the excitability of individual soleus motoneurones in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 910–19.

Ashby, P. & Wiens, M. (1989). Reciprocal inhibition following lesions of the spinal cord in man. *Journal of Physiology (London)*, **414**, 145–57.

Ashby, P. & Zilm, D. (1978). Synaptic connections to individual tibialis anterior motoneurons in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **41**, 684–9.

Aymard, C., Chia, L., Katz, R., Lafitte, C. & Pénicaud, A. (1995). Reciprocal inhibition between wrist flexors and extensors in man: a new set of interneurones? *Journal of Physiology (London)*, **487**, 221–35.

Baldissera, F., Campadelli, P. & Cavallari, P. (1983). Inhibition of H-reflex in wrist flexors by group I afferents in the radial nerve. *Electromyography and Clinical Neurophysiology*, **23**, 187–93.

Baldissera, F., Cavallari, P., Fournier, E., Pierrot-Deseilligny, E. & Shindo, M. (1987). Evidence for mutual inhibition of opposite Ia interneurones in the human upper limb. *Experimental Brain Research*, **66**, 106–14.

Baret, M., Katz, R., Lamy, J. C., Pénicaud, A. & Wargon, I. (2003). Evidence for recurrent inhibition of reciprocal inhibition between antagonistic ankle muscles in man. *Experimental Brain Research*, **152**, 133–6.

Bayoumi, A. & Ashby, P. (1989). Projections of group Ia afferents to motoneurons of thigh muscles in man. *Experimental Brain Research*, **76**, 223–8.

Berbrayer, D. & Ashby, P. (1990). Reciprocal inhibition in cerebral palsy. *Neurology*, **40**, 653–6.

Boorman, G., Hulliger, M., Lee, R. G., Tako, K. & Tanaka, R. (1991). Reciprocal Ia inhibition in patients with spinal spasticity. *Neuroscience Letters*, **127**, 57–60.

Brouwer, B. & Ashby, P. (1991). Altered corticospinal projections to lower limb motoneurons in subjects with cerebral palsy. *Brain*, **114**, 1395–407.

Brouwer, B. & Smits, E. (1996). Corticospinal input onto motor neurones projecting to ankle muscles in individuals with cerebral palsy. *Developmental Medicine and Child Neurology*, **38**, 787–96.

Burke, R. E., Fedina, L. & Lundberg, A. (1971). Spatial synaptic distribution of recurrent and group Ia inhibitory systems in cat spinal motoneurones. *Journal of Physiology (London)*, **214**, 305–26.

Capaday, C. (1997). Neurophysiological methods for studies of the motor system in freely moving human subjects. *Journal of Neuroscience Methods*, **74**, 201–18.

Capaday, C., Cody, F. W. J. & Stein, R. B. (1990). Reciprocal inhibition of soleus motor output in humans during walking

and voluntary tonic activity. *Journal of Neurophysiology*, **64**, 607–16.

Chen, R. S., Tsai, C. H. & Lu, C. S. (1995). Reciprocal inhibition in writer's cramp. *Movement Disorders*, **10**, 556–61.

Crone, C. & Nielsen, J. (1989a). Spinal mechanisms in man contributing to reciprocal inhibition during voluntary dorsiflexion of the foot. *Journal of Physiology (London)*, **416**, 255–72.

(1989b). Methodological implications of the post-activation depression of the soleus H-reflex in man. *Experimental Brain Research*, **78**, 28–32.

Crone, C., Hultborn, H. & Jespersen, B. (1985). Reciprocal Ia inhibition from the peroneal nerve to soleus motoneurones with special reference to the size of the test reflex. *Experimental Brain Research*, **59**, 418–22.

Crone, C., Hultborn, H., Jespersen, B. & Nielsen, J. (1987). Reciprocal Ia inhibition between ankle flexors and extensors in man. *Journal of Physiology (London)*, **389**, 163–85.

Crone, C., Nielsen, J., Petersen, N., Ballegaard, M. & Hultborn, H. (1994). Disynaptic reciprocal inhibition of ankle extensors in spastic patients. *Brain*, **117**, 1161–8.

Crone, C., Nielsen, J., Petersen, N., Tijssen, M. A. & Van Dijk, J. G. (2001). Patients with the major and minor form of hyperekplexia differ with regards to disynaptic reciprocal inhibition between ankle flexor and extensor muscles. *Experimental Brain Research*, **140**, 190–7.

Crone, C., Johnsen, L. L., Biering-Sørensen, F. & Nielsen, J. B. (2003). Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury. *Brain*, **126**, 495–507.

Curtis, D. R. (1959). Pharmacological investigations upon inhibition of spinal motoneurones. *Journal of Physiology (London)*, **145**, 175–92.

Day, B. L. & Rothwell, J. C. (1983). Estimation of the central delay in the reciprocal Ia inhibitory pathway of the human forearm. *Journal of Physiology (London)*, **336**, 32.

Day, B. L., Marsden, C. D., Obeso, J. A. & Rothwell, J. C. (1981). Peripheral and central mechanisms of reciprocal inhibition in the human forearm. *Journal of Physiology (London)*, **317**, 59–60.

(1984). Reciprocal inhibition between the muscles of the human forearm. *Journal of Physiology (London)*, **349**, 519–34.

Delwaide, P. J. (1985). Electrophysiological testing of spastic patients: its potential usefulness and limitation. In *Clinical Neurophysiology in Spasticity*, ed. P. E. Delwaide & R. R. Young, pp. 185–203. Amsterdam: Elsevier.

Delwaide, P. J., Pepin, J. L. & Maertens De Noordhout, A. (1993). Contribution of reticular nuclei to the pathophysiology of parkinsonian rigidity. *Advances in Neurology*, **60**, 381–5.

Eccles, R. M. & Lundberg, A. (1958). Integrative pattern of Ia synaptic actions of motoneurones of hip and knee muscles. *Journal of Physiology (London)*, **144**, 271–98.

Eccles, J. C., Fatt, P. & Landgren, S. (1956). The central pathway for the direct inhibitory action of impulses in the largest afferent nerve fibers to muscle. *Journal of Neurophysiology*, **19**, 75–98.

Eccles, J. C., Eccles, R. M. & Lundberg, A. (1960). Types of neurone in and around the intermediate nucleus of the lumbosacral cord. *Journal of Physiology (London)*, **154**, 89–114.

Enriquez-Denton, M., Nielsen, J., Perreault, M. C., Morita, H., Petersen, N. & Hultborn, H. (2000). Presynaptic control of transmission along the pathways mediating disynaptic reciprocal inhibition in the cat. *Journal of Physiology (London)*, **526**, 623–37.

Fedina, L. & Hultborn, H. (1972). Facilitation from ipsilateral primary afferents of interneuronal transmission in the Ia inhibitory pathway to motoneurones. *Acta Physiologica Scandinavica*, **94**, 198–221.

Fetz, E. E. (1992). Are movement parameters recognizably coded in the activity of single neurons? *Behavioral and Brain Sciences*, **15**, 679–90.

Fetz, E. E. & Cheney, P. D. (1987). Functional relations between primate motor cortex cells and muscles: fixed and flexible. *CIBA Foundation Symposia*, **132**, 98–117.

Floeter, M. K., Andermann, F., Andermann, E., Nigro, M. & Hallet, M. (1996). Physiological studies of spinal inhibitory pathways in patients with hereditary hyperekplexia. *Neurology*, **46**, 766–72.

Gottlieb, G. L. & Myklebust, B. M. (1993). Hyper-reflexia and disordered voluntary movement. In *Spasticity: Mechanisms and Management*. ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 155–66. Berlin: Springer.

Hammar, I., Slawinska, U. & Jankowska, E. (2002). A comparison of postactivation depression of synaptic actions evoked by different afferents and at different locations in the feline spinal cord. *Experimental Brain Research*, **145**, 126–9.

Hayashi, A., Kagamihara, Y., Nakajima, Y., Narabayahi, H., Okuma, Y. & Tanaka, R. (1988). Disorder in reciprocal Ia inhibition upon initiation of voluntary movements in patients with Parkinson's disease. *Experimental Brain Research*, **70**, 437–40.

Hoffmann, P. (1918). Über die Beriehungen der Sehnenreflexe zur willkürlichen Bewegung und zum Tonus. *Zeitschrift für Biologie*, **68**, 351–70.

Hongo, T., Lundberg, A., Phillips, C. G. & Thompson, R. F. (1984). The pattern of monosynaptic Ia-connections to hindlimb

motor nuclei in the baboon: a comparison with the cat. *Proceedings of the Royal Society London B*, **221**, 261–89.

Hultborn, H. (1976). Transmission in the pathway of reciprocal Ia inhibition to motoneurones and its control during the tonic reflex. In *Understanding the Stretch Reflex. Progress in Brain Research*, Vol. 44, ed. S. Homma, pp. 235–55. Amsterdam: Elsevier.

Hultborn, H. & Udo, M. (1972a). Convergence in the reciprocal Ia inhibitory pathway of excitation from descending pathways and inhibition from motor axon collaterals. *Acta Physiologica Scandinavica*, **84**, 95–108.

(1972b). Convergence of large muscle spindle (Ia) afferents at interneuronal level in the reciprocal Ia inhibitory pathway to motoneurones. *Acta Physiologica Scandinavica*, **84**, 493–9.

Hultborn, H., Jankowska, E., Lindström, S. & Roberts, W. (1971a). Neuronal pathway of the recurrent facilitation of motoneurones. *Journal of Physiology (London)*, **218**, 495–514.

Hultborn, H., Jankowska, E. & Lindström, S. (1971b). Recurrent inhibition of interneurones monosynaptically activated from group Ia afferents. *Journal of Physiology (London)*, **215**, 613–36.

Hultborn, H., Illert, M. & Santini, M. (1976a). Convergence on interneurones mediating the reciprocal Ia inhibition of motoneurones. I. Disynaptic Ia inhibition of Ia inhibitory interneurones. *Acta Physiologica Scandinavica*, **96**, 193–201.

(1976b). Convergence on interneurones mediating the reciprocal Ia inhibition of motoneurones. III. Effects from supraspinal pathways. *Acta Physiologica Scandinavica*, **96**, 368–91.

Iles, J. F. (1983). Modulation of inhibition of human soleus motoneurones during isometric contractions. *Journal of Physiology (London)*, **345**, 165*P*.

(1986). Reciprocal inhibition during agonist and antagonist contraction. *Experimental Brain Research*, **62**, 212–14.

Iles, J. F. & Pisini, J. V. (1992a). Vestibular-evoked postural reactions in man and modulation of transmission in spinal reflex pathways. *Journal of Physiology (London)*, **455**, 407–24.

(1992b). Cortical modulation of transmission in spinal reflex pathways of man. *Journal of Physiology (London)*, **455**, 425–46.

Illert, M. & Tanaka, R. (1978). Integration in descending motor pathways controlling the forelimb in the cat. 4. Corticospinal inhibition of forelimb motoneurones mediated by short propriospinal neurones. *Experimental Brain Research*, **31**, 131–41.

Jankowska, E. (1992). Interneuronal relay in spinal pathways from proprioceptors. *Progress in Neurobiology*, **38**, 335–78.

Jankowska, E. & Lindström, S. (1972). Morphology of interneurones mediating Ia reciprocal inhibition of motoneurones in the spinal cord of the cat. *Journal of Physiology (London)*, **226**, 805–23.

Jankowska, E. & Lundberg, A. (1981). Interneurones in the spinal cord. *Trends in Neurosciences*, **4**, 230–3.

Jankowska, E. & Roberts, W. (1972). Synaptic actions of single interneurones mediating reciprocal Ia inhibition of motoneurones. *Journal of Physiology (London)*, **222**, 623–42.

Jankowska, E., Padel, Y. & Tanaka, R. (1976). Disynaptic inhibition of spinal motoneurones from the motor cortex in the monkey. *Journal of Physiology (London)*, **258**, 467–87.

Kagamihara, Y. & Tanaka, R. (1985). Reciprocal inhibition upon initiation of voluntary movement. *Neuroscience Letters*, **55**, 23–7.

Katz, R., Pénicaud, A. & Rossi, A. (1991). Reciprocal Ia inhibition between elbow flexors and extensors in the human. *Journal of Physiology (London)*, **437**, 269–86.

Komiyama, T. & Kasai, T. (1997). Changes in the H-reflexes of ankle extensor and flexor muscles at the initiation of a stepping movement in humans. *Brain Research*, **766**, 227–35.

Kots, Y. M. (1969). Supraspinal control of the segmental centres of muscle antagonists in man. I. Reflex excitability of the motoneurones of muscle antagonists in the period of organization of voluntary movement. *Biofizika*, **14**, 167–72.

Kots, Y. M. & Zhukov, V. I. (1971). Supraspinal control of the segmental centres of muscle antagonists in man. III. 'Tuning' of the spinal apparatus of reciprocal inhibition in the period of organization of voluntary movement. *Biofizika*, **16**, 1085–91.

Kudina, L. P. (1980). Reflex effects of muscle afferents in antagonist studied on single firing motor unit in man. *Electroencephalography and Clinical Neurophysiology*, **50**, 214–21.

Kudina, L., Ashby, P. & Downes, L. (1993). Effects of cortical stimulation on reciprocal inhibition in humans. *Experimental Brain Research*, **94**, 533–8.

Lamy, J. C., Wargon, I., Baret, M. *et al.* (2005). Post-activation depression in various group I spinal pathways in humans. *Experimental Brain Research* (in press).

Laporte, Y. & Lloyd, D. P. C. (1952). Nature and significance of the reflex connections established by large afferents fibers of muscular origin. *American Journal of Physiology*, **169**, 609–21.

Lelli, S., Panizza, M. & Hallett, M. (1991). Spinal inhibitory mechanisms in Parkinson's disease. *Neurology*, **41**, 553–6.

Livingston, R. B., Paillard, J., Tournay, A. & Fessard, A. (1951). Plasticité d'une synergie musculaire dans l'exécution d'un

mouvement volontaire chez l'Homme. *Journal de Physiologie (Paris)*, **43**, 605–19.

Lloyd D. P. C. (1941). A direct central inhibitory action on dromically conducted impulses. *Journal of Neurophysiology*, **4**, 184–90.

(1946). Facilitation and inhibition of spinal motoneurones. *Journal of Neurophysiology*, **9**, 317–26.

Lundberg, A. (1970). The excitatory control of the Ia inhibitory pathway. In *Excitatory Synaptic Mechanisms*, ed. P. Andersen & J. K. S. Jansen, pp. 333–40. Oslo: Universitetforlaget.

Lundberg, A. & Voorhoeve, P. (1962). Effects from the pyramidal tract on spinal reflex arcs. *Acta Physiologica Scandinavica*, **56**, 201–19.

Mao, C. C., Ashby, P., Wang, M. & McCrea, D. (1984). Synaptic connections from large muscle afferents to the motoneurones of various leg muscles in man. *Experimental Brain Research*, **56**, 341–50.

Meunier, S. & Morin, C. (1989). Changes in presynaptic inhibition of Ia fibres to soleus motoneurones during voluntary dorsiflexion of the foot. *Experimental Brain Research*, **76**, 510–18.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta, M. (1993). Pattern of monosynaptic heteronymous Ia connections in the human lower limb. *Experimental Brain Research*, **96**, 533–44.

Meunier, S., Pol, S., Houeto, J. L. & Vidailhet, M. (2000). Abnormal reciprocal inhibition between antagonist muscles in Parkinson's disease. *Brain*, **123**, 1017–26.

Mizuno, Y., Tanaka, R. & Yanagisawa, N. (1971). Reciprocal group I inhibition of triceps surae motoneurones in man. *Journal of Neurophysiology*, **34**, 1010–17.

Morin, C. & Pierrot-Deseilligny, E. (1977). Role of Ia afferents in the soleus motoneurone inhibition during a tibialis anterior voluntary contraction in man. *Experimental Brain Research*, **27**, 509–22.

Morita, H., Crone, C., Christenhuis, D., Petersen, N. T. & Nielsen, J. B. (2001). Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity. *Brain*, **124**, 826–37.

Morita, H., Shindo, M., Morita, S., Hashimoto, T., Tada, T. & Ikeda, S. (2002). Abnormal conditioning effect of transcranial magnetic stimulation on soleus H-reflex during voluntary movement in Parkinson's disease. *Clinical Neurophysiology*, **113**, 1316–24.

Nakashima, K., Rothwell, J. C., Day, B. L., Thompson, P. D., Shannon, K. & Marsden, C. D. (1989). Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. *Brain*, **112**, 681–97.

Nakashima, K., Shimoyama, R., Yokoyama, Y. & Takahashi, K. (1994). Reciprocal inhibition between the forearm muscles in patients with Parkinson's disease. *Electromyography and Clinical Neurophysiology*, **34**, 67–72.

Nielsen, J. & Kagamihara, Y. (1992). The regulation of disynaptic reciprocal Ia inhibition during co-contraction of antagonistic muscles in man. *Journal of Physiology (London)*, **456**, 373–91.

(1993). The regulation of presynaptic inhibition during co-contraction of antagonistic muscles in man. *Journal of Physiology (London)*, **464**, 575–93.

Nielsen, J., Kagamihara, Y., Crone, C. & Hultborn, H. (1992). Central facilitation of Ia inhibition during tonic ankle dorsiflexion revealed after blockade of peripheral feedback. *Experimental Brain Research*, **88**, 651–6.

Nielsen, J., Petersen, N., Deuschl, G. & Ballegaard, M. (1993). Task-related changes in the effect of magnetic brain stimulation on spinal neurones in man. *Journal of Physiology (London)*, **471**, 223–43.

Nielsen, J., Crone, C., Sinkjaer, T., Toft, E. & Hultborn, H. (1995). Central control of reciprocal inhibition during fictive dorsiflexion in man. *Experimental Brain Research*, **104**, 99–106.

Nielsen, J. B., Tijssen, M. A. J., Hansen, N. L. *et al.* (2002). Corticospinal transmission to leg motoneurones in human subjects with deficient glycinergic inhibition. *Journal of Physiology (London)*, **544**, 631–40.

Obeso, J. A., Quesada, P., Artieda, J. & Martînez-Lage, J. M. (1985). Reciprocal inhibition in rigidity and dystonia. In *Clinical Neurophysiology in parkinsonism*, ed. P. J. Delwaide & A. Agnelli, pp. 9–18. Amsterdam: Elsevier.

Oda, Y., Charpier, S., Murayama, Y., Suma, C. & Korn, H. (1995). Long-term potentiation of glycinergic inhibitory synaptic transmission. *Journal of Neurophysiology*, **74**, 1056–74.

Okuma, Y. & Lee, R. G. (1996). Reciprocal inhibition in hemiplegia: correlation with clinical features and recovery. *Canadian Journal of Neurological Sciences*, **23**, 15–23.

Okuma, Y., Mizuno, Y. & Lee, R. G. (2002). Reciprocal Ia inhibition in patients with asymmetric spinal spasticity. *Clinical Neurophysiology*, **113**, 292–7.

Ørsnes, G., Crone, C., Krarup, C., Petersen, N. & Nielsen, J. (2000). The effect of baclofen on the transmission in spinal pathways in spastic multiple sclerosis patients. *Clinical Neurophysiology*, **111**, 1372–9.

Panizza, M. E., Hallett, M. & Cohen, L. G. (1987). Abnormality of reciprocal inhibition in patients with hand cramps. *Annals of Neurology*, **22**, 146.

Perez, M. A. & Field-Fote, E. C. (2003). Impaired posture-dependent modulation of disynaptic reciprocal Ia

inhibition in individuals with incomplete spinal cord injury. *Neuroscience Letters*, **341**, 225–8.

Perez, M. A., Field-Fote, E. C. & Floeter, M. K. (2003). Patterned sensory stimulation induces plasticity in reciprocal Ia inhibition in humans. *Journal of Neuroscience*, **23**, 2014–18.

Petersen, N., Morita, H. & Nielsen, J. (1998). Evaluation of reciprocal inhibition of the soleus H-reflex during tonic plantar flexion in man. *Journal of Neurosciences Methods*, **84**, 1–8.

(1999). Modulation of reciprocal inhibition between ankle extensors and flexors during walking in man. *Journal of Physiology* (*London*), **520**, 605–19.

Pierrot-Deseilligny, E. & Lacert, P. (1973). Amplitude and variability of monosynaptic reflexes prior to various voluntary movements in normal and spastic man. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 538–49. Basel: Karger.

Pierrot-Deseilligny, E., Lacert, P. & Cathala, H. P. (1971). Amplitude et variabilité des réflexes monosynaptiques avant un mouvement volontaire. *Physiology and Behavior*, **7**, 495–508.

Pierrot-Deseilligny, E., Morin, C., Bergego, C. & Tankov, N. (1981). Pattern of group I fibre projections from ankle flexor and extensor muscles in man. *Experimental Brain Research*, **42**, 337–50.

Pierrot-Deseilligny, E., Katz, R. & Hultborn, H. (1983). Functional organization of recurrent inhibition: changes in recurrent inhibition preceding and accompanying voluntary movements in man. *Advances in Neurology*, **39**, 443–57.

Rossi, A. & Mazzocchio, R. (1988). Cutaneous control of group I pathways from ankle flexors to extensors in man. *Experimental Brain Research*, **73**, 8–14.

Rossi, A., Mazzocchio, R. & Scarpini, C. (1988). Changes in Ia reciprocal inhibition from the peroneal nerve to soleus α-motoneurones with different static body position in man. *Neuroscience Letters*, **84**, 283–6.

Rossi, A., Zalaffi, A. & Decchi, B. (1994). Heteronymous recurrent inhibition from gastrocnemius muscle to soleus motoneurones in humans. *Neuroscience Letters*, **169**, 141–4.

Rossi, A., Decchi, B., Zalaffi, A. & Mazzocchio, R. (1995). Group Ia non-reciprocal inhibition from wrist extensor to flexor motoneurones in humans. *Neuroscience Letters*, **191**, 205–7.

Sato, T., Tsuboi, T., Miyazaki, M. & Sakamoto, K. (1999). Post-tetanic potentiation of reciprocal Ia inhibition in human lower limb. *Journal of Electromyography and Kinesiology*, **9**, 59–66.

Schieppati, M., Gritti, I. & Romano, C. (1991). Recurrent and reciprocal inhibition of the human monosynaptic reflex shows opposite changes following intravenous administration of acetylcarnitine. *Acta Physiologica Scandinavica*, **143**, 27–32.

Sears, T. A. (1964). Investigations on respiratory motoneurones of the thoracic spinal cord. In *Physiology of Spinal Neurons. Progress in Brain Research*, vol. 12, ed. J. C. Eccles & J. P. Schadé, pp. 259–73. Amsterdam: Elsevier.

Sherrington, C. S. (1897). On reciprocal innervation of antagonist muscles. Third note. *Proceedings of the Royal Society*, **60**, 408–17.

Shindo, M., Harayama, H., Kondo, K., Yanagisawa, N. & Tanaka, R. (1984). Changes in reciprocal Ia inhibition during voluntary contraction in man. *Experimental Brain Research*, **53**, 400–8.

Shindo, M., Yanagawa, S., Morita, H. & Yanagisawa, N. (1995). Increase in reciprocal Ia inhibition during antagonist contraction in the human leg: a study of motor units and the H reflex. *Journal of Physiology (London)*, **489**, 275–86.

Simoyama, M. & Tanaka, R. (1974). Reciprocal Ia inhibition at the onset of voluntary movements in man. *Brain Research*, **82**, 334–7.

Takada, Y., Miyahara, T., Tanaka, T., Ohyama, T. & Nakamura, Y. (2000). Modulation of H reflex of pretibial muscles and reciprocal Ia inhibition of soleus muscle during voluntary teeth clenching in humans. *Journal of Neurophysiology*, **83**, 2063–70.

Tanaka, R. (1974). Reciprocal Ia inhibition during voluntary movements in man. *Experimental Brain Research*, **2**, 529–40.

Tsai, C. H., Chen, R. S. & Lu, C. S. (1997). Reciprocal inhibition in Parkinson's disease. *Acta Neurologica Scandinavica*, **95**, 13–18.

Valls-Sole, J., Hallett, M. & Brasil-Neto, J. (1998). Modulation of vastus medialis motoneuronal excitability by sciatic nerve afferents. *Muscle and Nerve*, **21**, 936–9.

Wargon, I., Lamy, J. C., Baret, M., Aymard, C., Pénicaud, A. & Katz, R. (2005). The disynaptic inhibition between wrist flexor and extensor muscles revisited in humans. *Experimental Brain Research*, submitted.

Wolpaw, J. R. & Lee, C. L. (1989). Memory traces in primates spinal cord produced by operant conditioning of H-reflex. *Journal of Neurophysiology*, **61**, 563–72.

Yanagisawa, N., Tanaka, R. & Ito, Z. (1976). Reciprocal Ia inhibition in spastic hemiplegia of man. *Brain*, **99**, 555–74.

6

Ib pathways

Views about the functional role of Ib pathways have evolved more over the years than for any other spinal circuit. The initial opinion that Ib inhibition subserved an autogenetic protective reflex has been replaced by the view that tendon organs continuously provide information about the extent of muscle contraction. Projections of 'Ib' interneurones were then shown to be more widely distributed than implied by the term 'autogenetic inhibition', and, because of the extensive convergence from peripheral afferents onto the relevant interneurones, the term of 'non-reciprocal group I inhibition' has been introduced to refer to inhibition conveyed by this pathway. Finally, the recent finding that, during locomotion, Ib (or non-reciprocal group I) inhibition is replaced by di- and polysynaptic excitation has completely altered views on the functional significance of Ib pathways. The multitude of controls (pre- and post-synaptic, peripheral and descending) on Ib pathways and the numerous possible alternative patterns suggest that they might play multiple roles. Studies during various motor tasks in human subjects could be particularly important in helping to understand these roles but, because of the difficulty in investigating Ib pathways selectively in human subjects, they have not yet been explored to any great extent during human movement.

Background from animal experiments

Initial findings

In the chronic spinal dog, forced flexion of the knee produces, after the initial stretch reflex, the clasp-knife phenomenon, in which the reflex resistance suddenly 'melts away' (Sherrington, 1909). This phenomenon should be differentiated from the 'lengthening reaction' of the decerebrate cat, with which it is often erroneously equated. The former depends on active inhibition from 'flexor reflex afferents' (FRA, see Chapter 12, p. 558), while the latter results merely from the subsidence of force once the dynamic phase of stretch has ceased (see Burke *et al.*, 1972). Granit (1950) demonstrated autogenetic inhibition in cat extensor motoneurones during contraction of the homonymous muscle. Because of the high threshold of Golgi tendon organs to passive stretch (B. H. C. Matthews, 1933), Ib inhibition was long thought to serve a protective reflex against overloading and to be responsible for the clasp-knife phenomenon. This position became untenable with the demonstration that contractions of single motor units may activate tendon organs (Houk & Henneman, 1967), and that knee joint position rather than force of contraction was the

trigger for a clasp-knife response (see Chapter 7, p. 326). Stretch-responsive slowly conducting afferents (non-spindle group II and group III-group IV afferents) are necessary for the initiation of the clasp-knife phenomenon, rather than Ib or group II muscle afferents (Rymer, Houk & Crago, 1979). Using monosynaptic reflex testing, Laporte & Lloyd (1952) presented the first evidence for short-latency Ib inhibition of homonymous extensor motoneurones. Intra-cellular recordings from motoneurones revealed a much wider distribution of Ib effects (Eccles, Eccles & Lundberg, 1957), while recordings from interneurones subsequently documented the alternative pathways accessed by Ib afferents (for references, see Jankowska, 1992).

Golgi tendon organs and Ib afferents

Golgi tendon organs

Ib afferents originate from Golgi tendon organs, which are located exclusively at muscle-tendon or muscle-aponeurosis junctions and not within tendons. The adequate stimulus for Golgi tendon organs is not muscle stretch, to which they have a high threshold and rapid adaptation, but muscle contraction. They are silent at rest and start discharging as soon as motor units in series with the receptor start contracting. Tendon organs can signal quite small variations of contractile force better than mean force level (for review, see Jami, 1992). Contrary to muscle spindle primary endings, tendon organs are virtually insensitive to vibration of low amplitude applied longitudinally to the tendon (but this is not necessarily the situation in human studies, see Chapter 3, pp. 130–1).

Each tendon organ is usually innervated by a single Ib afferent fibre

Ib afferents are fast-conducting fibres with, in the cat, conduction velocities slightly slower than those of Ia afferents, but largely overlapping them, as do their diameters. This explains why it is difficult to separate Ib from Ia afferents on the basis of their threshold for electrical stimulation in animal (and human) experiments (see P. B. C. Matthews, 1972). The insensitivity to vibration of tendon organs has been used to develop an elegant method that allows selective electrical stimulation of Ib afferents (Coppin, Jack & MacLennan, 1970; Fetz *et al.*, 1979). Prolonged vibration to a tendon produces an activity-dependent hyperpolarisation of the activated Ia fibres and raises their electrical threshold, so that electrical stimulation may then recruit Ib afferents at lower threshold than Ia afferents.

General features

Denomination

Interneurones intercalated in reflex pathways from Ib afferents are referred to as 'Ib' interneurones because of their dominant input. However, these interneurones are co-excited by Ib and Ia afferents, and the terms 'non-reciprocal group I inhibition' and 'oligosynaptic group I excitation' have been introduced (Jankowska, McCrea & Mackel, 1981). The terms 'Ib' pathways and 'Ib' interneurones are, however, retained in this chapter, because they have usually been used in human studies of the corresponding pathways.

Location

Ib interneurones are located in lamina VI and in the dorsal part of lamina VII (see Jankowska, 1992).

Connections

The dominant Ib effects are inhibition of homonymous and synergistic motoneurones through di- and tri-synaptic pathways and excitation of antagonistic motoneurones through trisynaptic pathways (Eccles, Eccles & Lundberg, 1957).

Absence of inhibitory projections from Renshaw cells to Ib interneurones

The absence of projections from Renshaw cells is in contrast to the situation with interneurones mediating disynaptic reciprocal Ia inhibition, and serves to

distinguish these two types of interneurones, both of which are excited by Ia afferents (see Chapter 5, p. 200 and pp. 205–8).

Projections of Ib afferents

Projections to α motoneurones

Views concerning the pattern of these projections have evolved with the techniques available for studying them. Thus the picture has become more and more complex and confusing – from the relatively simple autogenetic Ib inhibition of extensor muscles as initially described, to the alternative patterns seen in different preparations or due to the mutual inhibition of Ib interneurones.

(i) Using monosynaptic reflex testing in spinal preparations, Laporte & Lloyd (1952) showed that slightly increasing the strength of a conditioning group I volley from an extensor muscle caused the initial (Ia) effect, i.e. the facilitation of synergistic and the inhibition of antagonistic motoneurones, to change in the opposite direction. This occurred at a latency consistent with a disynaptic pathway activated by afferents from tendon organs. They coined the term 'inverse myotatic reflex' to describe these effects because they appeared to be the opposite of those of the stretch reflex.

(ii) Intracellular recordings by Eccles, Eccles & Lundberg (1957) revealed that Ib reflex effects are more widely distributed, reaching almost all motoneurone pools of the ipsilateral limb, without particular preference for autogenetic or direct antagonistic effects (see the sketch in Fig. 6.1(*a*)). In the low spinal cat, the effects from extensors are strong, with disynaptic inhibition of extensor motoneurones and trisynaptic excitation of flexor motoneurones, but those from flexors are weak if present. However, Ib effects from flexors, with weak inhibition of flexor motoneurones and even extensor excitation, have been seen after stimulation of the red nucleus (Hongo, Jankowska & Lundberg, 1969).

(iii) Intracellular recordings from interneurones have shown that Ib afferents from many muscles, flexors and extensors, often terminate on the same Ib interneurones and mutually facilitate each other (see Jankowska, 1992). Thus, alternative interneuronal pathways between Ib afferents and motoneurones allow individual motoneurones to be either excited or inhibited by Ib afferents from a variety of muscles. The final effect depends on which of the interneuronal subpopulations is selected, through segmental and descending activation of Ib interneurones, and mutual inhibition of Ib interneurones (see below).

Other projections from Ib interneurones

γ motoneurones

Stimuli activating group I afferents produce inhibition or excitation of γ motoneurones in parallel with inhibition or excitation of corresponding α motoneurones, probably through the same Ib interneurones (see Jankowska, 1992).

Ib interneurones inhibit other Ib interneurones

Through this mutual inhibition, any input exciting some Ib interneurones may inhibit others (Brink *et al.*, 1983). Mutual inhibition may be used to select the most appropriate alternative pathways for the desired pattern of Ib actions.

Ascending tract neurones

Ib inhibitory interneurones project onto the cells of origin of the ventral and dorsal spino-cerebellar tracts. They could thereby provide information about their action on motoneurones and could serve to dampen activity of these ascending neurones (see Jankowska, 1992). A cortical projection to area 3a via the dorsal spinocerebellar tract and nucleus Z has been documented (McIntyre, Proske & Rawson, 1984, 1985), and it is possible that tendon organ

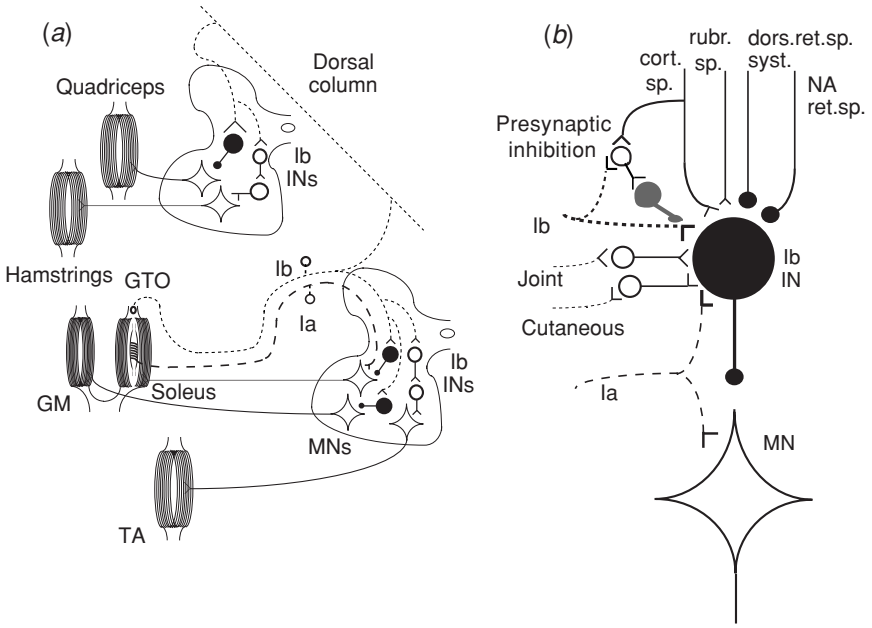


Fig. 6.1. Wiring diagram of the connections of Ib pathways. (*a*), (*b*) In this and subsequent figures, excitatory synapses are represented by Y-shaped bars and inhibitory synapses by small filled circles, excitatory interneurones (IN) by open circles and inhibitory INs by large filled circles, Ib afferents by dotted lines, Ia afferents by dashed lines, cutaneous and joint afferents by thin dotted lines. (*a*) Projections of Ib afferents originating from Golgi tendon organs (GTO) of the soleus are shown to have disynaptic inhibitory projections to homonymous soleus motoneurones (MN), and to heteronymous MNs supplying its close synergist, the gastrocnemius medialis (GM), and also, after running in the dorsal column, to MNs of the remote quadriceps. They have trisynaptic excitatory projections to MNs of the direct antagonist, tibialis anterior (TA), and also to MNs of the flexors of the knee (hamstrings). (*b*) Extensive convergence onto a Ib inhibitory IN of various afferents and descending tracts, with excitatory projections from Ib, Ia, and, via interposed first-order INs, cutaneous and joint afferents, and of the corticospinal (cort.sp.) and rubrospinal (rubr.sp.) tracts, and inhibitory projections from the dorsal reticulospinal system (dors.ret.syst.) and the noradrenergic reticulospinal system (NA ret.sp.syst.). The pathway of presynaptic inhibition of Ib terminals facilitated by Ib afferents and corticospinal fibres is also represented. Modified from Lundberg, Malmgren & Schomburg (1978) (*b*), with permission.

impulses play a role in the perception of force (see Nicolas *et al.*, 2005).

Input to Ib interneurones

Extensive convergence from peripheral afferents and descending tracts onto Ib interneurones has been described by Lundberg, Jankowska and colleagues (see the sketch in Fig. 6.1(*b*)), and the functional significance of this convergence has been discussed in a comprehensive review by Jankowska & Lundberg (1981).

Peripheral afferents

Interneurones mediating Ib inhibition are activated by Ib and, to a lesser extent, Ia afferents and through one or two interposed interneurones by group II, cutaneous, joint and interosseous afferents (see Harrison & Jankowska, 1985). Subthreshold effects from many sources may thus converge to

fire these interneurones. Given that any movement will activate receptors in muscles, joints and skin, it seems 'sensible that different receptors which can give useful information combine in the feed-back control, and this is best achieved by convergence onto interneurones in a common reflex pathway' (Jankowska & Lundberg, 1981).

Descending tracts

Ib interneurones receive monosynaptic excitation from the corticospinal and rubrospinal tracts and are inhibited from the dorsal reticulospinal system and the noradrenergic reticulospinal system. Because of the wide convergence on Ib interneurones, receptors activated by the movement may modulate the component of the descending command mediated through these interneurones at a premotoneuronal level, i.e. *en route* to the motoneurones (Jankowska & Lundberg, 1981).

Contraction-induced Ib inhibition

In the anaesthetised cat, Ib inhibition produced by gastrocnemius medialis muscle contractions evoked by electrical stimulation of the distal end of a cut branch of the nerve innervating this muscle has been explored in different muscles. Group I IPSPs in triceps surae motoneurones were maximal at the onset of contraction and with abrupt increases in the contraction force (Zytnicki *et al.*, 1990). However, group I afferent volleys elicited by the same gastrocnemius medialis contraction were insufficient by themselves to evoke IPSPs in quadriceps motoneurones (Lafleur *et al.*, 1993).

Presynaptic inhibition and post-activation depression

Ib afferents are subject to potent presynaptic inhibition with PAD

This inhibition is (i) evoked by Ib afferents themselves, and not by Ia afferents, and (ii) facilitated from the corticospinal tract (see Rudomin & Schmidt 1999; Fig. 6.1(*b*)). Presynaptic inhibition of Ib afferents evoked by the contraction-induced Ib discharge is the mechanism responsible for the decline of autogenetic Ib inhibition of triceps surae motoneurones after the onset of gastrocnemius medialis contractions produced by electrical nerve stimulation in the cat (Zytnicki *et al.*, 1990; Lafleur *et al.*, 1992).

Post-activation depression

Post-activation depression of interneurones of the feline intermediate zone fed by group I afferents is marginal (Hammar, Slawinska & Jankowska, 2002).

Reflex reversal during fictive locomotion

In the cat, the termination of the stance phase and the initiation of the swing phase of locomotion are signalled by the decrease in afferent activity from load receptors when the extensor muscles are unloaded in the late stance phase (see Duysens, Clarac & Cruse, 2000). If the unloading is prevented, the stance phase is prolonged. Experiments during fictive locomotion in the decerebrate cat have provided evidence that the central pathway responsible for this effect is a reversal of Ib inhibition to excitation (see Hultborn *et al.*, 1998; McCrea, 1998). Thus, stimulation of group I (mainly Ib) afferents evokes autogenetic inhibition in extensor motoneurones at rest, but produces excitation during the extensor phase of walking (Gossard *et al.*, 1994). Two different pathways mediate this excitation. One involves a disynaptic excitatory pathway to extensor motoneurones (McCrea *et al.*, 1995). The other has a longer latency and is thought to involve several interneurones, some of which are part of the spinal network generating locomotor activity in the cat (Gossard *et al.*, 1994). It is probably this pathway that is responsible for the resetting of the locomotor cycle when group I afferents are stimulated. Similarly, it has been demonstrated that the Ib inhibition of flexor and bifunctional motoneurones at rest is reversed to disynaptic excitation during fictive locomotion in the cat (Quevedo *et al.*, 2000).

Methodology

Ib inhibition

Underlying principles

Ib effects can be assessed in motoneurones by testing the effects on the H reflex or the PSTHs of single units of electrically-induced group I volleys. Four features suggest that the resulting inhibition is of Ib origin: (i) elicitation by large diameter muscle afferents, (ii) central delay consistent with disynaptic transmission, (iii) distribution to homonymous and synergistic motoneurones, and (iv) the fact that the stimulus is below the threshold for the H and M responses and is therefore not due to recurrent inhibition.

Inhibition of the H reflex at rest

Ib inhibition is most readily disclosed using the H reflex of a relaxed muscle, because voluntary activation of a muscle depresses Ib inhibition to its motoneurones (see pp. 268–71).

Biphasic group I effects

Because of the extensive distribution of homonymous and heteronymous monosynaptic Ia excitation in the upper and lower limbs of human subjects (cf. Chapter 2), Ib inhibition is usually preceded by an early facilitation of the test H reflex. The monosynaptic Ia excitation increases over 1–2 ms, then decreases and is replaced by an inhibition that is maximal ~5–6 ms after the onset of facilitation and lasts less than 10 ms. Such a biphasic pattern, with inhibition truncating the monosynaptic Ia excitation, has been observed in many combinations: from the inferior soleus nerve to soleus and quadriceps (Fig. 6.2(*b*)), the gastrocnemius medialis nerve to quadriceps (Fig. 6.4(*b*)) and biceps femoris (Fig. 6.2(*d*)), the femoral nerve to soleus (Fig. 2.3(*d*)), or the median nerve to biceps brachii (Fig. 6.3(*f*)) (Pierrot-Deseilligny *et al.*, 1981b; Fournier, Katz & Pierrot-Deseilligny, 1983; Hultborn *et al.*, 1987; Cavallari & Katz, 1989). Sometimes there is no overt depression of the H reflex below its control value, and the inhibition only manifests itself as an abrupt termination of the Ia excitation 0.5–1 ms after its onset. However, this still suggests that the monosynaptic Ia EPSP is truncated by a disynaptic IPSP, e.g. see the modulation of the soleus and quadriceps H reflexes by group I afferents in the tibial nerve (Marque *et al.*, 2001; Fig. 10.14(*d*), (*e*)). In any event, whether overt or not, inhibition is contaminated by Ia facilitation, and the size of the H reflex will be determined by the balance between the two.

Isolated inhibition

With some projections, there are no monosynaptic Ia connections, and stimulation of a nerve below 1 × MT produces inhibition of the test reflex. This inhibition is not preceded by reflex facilitation and its onset can therefore be accurately measured. Such combinations are rare but present in both the lower and upper limbs. The first evidence for Ib inhibition in human subjects was from gastrocnemius medialis to soleus (Pierrot-Deseilligny, Katz & Morin, 1979). The gastrocnemius medialis nerve may be stimulated selectively in the lower and medial part of the popliteal fossa (~10 cm below the electrode eliciting the soleus H reflex). Taking advantage of the absence of a monosynaptic Ia projection from medial gastrocnemius to soleus motoneurones (Chapter 2, p. 82), stimulation of this nerve produces only inhibition of the soleus H reflex. The inhibition is relatively weak, starts at the 2 ms ISI, peaks at 6 ms and is over at the 9 ms ISI (Fig. 6.2(*d*)). In the upper limb, there are no monosynaptic Ia projections from proximal to distal muscles either (Chapter 2, p. 84). Thus, stimuli to group I afferents in the musculo-cutaneous or the triceps brachii nerves elicit uncontaminated inhibition of the FCR H reflex (Cavallari, Katz & Pénicaud, 1992; Fig. 6.3(*c*)).

Inhibition in the PSTHs of single units

When there is monosynaptic Ia excitation, the after-hyperpolarisation (AHP) following the discharge of the unit prevents it from discharging again at longer

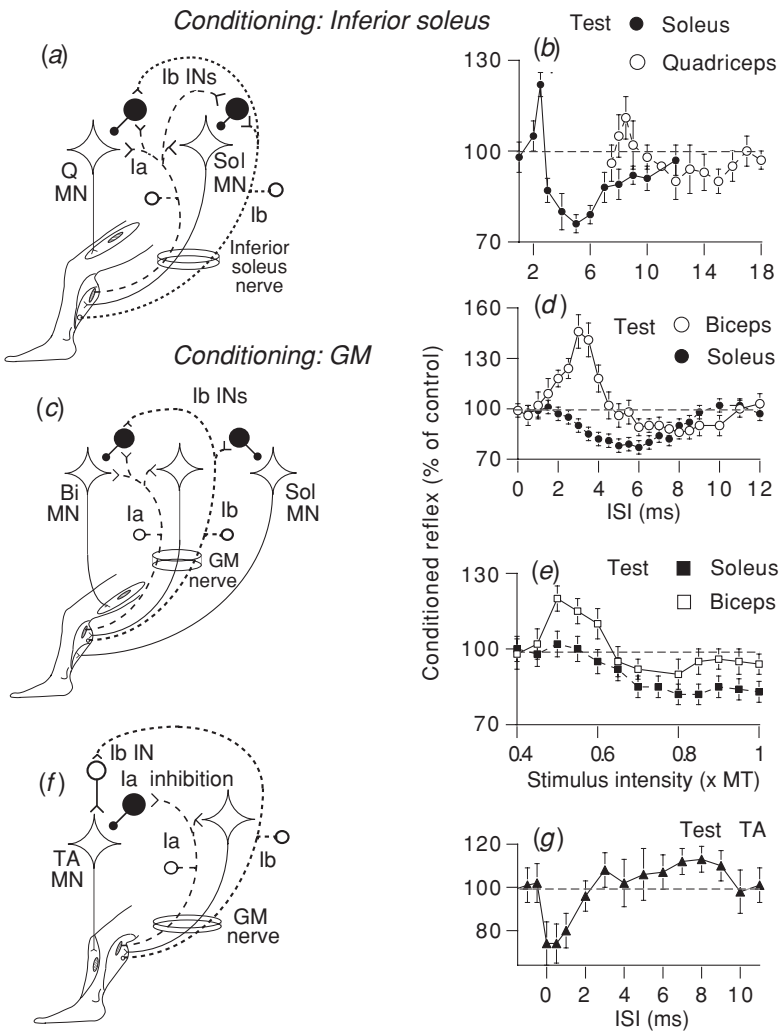


Fig. 6.2. Methodology to investigate Ib pathways in the lower limb. (*a*), (*c*), (*f*) Sketches of the Ib inhibitory pathways from inferior soleus (Inf Sol) to soleus (Sol) and quadriceps (Q) motoneurones (MN) (*a*), from gastrocnemius medialis (GM) to Sol and biceps femoris (Bi) MNs (*c*), and of the Ib excitatory pathway from GM to tibialis anterior (TA) MNs ((*f*) a trisynaptic pathway including two INs, though only one IN is sketched. The pathway of reciprocal Ia inhibition is also represented). (*b*), (*d*), (*e*), (*g*) Changes in the amplitude of the conditioned H reflex, expressed as a percentage of its unconditioned value. Each symbol represents the mean of 20 ((*b*), (*e*)), 30 (*g*), 40 ((*d*), ❍) or 100 ((*d*), ●) measurements. Vertical bars ±1 SEM. (*b*) The amplitude of the H reflexes of Sol (●) and of Q (❍) after stimulation of the Inf Sol nerve (0.95 × MT, at the lower border of the soleus) plotted against the interstimulus interval (ISI). (*d*), (*e*) The amplitude of the H reflexes of Sol (●) and Bi (❍) after stimulation of the GM nerve (in the lower and medial part of the popliteal fossa, ∼10 cm below the electrode eliciting the Sol H reflex) is plotted against the ISI ((*d*), 0.95 × MT), and the conditioning stimulus intensity ((*e*), ■, Sol, 5 ms ISI; □, Bi, 9 ms ISI). (*g*) The amplitude of the TA H reflex after stimulation of the GM nerve plotted against the ISI ((*d*), 0.95 × MT). Modified from Fournier, Katz & Pierrot-Deseilligny (1983) (*b*) and Pierrot-Deseilligny *et al.* (1981b) ((*d*), (*e*), (*g*)), with permission.

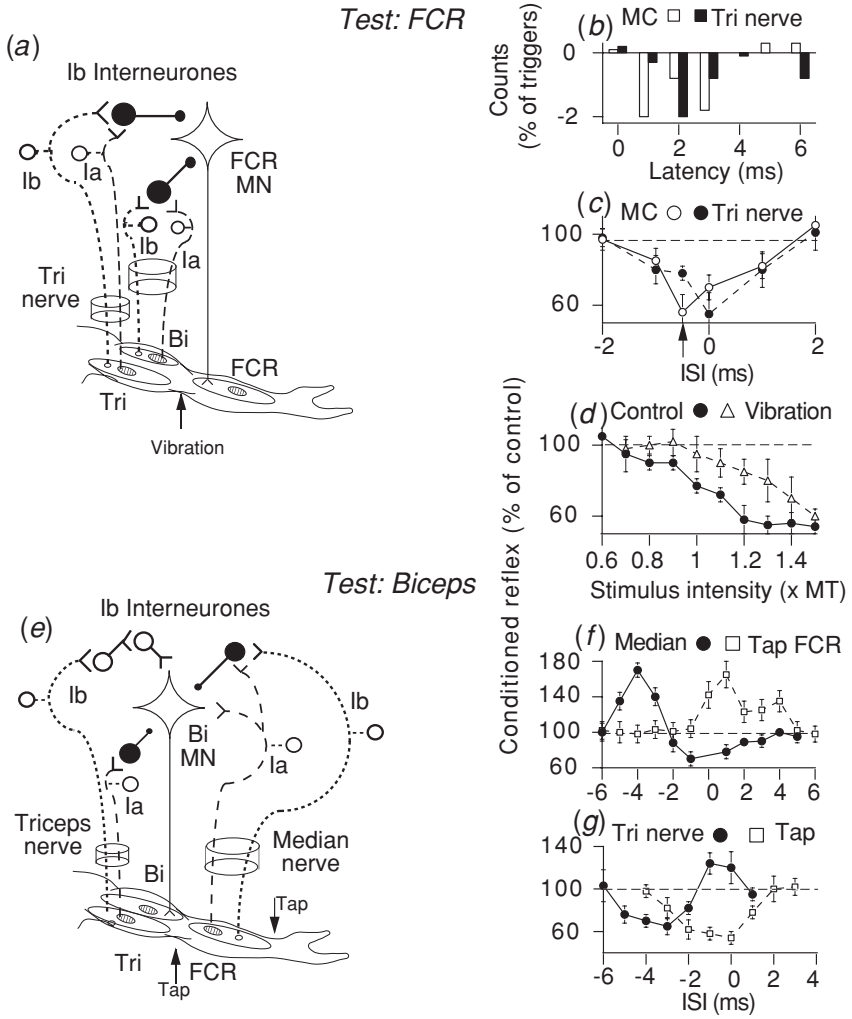


Fig. 6.3. Methodology to investigate Ib pathways in the upper limb. (*a*) Sketch of the Ib pathways from biceps (Bi) and triceps (Tri) to FCR motoneurones (MNs). (*b*) PSTHs of a single FCR motor unit (after subtraction of the background firing, 1 ms bin width) after stimulation of the musculo-cutaneous (MC, □) and Tri (■) nerves at 0.95 × MT. The zero of the abscissa indicates the expected time of arrival of the conditioning volley at the MN. (*c*), (*d*), (*f*), (*g*) Changes in the amplitude of the conditioned H reflex of FCR ((*c*), (*d*)) and biceps tendon jerk ((*f*), (*g*)), expressed as a percentage of unconditioned value. Each symbol represents the mean of 20 measurements. Vertical bars ±1 SEM. (*c*) Amplitude of the FCR H reflex after stimulation of the MC (○) and of the Tri (●) nerves at 0.95 × MT plotted against the interstimulus interval (ISI). Conditioning volleys are applied more proximally than the test volley and the arrow at the −0.5 ms ISI indicates the simultaneous arrival of conditioning and test volleys at spinal level. (*d*) Amplitude of the FCR H reflex plotted against the intensity of the Tri nerve stimulus (−0.5 ms ISI) in the control situation (●) and after a vibration (△, 166 Hz for 25 minutes) of the Tri tendon. Because of the absence of recurrent inhibition in this experimental paradigm (see Table 4.2), it is possible to use conditioning stimuli above 1 × MT. (*e*) Sketch of the Ib inhibitory pathway from FCR to Bi MNs, and of the Ib excitatory pathway (and reciprocal Ia inhibition) from Tri to Bi MNs. (*f*), (*g*) The amplitude of the Bi tendon jerk plotted against the ISI after various stimuli: (*f*) stimulation of the median nerve (0.95 × MT, ●) and tap to the FCR tendon (□); (*g*) electrical stimulation of the triceps nerve (1 × MT, ●) and tap to the triceps tendon (□). Because of the mechanical delay introduced by the tap responsible for the test tendon jerk, the synchronous arrival of the conditioning and test volleys at motoneuronal level occurs when the conditioning stimulation is delivered *after* the test tap (negative ISIs). Modified from Cavallari, Katz & Pénicaud (1992) ((*b*)–(*d*)), Cavallari & Katz (1989) (*f*), and Katz, Pénicaud & Rossi (1991) (*g*), with permission.

latencies. This, together with Ib inhibition elicited by the conditioning volley and recurrent inhibition due to the reflex discharge, contributes to the trough following the monosynaptic peak. It is difficult to establish the relative contribution of these factors. However, the AHP cannot produce a reduction in discharge that is greater than the peak of excitation, and Ib inhibition should not last longer than 10 ms, while recurrent inhibition typically does so (see Chapter 4, p. 166). Even in the absence of monosynaptic Ia excitation (gastrocnemius medialis to soleus, Mao *et al.*, 1984; musculo-cutaneous and triceps brachii to forearm muscles, Cavallari, Katz & Pénicaud, 1992; Fig. 6.3(*b*)), demonstrable Ib inhibition is only found in 20–30% of the units. This relative scarcity is probably because PSTHs require a background contraction, and Ib inhibition is depressed during contraction of the target muscle (see pp. 268–71).

Evidence for Ib inhibition

Evidence that the conditioning volley is Ib in origin

Electrical threshold

The electrical threshold of the inhibition is best measured when inhibition is not contaminated by Ia excitation, and is low: 0.6 × MT for the gastrocnemius medialis-induced inhibition of the soleus H reflex (Pierrot-Deseilligny *et al.*, 1981b; Fig. 6.2(*e*); 0.8 × MT, Yanagawa, Shindo & Nakagawa, 1991), and 0.7 × MT for the triceps brachii-induced inhibition of the FCR H reflex (Cavallari, Katz & Pénicaud, 1992; Fig. 6.3(*d*)). These thresholds are within the range of the largest afferent fibres (see Chapter 2, pp. 67–9 and 75). When the inhibition is associated with monosynaptic Ia excitation, it may be possible to compare the thresholds of the two effects. Thus, in Fig. 6.2(*e*), the reflex facilitation of the biceps femoris H reflex after gastrocnemius medialis stimulation appears at 0.5 × MT and decreases at 0.55 × MT, suggesting the appearance of an inhibitory process. This becomes obvious as further increases in stimulus intensity cause the reflex to decrease below its control value. In all combinations with biphasic effects in the lower and upper limbs (Pierrot-Deseilligny *et al.*, 1981b; Hultborn *et al.*, 1987; Cavallari & Katz, 1989), the threshold of the inhibition has similarly been found to be close to that of the monosynaptic Ia excitation. This indicates that afferents responsible for the inhibition are of similar size to or, at most, only slightly smaller than Ia afferents. The Ib input needs to discharge an interneurone before it can reach the motoneurone, so that a slightly higher threshold is inevitable even if Ib and Ia afferents are of the same size.

Effects of ischaemia

The effects of ischaemia on the inferior soleus group I modulation of the soleus H reflex have confirmed this interpretation. During ischaemia of the leg, the homonymous reflex facilitation disappeared at the same time as the Achilles tendon jerk and was replaced by an inhibition which also disappeared about 5 minutes later (Pierrot-Deseilligny *et al.*, 1981b; Fig. 2.2(*g*)). This is consistent with ischaemic blockade of Ia afferents, the exposure of the Ib inhibition, and then blockade of Ib afferents, a sequence that suggests lesser susceptibility of Ib afferents to ischaemia (it is known that ischaemia affects the largest fibres preferentially, cf. Chapter 2, p. 69).

Effects of tendon taps

These effects have been compared to those of electrical stimuli in an attempt to distinguish between the effects of Ia and Ib afferents because, at rest, tendon taps are a potent stimulus for muscle spindle primary endings (cf. Chapter 2, p. 67), whereas electrical stimulation will activate Ia and Ib afferents to a similar extent. Thus, electrical stimulation of group I afferents in the median nerve and a tap applied to the FCR tendon produced a similar early facilitation of the biceps brachii tendon jerk. This was followed by an inhibition of the reflex below its control value with electrical stimulation but not with the tap (Cavallari & Katz, 1989; Fig. 6.3(*f*)). Similar results have been obtained in the lower limb after electrical

and mechanical stimulation of group I afferents from the triceps surae (Pierrot-Deseilligny *et al.*, 1981b). These results are consistent with the view that the inhibition observed after electrical stimulation is predominantly Ib in origin (even though Ia afferents may contribute to it, see pp. 260–1).

Absence of effects from cutaneous afferents

A possible role for cutaneous afferents in the inhibition has been excluded, because cutaneous stimulation mimicking the sensation elicited by the mixed nerve volley does not produce a similar inhibition (Pierrot-Deseilligny *et al.*, 1981b; Cavallari, Katz & Pénicaud, 1992).

Evidence for disynaptic transmission

Modulation of the H reflex

(i) The onset of the gastrocnemius medialis-induced inhibition of the soleus H reflex 2 ms after the expected arrival of the conditioning Ia volley at motoneuronal level can be explained almost completely by the extra peripheral conduction time of the conditioning volley, which is evoked ∼10 cm more distally. There is little need to take into account the central delay of this presumably oligosynaptic effect. Similarly, despite the interneurone(s) interposed in the inhibitory pathway, the inhibition of the FCR H reflex by conditioning volleys to the musculocutaneous or the triceps brachii nerve starts at the –1 ms ISI, i.e. earlier than the synchronous arrival of conditioning and test volleys at motoneuronal level (arrow at the –0.5 ms ISI in Fig. 6.3(*c*)). These 'too early' onsets are peculiar to the H reflex technique, which will consistently underestimate the central delay of conditioning effects (cf. Chapter 1, pp. 9–10).

(ii) The onset of the inhibition may be reliably compared to that of the early Ia excitation when there is a biphasic effect. Changes in the early gastrocnemius medialis-induced facilitation of the quadriceps H reflex with the conditioning stimulus intensity have been investigated at various ISIs, using 0.1 ms steps (Pierrot-Deseilligny *et al.*, 1981b). At early ISIs, increasing the intensity of the conditioning stimulus from 0.5 to 1 × MT resulted in a continuous increase in reflex facilitation, but Ib inhibition curtailed this continuous increase when the ISI was 0.8 ms after the onset of the reflex facilitation. Similarly, cutaneous suppression of Ib inhibition reveals the full extent of the Ia facilitation, and the onset of the cutaneous suppression is then 0.8 ms after the onset of the facilitation (Pierrot-Deseilligny *et al.*, 1981a; p. 261; Fig. 6.4(*c*)). These findings indicate that the inhibition occurs 0.8 ms later than the facilitation. Given that the heteronymous Ia excitation is monosynaptic (see Table 2.1), the inhibition is presumably mediated through a disynaptic pathway.

PSTHs of single units

(i) The suppression of the late part of the peak of homonymous Ia excitation evoked in the PSTHs of single quadriceps units by various conditioning volleys supports the above conclusion. As discussed on pp. 263–7, this suppression results from the facilitation by cutaneous and/or joint volleys of Ib interneurones activated by the homonymous femoral group I volley (cf. Marchand-Pauvert *et al.*, 2002). The suppression spares the first 0.7 ms of the monosynaptic Ia peak (Figs. 6.6(*d*)–(*g*), 6.7(*d*)–(*j*)), and this indicates an inhibitory pathway with one interposed interneurone.

(ii) When heteronymous Ib inhibition occurs without preceding Ia excitation, a method analogous to that used for estimating the central delay of heteronymous Ia excitation may be employed (cf. Chapter 2, pp. 70–2): the expected time of arrival of the heteronymous group I conditioning volley at motoneuronal level (zero on the abscissa in Fig. 6.3(*b*)) is inferred from the latency of the peak of homonymous monosynaptic Ia excitation and the difference in peripheral afferent conduction times of the homonymous Ia and conditioning heteronymous group I volleys. Figure 6.3(*b*) shows that the inhibition evoked in a FCR unit by stimulation of the musculo-cutaneous or the triceps brachii nerves starts with a central delay of ∼1 ms, consistent with

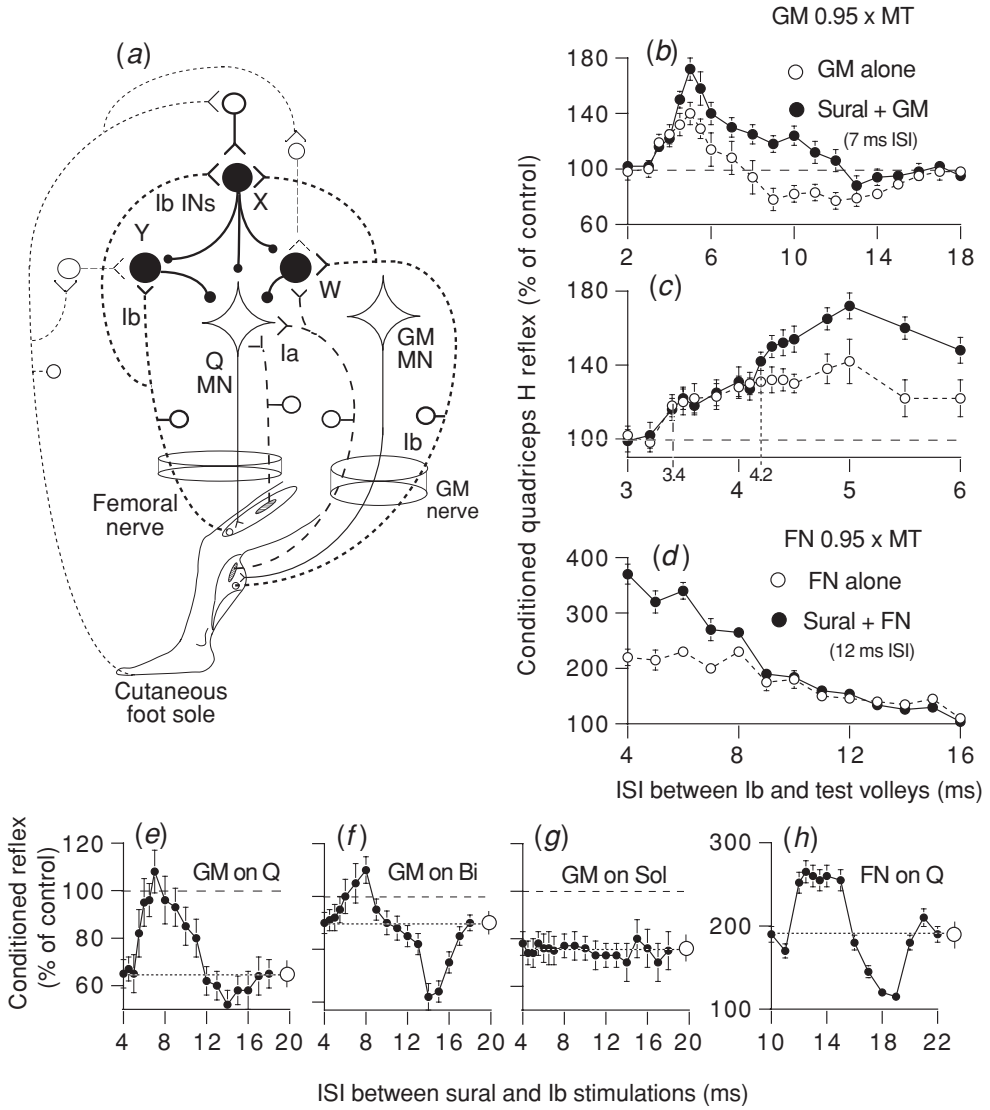


Fig. 6.4. Cutaneous suppression of Ib inhibition to motoneurones of knee muscles. (*a*) Sketch of the presumed Ib inhibitory pathways from gastrocnemius medialis (GM) and quadriceps (Q) to Q motoneurones (MN). Ib inhibitory interneurone (IN) 'X' elicits, through mutual inhibition of Ib INs, inhibition of Ib INs 'W' and 'Y' and, at rest, INs mediating cutaneous facilitation of Ib INs do not receive descending facilitation. (*b*)–(*h*) Changes in the amplitude of the conditioned H reflex expressed as a percentage of its unconditioned value (dashed horizontal lines, size of the unconditioned reflex). Each symbol represents the mean of 20 measurements. Vertical bars, ±1 SEM. (*b*)–(*d*) The amplitude of the Q H reflex conditioned by stimulation at 0.95 × MT to the GM nerve ((*b*), (*c*)) or to the femoral nerve (FN) (*d*) and plotted against the interstimulus interval (ISI) between conditioning (GM or FN) Ib and test volleys in the absence (○) and in the presence (●) of a cutaneous volley to the sural nerve at 2 × PT preceding the Ib volley by 7 ms ((*b*), (*c*)) or 12 ms (*d*). (*c*) Onset of the curve in (*b*) on an expanded abscissa (the dashed and dotted vertical lines indicate the onset of the Ia excitation and Ib inhibition, respectively; the large reflex facilitation was obtained with regular alternation of conditioned and unconditioned reflexes). (*d*) Time course of homonymous facilitation shown after the initial 4 ms period of refractoriness of Ia afferents. (*e*)–(*h*) The Ib volley (0.95 × MT) is applied to the GM nerve ((*e*)–(*g*)) or to the FN (*h*), and the ISI between the Ib and test volleys is constant (9 ms (*e*), 6 ms (*f*), 5 ms (*g*), (*h*)). The large open circles on the right of each graph and the dotted horizontal lines indicate the effects of the conditioning group I volley in the absence of cutaneous stimulation. The amplitudes of the H reflexes of Q ((*e*), (*h*)), biceps (*f*) and soleus (*g*) are plotted against the ISI between sural (2 × PT) and test volleys. Modified from Pierrot-Deseilligny *et al.* (1981a), with permission.

a disynaptic pathway (Cavallari, Katz & Pénicaud, 1992).

Ib versus reciprocal Ia inhibition

The disynaptic pathways mediating both reciprocal Ia inhibition and Ib inhibition are fed by Ia afferents. In the cat, the two inhibitions differ in two respects: (i) recurrent inhibition of Ia inhibitory interneurones but not Ib interneurones (see pp. 245–6), (ii) reciprocal Ia inhibition exists between strict antagonists operating at the same joint (however, see p. 199), whereas Ib inhibition is more widespread, directed to homonymous and synergistic motoneurones. Accordingly, in human subjects, reciprocal Ia inhibition between strict antagonists at hinge joints (ankle and elbow) is inhibited by recurrent inhibition (Chapter 5, pp. 205–8) and followed by oligosynaptic group I excitation (see p. 258), whereas Ib inhibition is not subjected to recurrent inhibition, and is generally preceded by monosynaptic Ia excitation. The absence of recurrent inhibition of the interneurones mediating reciprocal inhibition between flexors and extensors in the forearm argues against mediation via 'true' Ia inhibitory interneurones. Several other features confirm that this inhibition is mediated through the interneurones intercalated in the pathway of non-reciprocal group I inhibition, i.e. that it represents 'Ib' inhibition, not reciprocal Ia inhibition (see Chapter 5, pp. 211–14; Chapter 11, pp. 522–4).

Short duration

Figures 6.2 and 6.3 show that Ib inhibition of the test monosynaptic reflex lasts less than 10 ms. Such a short duration is due to the fact that the inhibition of the monosynaptic test reflex is very small during the decay phase of the underlying IPSP evoked by a synchronised group I volley (Araki, Eccles & Ito, 1960; Chapter 1, p. 27). Note, however, that the Ib inhibition is longer than the reciprocal Ia inhibition, probably because the pathway has a trisynaptic component unlike the Ia inhibitory pathway (see p. 245). A long-lasting inhibition should raise the possibility of another mechanism, e.g. (i) recurrent inhibition, if the conditioning stimulus evokes a motor discharge (orthodromic with the H reflex; antidromic with the M wave, cf. Chapter 4), or (ii) presynaptic inhibition of Ia afferents responsible for the test reflex, particularly with conditioning volleys in group I afferents from flexor muscles (cf. Chapter 8, p. 350).

Oligosynaptic group I excitation

In the cat, the disynaptic reciprocal Ia inhibition between antagonists is followed by a trisynaptic group I excitation. Accordingly, when conditioning the biceps brachii tendon jerk by an electrical volley to the nerve supplying triceps, the early reciprocal Ia inhibition at the –5 ms ISI is curtailed by an excitation that peaks at the –1 ms ISI (Fig. 6.3(*g*); Katz, Pénicaud & Rossi, 1991). Figure 6.3(*g*) also shows that, in contrast, a triceps tendon tap that produces a similar amount of inhibition is not followed by excitation. Again, because, at rest, tendon taps preferentially activate muscle spindle primary endings, this is consistent with the view that the excitation observed after electrical stimulation is predominantly Ib in origin. Similarly, in the lower limb, stimulation of the gastrocnemius medialis nerve evokes early reciprocal Ia inhibition of the tibialis anterior H reflex, cut short by excitation, probably of Ib origin (Fig. 6.2(*g*)).

Critique of the tests to reveal Ib effects

Biphasic effects and presynaptic inhibition of Ia terminals

The existence of a preceding monosynaptic Ia excitation allows the following low-threshold disynaptic inhibition to be attributed to Ib pathways. However, the size of the test reflex (or of the peak of Ia excitation in the PSTHs of single units) is then the result of overlapping Ia excitation and Ib inhibition. Changes in the H reflex (or in the peak of Ia excitation in the PSTHs of single units) could therefore reflect changes in Ib inhibition and/or in monosynaptic Ia

excitation, the latter modulated by presynaptic inhibition of Ia terminals. In order to distinguish between these two possibilities, it is necessary to investigate the initial part of the excitation (the first 0.7 ms), which is not contaminated by Ib inhibition. Presynaptic inhibition of the Ia excitation should affect all of the excitation, and only changes sparing the initial 0.7 ms of the excitation may be attributed to alterations in Ib inhibition (Chapter 1, pp. 14–16).

Ib inhibition from gastrocnemius medialis to soleus

This inhibition is not contaminated by Ia excitation, and therefore represents a suitable experimental paradigm to assess Ib inhibition quantitatively. However, the resulting suppression of the reflex is variable and quite weak, when present, reducing the reflex by only ~10% or less of its control value (see below) (Pierrot-Deseilligny, Katz & Morin, 1979; Yanagawa, Shindo & Nakagawa, 1991; Delwaide, Pepin & Maertens de Noordhout, 1991; Downes, Ashby & Bugaresti, 1995; Stephens & Yang, 1996).

Overestimation with regular alternation

Projections of group I afferents from ankle muscles were initially investigated by regularly alternating control and conditioned test reflexes (Pierrot-Deseilligny *et al.*, 1981b). However, regular alternation produces erroneously large results (cf. Chapter 1, p. 9). In further investigations on H reflexes and the PSTHs of single units, random alternation of unconditioned and conditioned trials has revealed the same qualitative patterns of group I projections, but they were quantitatively weaker (Fournier, Katz & Pierrot-Deseilligny, 1984; Mao *et al.*, 1984; Meunier, Pierrot-Deseilligny & Simonetta, 1993).

Electrical stimulation over muscle tendons

Stimulation over muscle tendons produces a transient suppression of on-going voluntary EMG activity of the homonymous muscle. This occurs with a relatively long latency (~55 ms in forearm extensors and ~95 ms in the tibialis anterior). The suppression was claimed to arise from Golgi tendon afferents via a polysynaptic Ib pathway (Burne & Lippold, 1996). However, most Golgi tendon organs are not located within tendons (cf. p. 245), and Priori *et al.* (1998) have presented arguments showing that the EMG silence is due not to Ib afferents but to slowly conducting (possibly group III) afferents from receptors in the tendon producing presynaptic inhibition of Ia terminals.

Organisation and pattern of connections

The organisation of Ib pathways is not easily revealed for several reasons.

(i) Ib inhibition is usually superimposed on monosynaptic Ia excitation which obscures its full revelation.

(ii) Because of occlusion, an excitation of interneurones may result in a decrease in the amount of inhibition evoked by the conditioning volley in motoneurones. This is a drawback common to all interneuronal pathways, but the risk of occlusion is particularly high here because of the extensive convergence of many different afferents and descending tracts onto Ib interneurones.

(iii) Owing to the mutual inhibition of Ib interneurones, facilitation of some Ib interneurones produces inhibition of others, and the resulting net effect assessed in motoneurones may be facilitation or suppression of Ib inhibition, according to the subset of interneurones selected (see the sketch in Fig. 6.4(*a*), where interneurone 'X' inhibits interneurones 'W' and 'Y').

Pattern and strength of Ib inhibition

Homonymous Ib inhibition

This inhibition is difficult to investigate because: (i) changes in the H reflex after a conditioning group I volley in the same nerve may be dominated by changes in axonal excitability of Ia afferents (cf.

Chapter 1, p. 11) and by the creation of a subliminal fringe of excitation in the target motoneurone pool (see Chapter 4, pp. 154–5), both of which would obscure Ib inhibition; (ii) Ib inhibition cannot be distinguished readily from the AHP when the probability of firing of single units in the peak of homonymous Ia excitation in the PSTH is high, as it usually is (see p. 79); and (iii) the voluntary contraction necessary for the PSTH depresses transmission of Ib inhibition (cf. pp. 268–71). However, the existence of a significant homonymous Ib inhibition in resting conditions can be seen under two circumstances. (i) Inferior soleus nerve stimulation allows the investigation of homonymous Ib inhibition of the soleus H reflex (Fournier, Katz & Pierrot-Deseilligny, 1983; Fig. 6.2(*b*)). The changes in excitability of Ia afferents in the afferent volley of the test reflex are then minor, probably because conditioning and test stimuli tend to activate different group I afferents (cf. Chapter 2, p. 69). (ii) At rest, a sural nerve volley, ineffective by itself, enhances the homonymous femoral-induced facilitation of the quadriceps H reflex, because it suppresses Ib inhibition to quadriceps motoneurones (Pierrot-Deseilligny *et al.*, 1981a; p. 261; Fig. 6.4(*d*)). The amount of cutaneous-induced suppression of the femoral-induced facilitation may therefore be ascribed to homonymous Ib inhibition. Note, however, that in both cases Ib inhibition is superimposed on potent homonymous Ia excitation.

Heteronymous Ib inhibition

Heteronymous Ib inhibition has been found in almost all muscle–nerve combinations tested in the lower and upper limbs (except those between strict antagonists): from inferior soleus to quadriceps (Fig. 6.2(*b*)), from gastrocnemius medialis to soleus (Fig. 6.2(*d*)), quadriceps (Fig. 6.4((*b*)) and biceps femoris (Fig. 6.2(*d*)), from pretibial flexors to biceps femoris (Fig. 6.9(*b*)), from quadriceps to soleus (Fig. 2.3(*d*)–(*f*)), from intrinsic plantar muscles to soleus and quadriceps (Fig. 10.14(*d*), (*e*)), from flexors and extensors of the wrist to biceps and triceps brachii (Fig. 6.3(*f*)), biceps and triceps brachii to FCR (Fig. 6.3(*b*), (*c*)), FCU and ECR, and from intrinsic hand muscle to forearm muscles (see Pierrot-Deseilligny *et al.*, 1981b; Hultborn *et al.*, 1987; Marque *et al.*, 2001; Cavallari & Katz, 1989; Cavallari, Katz & Pénicaud, 1992; Marchand-Pauvert, Nicolas & Pierrot-Deseilligny, 2000).

The finding that Ib inhibition is generally relatively weak is probably related to technical limitations

Ib inhibition is usually superimposed on monosynaptic Ia excitation which obscures the full extent of the inhibition. Stimulation must be subthreshold for the H and M responses, in order to avoid recurrent inhibition, and therefore activates only some group I afferents (see Chapter 2, pp. 77–8). Thus, even in the absence of monosynaptic Ia excitation, as in the projections from gastrocnemius medialis to soleus motoneurones, Ib inhibition is weak (see p. 256). Yet, Ib inhibition from biceps and triceps brachii to forearm muscles may be strong (Fig. 6.3(*b*)), in agreement with results obtained in the cat, in which Ib inhibition is more pronounced in the forelimb than in the hindlimb (Illert, Lundberg & Tanaka, 1976).

Organisation in subsets with regard to the target motoneurones of Ib afferents

Ib pathways fed by afferents from triceps surae and projecting to soleus and quadriceps motoneurones are differentially controlled after cutaneous stimulation of the foot (at rest, p. 261) or during voluntary contraction involving selectively the triceps surae (pp. 272–3). Such a differential control implies that Ib inhibition from a given muscle is mediated to various motoneurone pools by separate subsets of Ib interneurones, a divergent organisation that was first established in human experiments (Fournier, Katz & Pierrot-Deseilligny, 1983) before being confirmed in the cat (see Jankowska, 1992).

Convergence of Ib afferents from different muscles

(i) In the lower limb, convergence of group I volleys from triceps surae and quadriceps onto

common Ib interneurones has been found, but in only a limited number of experiments, using the spatial facilitation technique and assessing the excitability of the target motoneurones with the soleus or the quadriceps H reflex (cf. Chapter 1; E. Fournier & E. Pierrot-Deseilligny, unpublished data). This scarcity could reflect occlusion at interneuronal level and/or mutual inhibition of Ib interneurones (see above). The convergence of group I volleys from gastrocnemius medialis and tibialis anterior onto inhibitory interneurones projecting to soleus motoneurones reported by Schieppati, Romano & Gritti (1990) has not been confirmed by others (Iles & Pisini, 1992b; Downes, Ashby & Bugaresti, 1995).

(ii) In the upper limb, there is convergence on the interneurones mediating the disynaptic non-reciprocal group I radial-induced inhibition of FCR motoneurones of group I volleys from biceps and triceps brachii and from median-innervated muscles (Aymard *et al.*, 1995; Wargon *et al.*, 2005, see Chapter 5, pp. 212–13).

Conclusions

For technical reasons, Ib inhibition is difficult to investigate in homonymous pathways, and is weak and underestimated in heteronymous pathways, although present in all nerve-muscle combinations tested. There is evidence that Ib afferents from different muscles converge onto common Ib interneurones, but there is also evidence for divergence in Ib pathways, since Ib inhibition from a given muscle is distributed to different motor nuclei through different subsets of interneurones.

Oligosynaptic group I excitation

Oligosynaptic group I excitation of antagonists operating at the same joint

Unequivocal oligosynaptic Ib excitation has only been reported in humans between antagonistic muscles at the same joint. The most frequent oligosynaptic group I excitation so far described is that following the reciprocal Ia inhibition between elbow flexors and extensors. A Ib origin appears likely because it is not evoked by a tendon tap (Katz, Pénicaud & Rossi, 1991; Fig. 6.3(*g*)). This excitation is greater from biceps to triceps than in the reverse direction. At wrist level, the initial group I inhibition between flexors and extensors can also be followed by a trend to facilitation that has a slightly higher threshold (Cavallari *et al.*, 1985; Fig. 6.5(*g*)). This could be Ib in origin. If so, there would be a non-reciprocal group I inhibition followed by an oligosynaptic group I excitation between these muscles, which can function as synergists or antagonists (see Chapter 11, pp. 522, 525). In the lower limb, oligosynaptic group I excitation is weak and inconstant from gastrocnemius medialis to tibialis anterior (Pierrot-Deseilligny *et al.*, 1981b; Fig. 6.2(*g*)). In contrast, there is no low-threshold short-latency excitation of the soleus H reflex after stimulation of the deep peroneal nerve in healthy subjects (Pierrot-Deseilligny *et al.*, 1981b; Crone *et al.*, 1987). It is therefore possible that the excitation found in the PSTHs of single soleus units after common peroneal stimulation (Mao *et al.*, 1984) was due to monosynaptic excitation of soleus motoneurones by Ia afferents in the superficial peroneal nerve (see Chapter 2; Table 2.1; Fig. 2.4(*c*)). The finding that the peroneal-induced oligosynaptic group I excitation of soleus is only revealed in patients with spasticity suggests that the activity in the relevant pathway is normally suppressed by a tonic inhibitory control that is disrupted in these patients (p. 278).

Common peroneal effects on quadriceps motoneurones

Stimulation of the common peroneal nerve produces potent excitation of quadriceps motoneurones, and this has been recorded consistently, whether as changes in the H reflex (Bergmans, Delwaide & Gadea-Ciria, 1978; Pierrot-Deseilligny *et al.*, 1981b), or as the modulation of the on-going voluntary

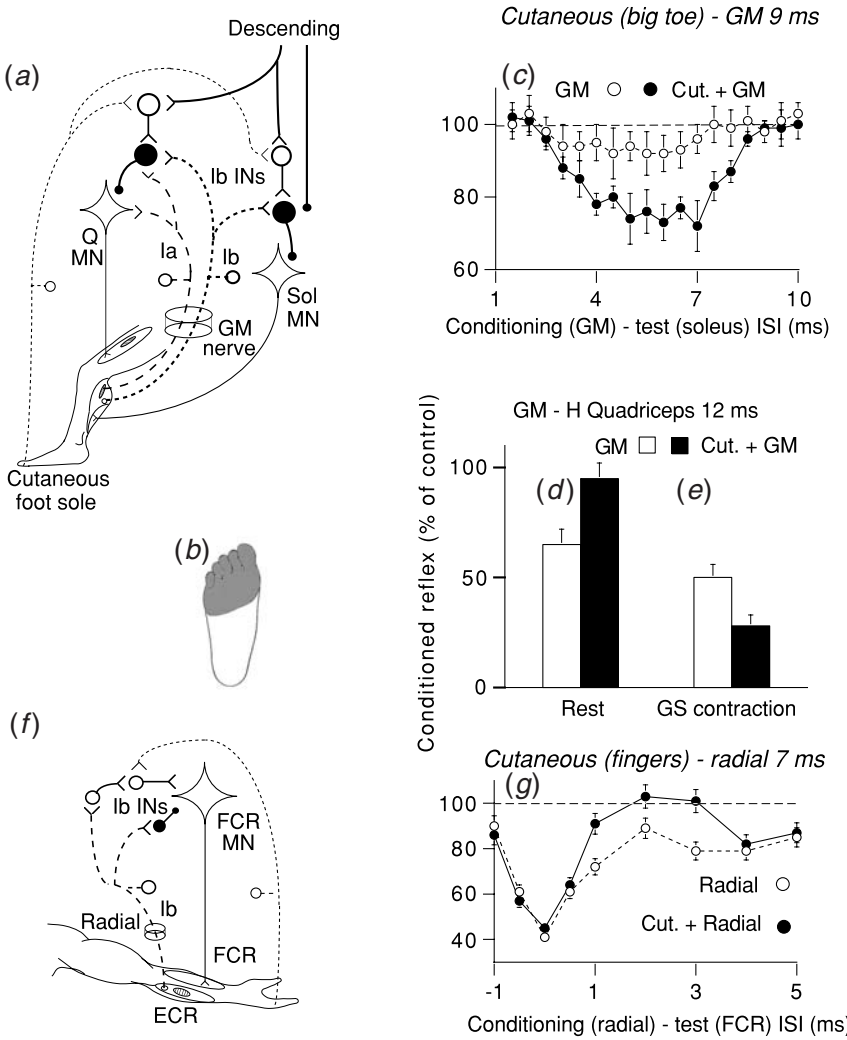


Fig. 6.5. Cutaneous facilitation of transmission in Ib pathways. (*a*) Sketch of the presumed Ib inhibitory pathways from gastrocnemius medialis (GM) to soleus (Sol) and quadriceps (Q) motoneurones (MN). During a selective voluntary contraction of gastrocnemius-soleus (GS), descending tracts depress the transmission in the pathway of Ib inhibition to Sol MNs (at a pre- or post-synaptic level), but facilitate the interneurones (INs) mediating cutaneous facilitation of 'Ib' INs. (The pathway of cutaneous suppression of Ib inhibition to Q MNs at rest, sketched in Fig. 6.4(*a*), is not represented.) (*b*) The grey area indicates the skin field of the foot sole from which cutaneous facilitation of GM-induced Ib inhibition is obtained during triceps surae contraction. (*c*), (*d*), (*e*), (*g*) Changes in the amplitude of the conditioned H reflex expressed as a percentage of its unconditioned value. Each symbol represents the mean of 20 measurements. Vertical bars ±1 SEM ((*c*), (*g*)) 1 SEM ((*d*), (*e*)). (*c*)–(*e*) Ib inhibition elicited by GM stimulation at 0.95 × MT of the H reflexes of Sol ((*c*), time course during GS voluntary contraction) and Q (12 ms ISI; (*d*) at rest, (*e*) during GS voluntary contraction) in the absence (○, □) and in the presence (●, ■) of cutaneous stimulation of the sole of the big toe at 3 × PT preceding GM stimulation by 9 ms. (*f*) Sketch of the pathway of Ib inhibition and excitation from ECR to FCR MNs. (*g*) Time course of the amplitude of the FCR H reflex conditioned by radial nerve stimulation at 0.95 × MT in the absence (○) and in the presence (●) of cutaneous stimulation to the dorsal side of fingers III–IV at 2 × PT, preceding the radial stimulation by 7 ms. Modified from Pierrot-Deseilligny & Fournier (1986) (*c*), Pierrot-Deseilligny, Bergego & Katz (1982) ((*b*), (*d*), (*e*)), Cavallari *et al.* (1985) (*g*), with permission.

EMG activity of the quadriceps (Brooke & McIlroy, 1989). The low threshold (~0.6 × MT) and the apparently short latency of this excitation led the authors to attribute it to segmental disynaptic Ib excitation. However, as is usual (cf. pp. 9–10), the central delay of the excitation was underestimated using the H reflex, and could not be measured accurately in the averaged on-going EMG. The central delay of this facilitation has been recalculated with a more precise method, i.e. comparing the latency of the peak of peroneal-induced excitation elicited in single quadriceps units to the expected time of arrival of the peroneal group I volley at motoneuronal level (cf. Chapter 2, pp. 70–2). While the central delay of a segmental group I effect should not exceed 2 ms even if trisynaptic, the central delay for the peroneal-induced excitation of quadriceps motoneurones has invariably been found to be 3–4 ms (Forget *et al.*, 1989). There is now considerable evidence that this longer-latency excitation is mediated by lumbar propriospinal neurones co-activated by group I and group II afferents (see Chapter 10, pp. 494–5). The peroneal facilitation of the quadriceps H reflex may be preceded by an earlier inhibition, initially reported using regular alternation of unconditioned and conditioned reflexes (Pierrot-Deseilligny *et al.*, 1981b). With random alternation of the reflexes, weak early inhibition is sometimes still observed, especially with selective stimulation of the *superficial* peroneal nerve (Forget *et al.*, 1989). The low threshold (0.5–0.6 × MT) and short latency of the effect (~1 ms) are consistent with a segmental Ib inhibitory pathway. It is of interest that, as usual before Ib inhibition, there is evidence for peroneal monosynaptic Ia excitation of quadriceps motoneurones (cf. Table 2.1).

Conclusions

Oligosynaptic group I excitation is rare and weak, and has been consistently found only between antagonistic muscles operating at the same joint, especially at elbow level. Low-threshold peroneal excitation of quadriceps motoneurones is not mediated through segmental Ib pathways.

Convergence of Ia afferents onto interneurones mediating Ib inhibition

High-frequency vibration of the tendon of the 'conditioning' muscle

Vibration has been used to demonstrate a contribution of Ia afferents to so-called Ib inhibition. Such vibration can raise the electrical threshold of Ia afferents from the vibrated muscle above that of Ib fibres (see p. 245). When the threshold of Ia afferents from the triceps brachii had been raised by vibration of the triceps tendon, the threshold of the triceps-induced inhibition of FCR H reflex was increased, and the inhibition was much less pronounced (Cavallari, Katz & Pénicaud, 1992; Fig. 6.3(*d*)). This suggests that Ia afferents contributed to the heteronymous 'Ib' inhibition from triceps to FCR in the control situation (although an alternative explanation would be a response of Ib afferents to vibration, as may occur at least with some human Ib afferents; see Chapter 3, pp. 130–1).

Use of presynaptic inhibition of Ia terminals

Presynaptic inhibition of Ia terminals elicited by a brief burst of tibialis anterior vibration (cf. Chapter 8, pp. 341–2) has been used to reduce the Ia inflow selectively (Rossi, Decchi & Ginanneschi, 1999). The vibration-induced Ia volleys should produce presynaptic inhibition of Ia afferents but not Ib afferents (see p. 248). Given the parallelism between presynaptic inhibition of Ia terminals on motoneurones and on Ia inhibitory interneurones (Enriquez-Denton *et al.*, 2000), it is likely that the vibration-induced Ia activity would produce similar gating of Ia terminals on Ib interneurones. Reducing the Ia inflow by this method significantly decreases the gastrocnemius medialis-induced Ib inhibition of the soleus H reflex. Again, however, these results depend

on the extent to which vibration applied transversely to the tendon in human subjects will activate primary spindle endings selectively (Chapter 3, pp. 130–1).

Conclusions

These findings indicate that, in humans as in the cat, there may be an important contribution of Ia afferents to 'Ib' inhibition which, strictly speaking, should then be termed 'non-reciprocal group I inhibition' in human subjects as well as in the cat. This does not imply that Ia afferents are solely responsible for the component of the reflex inhibition that was suppressed by high-frequecy vibration or presynaptic inhibition of Ia terminals. The response of the relevant interneurones depends on spatial summation of Ia and Ib inputs, and removal of either could have a quantitatively large effect. The possible functional role of the convergence of Ia afferents onto Ib interneurones is discussed on p. 272.

Effects of low-threshold cutaneous afferents

In the low spinal cat, the dominant effect of cutaneous afferents is disynaptic facilitation of interneurones conveying Ib inhibition (Lundberg, Malmgren & Schomburg, 1977). However, owing to the mutual inhibition of these interneurones, trisynaptic cutaneous IPSPs may also be recorded in Ib interneurones (see Brink *et al.*, 1983). Accordingly, under different circumstances, the same cutaneous stimulation can produce either suppression or facilitation of Ib inhibition.

Cutaneous suppression of Ib inhibition to knee muscles at rest

At rest, cutaneous volleys can depress Ib inhibition to motoneurones of knee muscles (Pierrot-Deseilligny *et al.*, 1981a). Evidence for cutaneous suppression is provided by the effect of a sural nerve volley on the gastrocnemius medialis-induced Ib inhibition of the quadriceps H reflex. In the control situation, the monosynaptic Ia excitation of the quadriceps H reflex is followed by Ib inhibition, but the sural volley suppressed the inhibition, thereby revealing the full extent of monosynaptic Ia excitation (Fig. 6.4(*b*)). Figure 6.4(*c*) illustrates the onset of the time course on an expanded abscissa, and shows that the suppression of Ib inhibition starts to modify the gastrocnemius medialis-induced effects 0.8 ms after the beginning of the monosynaptic Ia excitation, i.e. at the onset of the disynaptic Ib inhibition. This indicates cutaneous depression of transmission in the pathway of disynaptic Ib inhibition. Sural volleys similarly depress transmission of Ib inhibition from the inferior soleus or femoral nerves to quadriceps, and from the gastrocnemius medialis nerve to biceps femoris (Fig. 6.4(*d*)–(*f*)). In contrast, there is no change in the Ib inhibition of soleus motoneurones induced by group I volleys in the gastrocnemius medialis or inferior soleus nerves (Fig. 6.4(*g*)). Similar effects (and absence of effects in soleus) have been obtained from stimulation of various skin fields on the foot sole. The time course of the cutaneous effects when the ISI between cutaneous and conditioning group I volleys was varied shows an early suppression lasting for a few milliseconds followed by facilitation (Fig. 6.4(*e*), (*f*), (*h*)). Calculations based on the distances from stimulation sites to the spinal cord and the afferent conduction times of the cutaneous and group I volleys suggest that the early suppression is mediated through a short oligosynaptic pathway (see Pierrot-Deseilligny *et al.*, 1981a). At such a brief latency and for so short a duration, the suppression cannot be exerted presynaptically; it must result from a post-synaptic mechanism. A possible circuit for the cutaneous suppression is sketched in the diagram in Fig. 6.4(*a*). It is presumed that, at rest, in the absence of descending activity (see below), cutaneous excitation is dominant on a subpopulation of interneurones, e.g. 'X', inhibiting, through mutual inhibition of Ib interneurones, subpopulations 'W' and 'Y'. As a result, summation of the cutaneous and group I inputs causes the subpopulation of interneurones 'X' to discharge and to inhibit

interneurones 'W' and 'Y', reducing Ib inhibition to quadriceps motoneurones.

Cutaneous facilitation of transmission in reflex pathways from Ib afferents

However, the most frequently observed effect of low-threshold cutaneous volleys is facilitation of transmission in the pathway of Ib inhibition to motoneurones.

Cutaneous facilitation at rest

Even at rest, cutaneous facilitation of Ib inhibition to knee muscle motoneurones follows the initial cutaneous suppression. This effect is potent from gastrocnemius medialis to biceps and for homonymous quadriceps group I inhibition (Pierrot-Deseilligny *et al.*, 1981a; Fig. 6.4(*f*), (*h*)).

Cutaneous facilitation of gastrocnemius medialis-induced Ib inhibition during voluntary contractions of triceps surae

Gastrocnemius medialis-induced Ib inhibition to soleus is decreased with respect to rest during gastrocnemius-soleus voluntary contractions (see pp. 269–70), but is restored by cutaneous stimulation to the sole of the big toe (Pierrot-Deseilligny & Fournier, 1986; Fig. 6.5(*c*)). The same cutaneous volley, which suppresses the gastrocnemius medialis-induced Ib inhibition of the quadriceps H reflex at rest (see above; not illustrated in the sketch of Fig. 6.5(*a*)), facilitates Ib inhibition of quadriceps during contractions of gastrocnemius-soleus, i.e. the contraction produces a reversal in the cutaneous control of Ib inhibition (Pierrot-Deseilligny, Bergego & Katz, 1982; Fig. 6.5(*d*), (*e*)). This cutaneous facilitation of gastrocnemius medialis-induced Ib inhibition to soleus and quadriceps has been disclosed only when (i) the voluntary contraction involves the triceps surae, and (ii) the cutaneous stimulation is applied to the anterior part of the foot sole (grey area in Fig. 6.5(*b*)). The effects of the triceps surae contraction probably result from descending facilitation of first-order interneurones transmitting cutaneous facilitation to the relevant Ib interneurones (see the sketch in Fig. 6.5(*a*)).

Cutaneous facilitation of homonymous Ib inhibition of quadriceps has been observed during strong contractions of quadriceps

The facilitation of the quadriceps H reflex produced by cutaneous stimulation of the superficial peroneal nerve at rest is reversed to inhibition during a strong quadriceps contraction (Fig. 6.7(*b*)). The inhibition during contraction is the result of cutaneous facilitation of Ib inhibition activated by the test volley for the quadriceps H reflex (Marchand-Pauvert *et al.*, 2002). Such an inhibition of the quadriceps H reflex during quadriceps contraction has not been observed after stimulation of the sural nerve or of the foot sole (V. Marchand-Pauvert, G. Nicolas & E. Pierrot-Deseilligny, unpublished data).

Cutaneous facilitation of transmission in Ib pathways has also been observed in the upper limb

The initial radial-induced inhibition of the FCR H reflex is curtailed by a trend to facilitation attributed to Ib excitation (cf. p. 258), and this facilitation is enhanced by a cutaneous stimulus to the dorsal surface of the fingers (Cavallari *et al.*, 1985; Fig. 6.5(*g*)). Similar cutaneous facilitation has not been observed from the palmar side of the fingers.

Conclusions

Both suppression and facilitation of Ib inhibition have been observed after the same cutaneous stimulation in various situations, and this suggests that interneurones transmitting Ib inhibition to a given motoneurone pool are organised in subpopulations, which may be differentially selected in different tasks, through descending control and mutual inhibition of Ib interneurones. It will be argued that cutaneous facilitation of Ib inhibition might be used to curtail an exploratory movement (see pp. 271–2),

while the cutaneous suppression of Ib inhibition to quadriceps but not to soleus motoneurones by afferents from the foot sole might be related to the different role of these muscles in bipedal walking (see pp. 273–4).

Facilitation of Ib inhibition by joint afferents

So far, the effects of joint afferents have only been investigated on the pathways of Ib inhibition to quadriceps motoneurones.

Facilitation of homonymous Ib inhibition by joint afferents

Conditioning stimulation can be applied to the lateral articular nerve of the knee joint, which contains mainly joint afferents (Marchand-Pauvert *et al.*, 2002). Stimulation of joint afferents facilitates the quadriceps H reflex during weak quadriceps contractions, but this can be reversed to inhibition during strong contractions (Fig. 6.6(*b*)). However, during strong contractions, the same joint afferent volley facilitates the on-going voluntary EMG recorded in the quadriceps at corresponding central delays (Fig. 6.6(*c*)). The facilitation of the on-going EMG probably results from facilitation of motoneurones by joint afferents, as has been described in the cat after rubral stimulation (Hongo, Jankowska & Lundberg, 1969; sketch in Fig. 6.6(*a*)). The discrepancy between the effects on the EMG and H reflex during strong quadriceps contractions is explained by the existence of an inhibitory mechanism gating the afferent volley of the test reflex. Investigations performed on the PSTHs of single units have allowed this mechanism to be defined. Fig. 6.6(*d*)–(*f*) shows that the peak of homonymous monosynaptic Ia excitation evoked by femoral nerve stimulation in a voluntarily active vastus lateralis unit was reduced when it was preceded by an articular volley, which by itself did not modify the firing probability of the unit. The difference between the effect on combined stimulation and the sum of effects of separate stimuli shows that the suppression spared the first 0.8 ms of the femoral group I excitation (Fig. 6.6(*g*), between the dashed and dotted vertical lines). Because of this initial sparing, presynaptic inhibition of femoral Ia terminals by the articular volley may be ruled out (cf. Chapter 8, pp. 346–7). In contrast, the 0.8 ms delay is consistent with disynaptic post-synaptic inhibition (see p. 253). Recurrent inhibition produced by the discharge of the unit could not suppress the discharge of that same unit, and a Renshaw origin of the inhibition is unlikely. Gating of the femoral volley is therefore likely, and this is probably due to convergence of joint afferents and of group I afferents in the femoral volley onto inhibitory interneurones projecting to quadriceps motoneurones (see the sketch in Fig. 6.6(*a*)). Similar effects were observed with joint afferents from the ankle travelling in the deep peroneal nerve (Chapter 1, pp. 14–16 and 27 Figs. 1.7(*c*)–(*f*), 1.12(*b*), (*c*)).

Facilitation of heteronymous Ib inhibition by joint afferents

The effects of increased pressure in the knee joint caused by intra-articular infusion of saline (inducing no sensation of pain) have been investigated on the quadriceps H reflex (Iles, Stokes & Young, 1990). Increasing pressure progressively decreases the quadriceps H reflex both at rest and during quadriceps contractions. Joint distension also produces spatial facilitation of Ib inhibition of the quadriceps H reflex from group I afferents in the posterior tibial nerve. Inhibition of the H reflex can therefore be attributed to facilitation by knee joint afferents of interneurones mediating Ib inhibition to quadriceps motoneurones.

Conclusions

Joint afferents facilitate transmission of Ib inhibition to motoneurones. This facilitation of Ib inhibition could play a role in the relaxation of a muscle when joint afferents are activated in hyperflexion or -extension (see p. 272). Facilitation of Ib inhibitory interneurones by joint afferents could also have a protective role in preventing excessive contraction

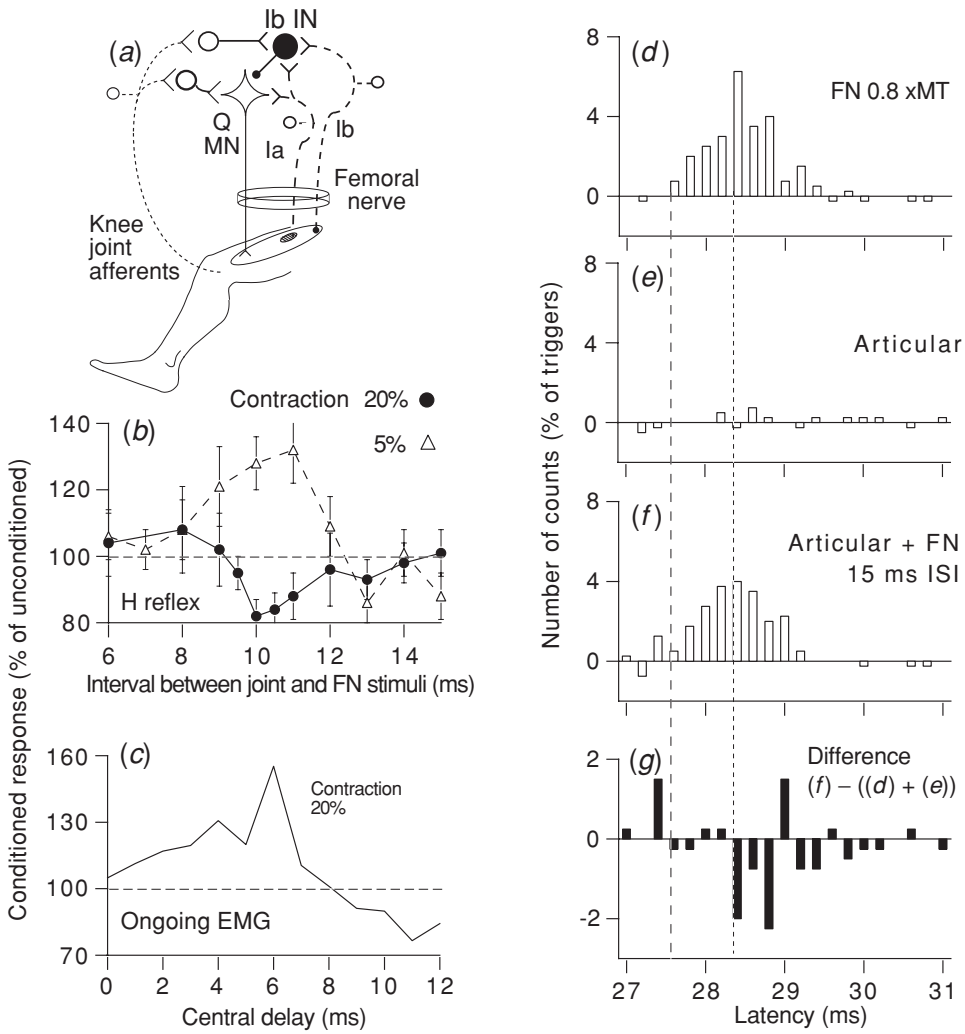


Fig. 6.6. Facilitation of autogenetic Ib inhibition of quadriceps by knee joint afferents. (*a*) Sketch of the presumed pathways. Ib and Ia afferents from quadriceps (Q) and knee joint afferents converge onto common Ib interneurones (INs) projecting onto Q motoneurones (MN). There is also a pathway mediating joint afferent excitation of MNs (revealed after rubral stimulation in the cat). (*b*) The time course of the effects of stimulation of the lateral articular nerve of the knee joint (for the technique, see Marchand-Pauvert *et al.*, 2002) on the Q H reflex during weak and strong Q contractions (5% MVC, △, and 20% MVC, ●). Each symbol is the mean of 20 measurements; vertical bars ±1 SEM. (*c*) Effects of the same articular stimulation during strong contractions at 20% MVC on the on-going averaged rectified quadriceps EMG (100 sweeps, 1 kHz sampling rate, expressed as a percentage of integrated control EMG, with the zero central delay corresponding to the expected arrival of the conditioning volley at spinal level). (*d*)–(*g*) PSTHs (after subtraction of the background firing, 0.2 ms bin width) of a single voluntarily activated vastus lateralis unit after separate stimulation of the femoral nerve ((*d*) at 0.8 × MT) and of the lateral articular nerve of the knee joint (*e*), and combined stimulation ((*f*) 15 ms ISI). (*g*) The suppression of the FN group I excitation, calculated as (*f*) – ((*d*) + (*e*)). Note the lack of suppression in the initial bins of the FN group I excitation (i.e., in the bins between the dashed and dotted vertical lines indicating the onset of the Ia excitation and the inhibition, respectively). Modified from Marchand-Pauvert *et al.* (2002), with permission.

from damaging the ligaments and capsule of the joint. The finding that the facilitation of autogenetic Ib inhibition of quadriceps motoneurones by knee joint afferents is seen only during strong quadriceps contractions (cf. above) would be consistent with this view.

Effects from nociceptive afferents

Tonic activation of nociceptors has been shown to produce changes in Ib inhibition from gastrocnemius medialis to both soleus and quadriceps motoneurones. These changes increase in parallel with the sensation of pain. Opposite changes have been observed from the skin (dorsal surface of the foot) and muscle (extensor digitorum brevis): stimulation of nociceptive cutaneous afferents increases Ib inhibition, whereas stimulation of nociceptive muscle afferents decreases it (Rossi & Decchi, 1995, 1997; Rossi *et al.*, 1999). Given that in the cat nociceptive afferents can excite and inhibit Ib interneurones (see Jankowska, 1992) and alter presynaptic inhibition of Ia and Ib afferents (see Rudomin & Schmidt, 1999), the exact mechanism of these changes is difficult to establish.

Descending effects

Corticospinal excitation

Spatial interactions have been found between cortically evoked and Ib inhibitions of the soleus H reflex (Iles & Pisini, 1992b). When cortical and Ib inhibitory actions are weak, the interaction is facilitatory, suggesting convergence onto interneurones mediating Ib inhibition, as demonstrated in the cat with a similar method (monosynaptic reflex testing) by Lundberg & Voorhoeve (1962). The facilitation is, however, weak and equivocal. Increasing the strength of cortical and group I inhibitory actions reverses the interaction, suppressing the inhibition. This has been interpreted as occlusion in Ib pathways, but might also reflect mutual inhibition of Ib interneurones.

Vestibular facilitation of Ib inhibition

Spatial interaction has also been found between gastrocnemius medialis-induced Ib inhibition and the inhibition of the soleus H reflex evoked by galvanic stimulation of vestibular afferents, producing a forward sway (Iles & Pisini, 1992a). Here also, the interaction is facilitatory when the inhibitions are weak, but reverses to occlusion when they are strong, providing evidence for convergence of vestibular signals onto interneurones mediating Ib inhibition.

Multiple convergence onto common interneurones

In the above sections, multiple peripheral and descending inputs have been shown to produce facilitation or inhibition of interneurones mediating Ib inhibition to motoneurones. The extent to which different inputs converge on the same subpopulations of interneurones has been approached by activating Ib inhibitory interneurones to quadriceps motoneurones by a femoral volley and combining this homonymous group I volley with various other inputs. Such experiments have been performed at rest and during voluntary contractions of different force (Marchand-Pauvert *et al.*, 2002).

Strong contractions

During strong contractions, cutaneous and joint afferents facilitate the transmission of homonymous Ib inhibition of quadriceps motoneurones (cf. pp. 262–3). The reasons why convergence of femoral group I and joint or cutaneous volleys is revealed only during strong contractions of the target muscle are discussed below.

Weak contractions

During weak contractions of the quadriceps, involving only one detectable unit, the convergence may be still demonstrable when there is convergence of several different afferent inputs. Thus, Fig. 6.7(*d*)–(*j*) shows that the peak of homonymous monosynaptic

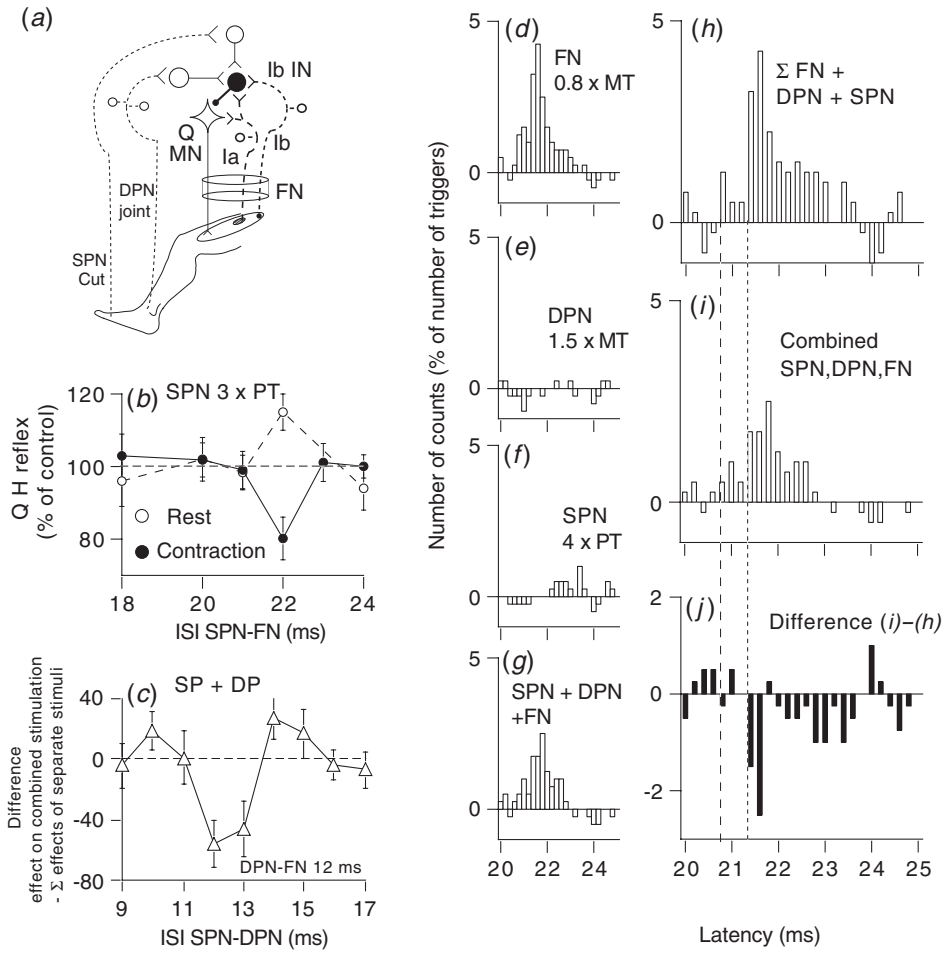


Fig. 6.7. Multiple convergence onto 'Ib' inhibitory interneurones. (*a*) Sketch of the presumed pathways. Ib and Ia afferents from quadriceps (Q) in the femoral nerve (FN), joint afferents in the deep peroneal (DPN) and cutaneous (Cut) afferents in the superficial peroneal (SPN) nerves converge onto common Ib interneurones (INs) projecting onto Q motoneurones (MN). Pathways through which separate stimulation of DP and SP nerves evoke facilitation of Q MNs are not represented. (*b*), (*c*) Changes in the amplitude of the Q H reflex as a percentage of its unconditioned value. Each symbol is the mean of 20 measurements. Vertical bars, ±1 SEM. (*b*) Effects of SP volleys at 3 × PT on the H reflex, at rest (○) and during tonic Q contraction (●, 20% of MVC) plotted against the ISI. (*c*) Difference between the effects of combined stimulation of DP (1.5 × MT, 12 ms ISI) and SP (5 × PT, variable ISI) and the sum (Σ) of effects of separate stimuli *at rest*, plotted against the ISI between SP and DP stimuli. Facilitation elicited by separate DP stimulation is not illustrated. (*d*)–(*j*) PSTHs (after subtraction of the background firing, 0.2 ms bin width) of a single voluntarily activated vastus lateralis unit after separate stimulation of the FN ((*d*) at 0.8 × MT), the DPN ((*e*) at 1.5 × MT), and the SPN ((*f*) at 4 × PT), and combined stimulation ((*g*) ISIs of 12 and 25 ms, respectively). (*h*) The sum (Σ) of the counts in histograms (*d*), (*e*) and (*f*). (*i*) Same data as in (*g*), but on a different scale. (*j*) The suppression of the FN group I excitation, calculated as (*i*)–(*h*). Note the lack of suppression in the initial bins of the peak of femoral excitation (i.e. in the bins between the dashed and dotted vertical lines indicating the onset of the Ia excitation and the inhibition, respectively). Modified from Marchand-Pauvert *et al.* (2002), with permission.

Ia excitation evoked by femoral nerve stimulation in a voluntarily activated vastus lateralis unit was reduced (*g*) when it was preceded by combined volleys from the deep and superficial peroneal nerves, which by themselves did not modify (or even increased) the firing probability of the unit ((*e*), (*f*)). If anything, in the absence of the femoral group I volley, combined stimulation of deep and superficial nerves produced some facilitation in the PSTH (not illustrated). This indicates that convergence of the two conditioning volleys with the femoral group I volley is required for the inhibition to manifest itself. Here again, the difference between the effect on combined stimulation (*i*) and the sum of effects of separate stimuli (*h*) reveals a profound suppression that spares the first 0.6 ms of the femoral group I excitation (*j*). This initial sparing confirms the convergence of the different volleys onto interneurones that are intercalated in a disynaptic inhibitory pathway to motoneurones and are fed by homonymous group I afferents, i.e. in the pathway of non-reciprocal group I inhibition to quadriceps motoneurones. When the interval between the two conditioning volleys was varied, the suppression due to convergence of the deep and superficial peroneal volleys occurred only over a narrow range of ISIs (1–2 ms). A similar convergence has been observed when combining afferent volleys in the superficial (or the deep) peroneal and the lateral articular nerve of the knee joint.

Resting conditions

At rest, stimulation of either the superficial or the deep peroneal nerves at appropriate ISIs and intensities facilitates the quadriceps H reflex (Figs. 6.7(*b*) and Fig. 7.4(*b*), respectively). Yet, when the two conditioning volleys were combined, the facilitation produced by either volley alone was reversed to significant suppression (Fig. 6.7(*c*)). The reversal was not due to occlusion in interneurones, because combined stimulation reduced the test reflex below its control value. Thus, suppression of the quadriceps H reflex, due to convergence of conditioning volleys in both deep and superficial peroneal nerves with the femoral test volley may be observed at rest. The brief duration of the inhibition of the quadriceps H reflex elicited by combined deep and superficial peroneal volleys in Fig. 6.7(*c*) is consistent with the narrow range of ISIs over which the suppression due to convergence of the same volleys occurred in PSTH experiments (see above).

Conclusions: necessity for convergence of multiple inputs

The above findings indicate that group I afferents in the femoral nerve converge with various conditioning joint and cutaneous volleys onto Ib interneurones projecting to quadriceps motoneurones. At rest, or during weak contractions, this convergence can only be disclosed when two conditioning volleys, articular and cutaneous, which excite Ib interneurones through first-order interneurones (see the sketch in Fig. 6.7(*a*)), are combined with the femoral volley. Such a convergence between the different conditioning volleys may occur at last-order (Ib) interneurones as well as first-order interneurones. However, during strong contractions, a single conditioning input (articular or cutaneous) can facilitate the Ib inhibition elicited by the femoral volley. The most parsimonious explanation would be that during such contractions there is a descending facilitation of the first-order interneurones mediating the conditioning (cutaneous or articular) input (Fig. 6.5(*a*)). Thus, descending voluntary drives would have two effects: (i) depression of transmission in Ib inhibitory pathways, which would prevent the Ib discharge from the contracting muscle from hindering the discharge of active motoneurones; and (ii) increased ability of peripheral afferents to restore transmission through interneurones mediating this Ib inhibition, thus allowing autogenetic inhibition to reappear when necessary to modulate contractions (see below, and Chapter 11, p. 515).

Motor tasks and physiological implications

Human tendon organs respond readily in isometric voluntary contractions and usually discharge

strongly during shortening contractions, even in the absence of an external load. The discharge increases during concentric contractions as EMG builds up (Burke, Hagbarth & Löfstedt, 1978). Changes in transmission in oligosynaptic pathways fed by Ib afferents during various motor tasks in humans have provided insight into the control of these pathways. The controls so disclosed suggest that these pathways might serve several functions. However, functional interpretations drawn from such experiments must be made with care because it cannot be taken for granted that the response of interneurones fed by Ib afferents to a natural desynchronised input would be the same as to the phasic synchronised input produced by artificial electrical volleys explored in the experiments below.

Suppression of Ib inhibition to voluntarily activated motoneurones

Changes in transmission of Ib inhibition to voluntarily active motoneurones have been investigated for the pathways from and to triceps surae during selective voluntary contractions of this muscle (Fournier, Katz & Pierrot-Deseilligny, 1983; Pierrot-Deseilligny & Fournier, 1986; Stephens & Yang, 1996). The effects of conditioning cutaneous and articular volleys on Ib interneurones have been investigated on the pathways of Ib inhibition to quadriceps motoneurones (see pp. 265–7). Accordingly, comparisons of the changes in the different situations discussed below rely on the assumption that results obtained for one motor nucleus apply to the other.

Evidence for suppression of the inhibition to voluntarily activated motoneurones

Homonymous Ib inhibition of soleus motoneurones is suppressed during tonic contractions of gastrocnemius-soleus

Thus, the early monosynaptic Ia facilitation of the soleus H reflex produced by stimulation of the inferior soleus nerve is followed by overt Ib inhibition at rest, but this inhibition is markedly depressed during a tonic contraction involving only the triceps surae (Fournier, Katz & Pierrot-Deseilligny, 1983; Fig. 6.8(*b*)). The stronger the force of the tonic contraction, the greater the suppression of the Ib inhibition (Pierrot-Deseilligny & Fournier, 1986; Fig. 6.8(*d*)).

Heteronymous Ib inhibition from quadriceps to soleus

During selective tonic contractions of triceps surae, Ib inhibition of the soleus H reflex produced by stimulation of the femoral nerve is also suppressed, and this reveals the heteronymous monosynaptic Ia excitation more fully (Pierrot-Deseilligny & Fournier, 1986). This suppression probably reflects the convergence of group I afferents from quadriceps and triceps surae onto common Ib interneurones projecting onto soleus motoneurones (cf. pp. 257–8).

Possible mechanisms underlying changes in transmission in Ib pathways

Three questions arise about the mechanism(s) responsible for the suppression of the group I inhibition of the soleus H reflex during triceps surae voluntary contractions: (i) Does a decrease in Ia excitation contribute to it? (ii) Is it due to a peripheral or descending mechanism? (iii) Is this mechanism pre- or post-synaptic?

Decrease in Ib inhibition or decrease in presynaptic inhibition of Ia terminals?

The changes elicited by the conditioning inferior soleus volley are the net result of two effects (monosynaptic Ia excitation and Ib inhibition), and the suppression of the inhibition during contraction could therefore result from a decrease in presynaptic inhibition of Ia terminals as well as a decrease in Ib inhibition. However, in a tonic contraction, there is no significant change in presynaptic inhibition of Ia terminals directed to involved motoneurones (see Chapter 8, p. 358). In addition, Fig. 6.8(*b*)

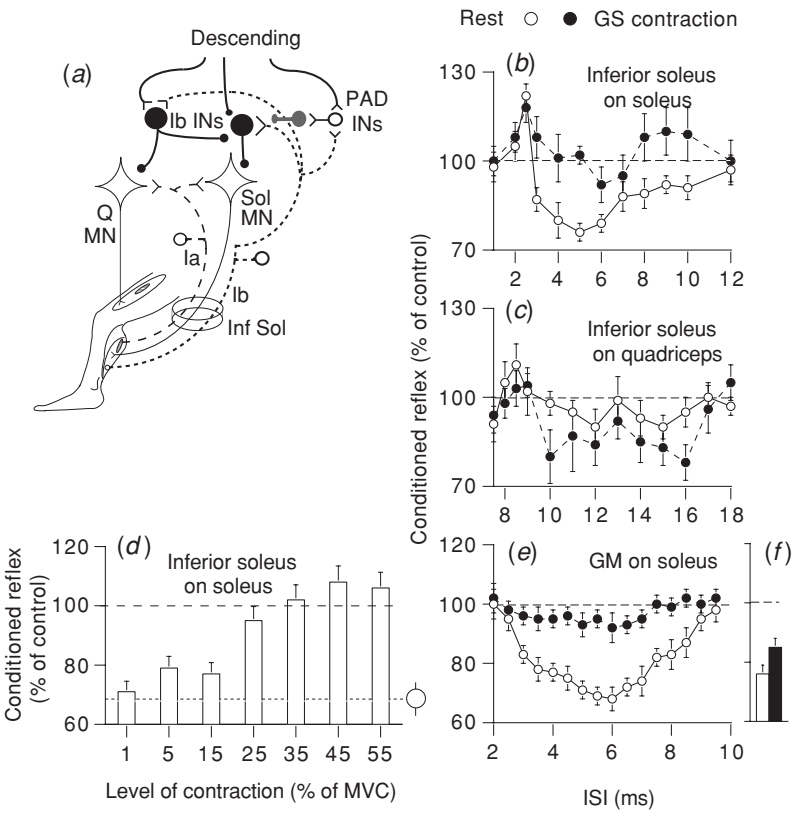


Fig. 6.8. Changes in Ib inhibition during voluntary contractions. (*a*) Sketch of the presumed pathways of Ib inhibition from inferior soleus (Inf Sol) to soleus (Sol) and quadriceps (Q) motoneurones (MN). The different descending actions possibly responsible for the depression of the transmission in Ib inhibitory pathways to soleus MNs are represented: facilitation of PAD interneurones (INs) mediating presynaptic inhibition of Ib terminals; mutual inhibition of Ib INs through facilitation of Ib INs mediating Ib inhibition of Q MNs; direct descending (reticulospinal) inhibition of Ib INs. (*b*)–(*f*) Changes in the amplitude of the conditioned H reflexes of Sol ((*b*), (*d*)–(*f*)) and Q (*c*) expressed as a percentage of their unconditioned values (dashed horizontal lines, size of the unconditioned reflex). Each symbol represents the mean of 20 measurements. Vertical bars, ±1 SEM ((*b*), (*c*), (*e*)), 1 SEM ((*d*), (*f*)). ((*b*), (*c*)) Changes in the H reflexes of Sol (*b*) and Q (*c*) after conditioning stimulation to the Inf Sol nerve at 0.95 × MT, at rest (○) and during a tonic contraction of the gastrocnemius-soleus (●, 30% of MVC) plotted against the interstimulus interval (ISI). (*d*) The amount of Ib inhibition of the Sol H reflex elicited by Inf Sol stimulation at 0.95 × MT, 8 ms ISI, at rest (large open circle on the right and dotted horizontal line) and during different levels of tonic contraction of the triceps surae (abscissa). (*e*), (*f*) Changes in the Sol H reflex after conditioning stimulation of the gastrocnemius medialis (GM) nerve at 0.95 × MT at rest (○, □), during tonic contraction (time course, (*e*), ●, 30% of MVC), and at the onset of GS contraction (5 ms ISI, (*f*), ■). Modified from Fournier, Katz & Pierrot-Deseilligny (1983) ((*b*), (*c*)), and Pierrot-Deseilligny & Fournier (1986), (*e*) and unpublished, ((*d*), (*f*)), with permission.

shows that the onset of the inferior soleus-induced Ia excitation is not altered: only its later part is modified, i.e. only when the excitation is being curtailed by Ib inhibition. This indicates that the decreased inhibition is not due to a reduction of the presynaptic inhibition of Ia terminals (see Chapter 8, p. 345). This conclusion is confirmed by the finding that the Ib inhibition from gastrocnemius medialis to soleus, which is not contaminated by Ia excitation (cf. p. 249), is suppressed to the same extent as the

inferior soleus-induced inhibition during tonic triceps surae contractions (Fig. 6.8(*e*); Pierrot-Deseilligny & Fournier, 1986; Stephens & Yang, 1996).

Peripheral or descending control?

(i) Evidence for descending control of Ib inhibition is provided by the finding that the Ib inhibition of the soleus H reflex, whether evoked from the inferior soleus or the gastrocnemius medialis nerves, is depressed at the onset of a triceps surae contraction or in the 50 ms preceding it (Fournier, Katz & Pierrot-Deseilligny, 1983; E. Fournier & E. Pierrot-Deseilligny, unpublished data; Fig. 6.8(*f*)). A reduction in Ib inhibition before the contraction-induced group I discharge from the triceps surae has reached the spinal cord indicates a change in the descending control of Ib pathways.

(ii) An interaction of the conditioning volley with the natural contraction-induced group I discharge could account for the finding that the suppression is more marked during tonic contractions than at the onset of contractions (Fig. 6.8(*e*), (*f*); E. Fournier & E. Pierrot-Deseilligny, unpublished data). Mechanisms directly related to the activation of the same afferents ('busy line') or synapses (post-activation depression) by the natural Ib afferent discharge and the conditioning volley are unlikely to be the cause of the suppression of the inhibition because the same effect is observed when the conditioning stimulus is to afferents from the inactive quadriceps. Neither could occlusion at the level of Ib interneurones between the contraction-induced group I discharge and the conditioning volley account for the suppression observed before the contraction-induced discharge reached the spinal cord.

Presynaptic mechanism?

Reduction of Ib inhibition by presynaptic inhibition of Ib terminals feeding Ib pathways to triceps surae but not quadriceps motoneurones may be produced in the cat by electrically-induced contractions of gastrocnemius medialis. This gating appears after the onset of contractions (Zytnicki *et al.*, 1990: Lafleur *et al.*, 1992, 1993, p. 248). The resulting gating of the conditioning Ib volleys would be consistent with the findings that the reduction of Ib inhibition is limited to the pathways mediating Ib inhibition to active motoneurones (see pp. 272–3) and more marked during tonic contractions than at the onset of contractions. On the other hand, PAD interneurones mediating presynaptic inhibition of Ib terminals receive corticospinal facilitation in the cat (see p. 248). A reduction in Ib inhibition before the contraction-induced Ib feedback has reached the motoneurones could then be explained by a focused corticospinal facilitation of PAD interneurones mediating presynaptic inhibition of Ib pathways to active motoneurones. There is so far no available method to investigate changes in presynaptic inhibition of Ib terminals in human subjects. However, such corticospinal changes in presynaptic inhibition would help focus activity on active motoneurones and would be in line with the changes at Ia terminals at the onset of voluntary contractions (see Chapter 8, pp. 359–60).

A descending post-synaptic mechanism?

This possibility has not been ruled out experimentally, but appears unlikely for two reasons.

(i) The differential control exerted on Ib inhibition directed to soleus and quadriceps motoneurones during the same triceps surae contraction (see pp. 272–3) is not easily explained by the diffuse effects of the reticulopinal systems which, in the cat, are responsible for descending inhibition to Ib interneurones (see p. 248).

(ii) This differential control could be explained by corticospinal facilitation of Ib interneurones to inactive quadriceps motoneurones, with mutual inhibition of Ib interneurones to soleus motoneurones (see the sketch in Fig. 6.8(*a*)). However, the finding that Ib inhibition to both soleus and quadriceps was suppressed during co-contraction of these muscles (E. Fournier & E. Pierrot-Deseilligny, unpublished data) would be difficult to explain solely on corticospinal facilitation of Ib interneurones.

Conclusions

There is strong evidence that the suppression of group I inhibition to active motoneurones during contractions results from decreased transmission in Ib inhibitory pathways, not a change in presynaptic inhibition on Ia terminals. The suppression of Ib inhibition is due to a descending control, which may be helped by the effects of the contraction-induced group I discharge. These controls probably act at a presynaptic level.

Functional implications

Suppression of autogenetic group I inhibition

Suppression of autogenetic group I inhibition to active motoneurones appears to be functionally appropriate, because otherwise Ib inhibition evoked by the discharge of Golgi tendon organs would hinder the maintained firing of active motoneurones and interfere with the recruitment of new units when the effort has to be increased. This view is supported by the finding that the suppression of autogenetic Ib inhibition increases along with an increase in contraction force (see above). However, even with strong tonic contractions (~30% of MVC), there is suppression rather than complete abolition of Ib inhibition (see the 6 ms ISI in Fig. 6.8(*b*)), and this could represent an operating level of inhibition that can be modulated in either direction.

Possible functional role of Ib inhibition

If suppression of autogenetic Ib inhibition to active motoneurones is of value, questions then arise about the functional role of Ib inhibition during voluntary contractions, given that Golgi tendon organs are specifically activated by muscle contraction. One answer is furnished by data from the anaesthetised cat. In this preparation, prolonged electrically-induced contractions of the triceps surae produce appreciable suppression of autogenetic Ib inhibition of homonymous and synergistic motoneurones, due to presynaptic inhibition evoked by the Ib discharge from the contracting muscle (see p. 248). However, Ib inhibition is active at the beginning of the contraction, and the gating mechanism still allows transient inhibitory potentials to appear in motoneurones when there are rapid increases in contraction force. These inhibitory potentials might help to limit the firing frequency of motoneurones and/or the recruitment of new motoneurones in order to keep a smooth profile of force development and avoid jerky movements (Zytnicki & Jami, 1998).

Facilitation of Ib inhibition by other afferent discharges

Ib inhibition may reappear when the transmission in Ib pathways is facilitated during appropriate phases of movement or by other peripheral afferent inputs which converge on the relevant Ib interneurones, as demonstrated in the cat by Lundberg and colleagues. Thus, despite the gating of transmission, summation of Ib inputs with other peripheral inputs can discharge Ib interneurones, and this is particularly likely when the transmission of the latter inputs through first-order interneurones receive descending facilitation (see p. 267; Fig. 6.5(*a*)). Various afferent inputs have been shown to be able to produce such a facilitation of transmission in Ib pathways.

Cutaneous facilitation

Cutaneous facilitation of transmission in Ib pathways could help curtail an exploratory movement on meeting an obstacle (Lundberg, Malmgren & Schomburg, 1977). The resulting exteroceptive volley would facilitate transmission of Ib inhibitory impulses to motoneurones of the contracting muscle (and its synergists), lessening contraction force. 'Post-synaptic inhibition of α motoneurones directly from the skin might serve the same purpose, but increasing gain in the Ib force loop provides an elegant solution since otherwise this feedback mechanism would tend to maintain constant tension. This hypothesis has bearing also on reciprocal Ib excitation, since excitation of antagonist muscles would indeed supplement Ib inhibition in giving a purposeful brake of the movement'. When proposing

this hypothesis, Lundberg, Malmgren & Schomburg (1977) assumed that the facilitation of the Ib pathways regulating an exploratory movement is from a skin field activated when the moving limb meets an obstacle. Experiments in human subjects have shown this appears to be so. Cutaneous facilitation of Ib pathways has a precise local sign, corresponding to the skin field that would come into contact with an obstacle during the contraction of the relevant muscle: (i) anterior part of the foot sole during triceps surae contraction, (ii) anterior aspect of the leg and dorsum of the foot during quadriceps contractions, and (iii) dorsal side of the fingers during wrist extensor contractions (see p. 262).

Facilitation by joint afferents

Facilitation of Ib interneurones by joint afferents can be considered in the same context as the facilitation from cutaneous afferents, i.e. an enhancement of Ib transmission that comes into operation in the particular phase of movement when joint receptors are activated (Lundberg, Malmgren & Schomburg, 1978). It has been demonstrated in both cats and humans that the vast majority of joint afferents are activated as the joint approaches the extremes of movement (see Ferrell, 1980; Burke, Gandevia & Macefield, 1988). The resulting facilitation of transmission in Ib inhibitory pathways would then decrease muscle activity as the extremes of movement are approached and so contribute to the termination of movement. As stated by Alstermark, Lundberg & Sasaki (1984), 'it would be a reasonable strategy to delegate part of the termination of the movement to spinal cord mechanisms, as termination must be one of the most difficult parameters of a movement for the brain to calculate'.

Convergence from Ia afferents

Convergence from Ia afferents adds the required dynamic component of length control to the tension control of muscles (Lundberg & Malmgren, 1988). During force control, the same perturbation, an increased load, produces Ia excitation of motoneurones and Ib inhibition (through activation of tendon organs), the latter being required to counteract the Ia-induced increment in excitation. However, the sensitivity to dynamic length changes is negligible for tendon organs as compared to spindle endings, particularly when spindles receive dynamic γ (or β) drive (see Proske, 1981). If a match is required at the motoneuronal level between stretch-evoked Ia excitation and Ib inhibition in tension-regulated movements (e.g. manipulatory movements), it would be an elegant solution to supply Ib inhibition with dynamic sensitivity from primary endings and Ia afferents. This dynamic sensitivity would complement that provided to the Ib feedback by its sensitivity to transients in force (see above).

Ib inhibition directed to motoneurones not involved in the voluntary contraction

Ib inhibition from contracting muscles to inactive synergists

During a tonic contraction involving only triceps surae, the changes in the group I inhibition of the soleus and quadriceps H reflexes differ: the group I inhibition following the monosynaptic Ia excitation is decreased in soleus and increased in quadriceps (Fournier, Katz & Pierrot-Deseilligny, 1983; Fig. 6.8(*b*), (*c*)). Because the initial Ia excitation of the quadriceps H reflex is depressed, it is possible that increased presynaptic inhibition of Ia terminals to quadriceps motoneurones contributes to the greater inhibition of the quadriceps H reflex induced by the inferior soleus volley. However, the weakness of this excitation at rest and the finding that the difference between the two situations is more marked at long ISIs suggest that Ib inhibition from soleus to quadriceps motoneurones is increased (Fig. 6.8(*c*)). If this is the case, the most parsimonious explanation for the differential control of Ib inhibitions from inferior soleus to soleus and quadriceps motoneurones would be the focused presynaptic inhibition of Ib terminals on soleus-coupled Ib interneurones. This gating, both peripheral and descending in origin (see above) would filter the peripheral input to soleus-coupled Ib

interneurones, but not that to quadriceps-coupled Ib interneurones. This would imply that presynaptic inhibition of Ib terminals is organised in subsets with regard to the target motoneurones, like that of Ia terminals (cf. Chapter 8, p. 348). In any event, the differential control of Ib pathways to active soleus and inactive quadriceps motoneurones would have a focusing action, increasing motor contrast (see Chapter 11, p. 517).

Ib inhibition to inactive motoneurones during voluntary contractions of the antagonists

Gastrocnemius medialis-induced Ib inhibition of the soleus H reflex has been investigated at the onset of a brief phasic contraction of pretibial flexors (Yanagawa, Shindo & Nakagawa, 1991). When the strength of the contraction was between 1 and 5% of MVC, Ib inhibition increased significantly or appeared when it did not exist at rest. This increased inhibition appeared before the contraction-induced peripheral feedback reached the spinal cord, and was presumably due to descending facilitation of Ib interneurones, probably of corticospinal origin. The enhanced inhibition returned to control values with small increases in contraction strength. This finding was attributed to occlusion in interneurones, and this implies that at least some Ib interneurones could be fired by the descending command. A movement due to contraction of the agonist (here, tibialis anterior) would produce a stretch-induced Ia discharge from the antagonist (soleus). However, the Ia discharge also projects to interneurones mediating non-reciprocal group I inhibition of these motoneurones (pp. 260–1). Thus, during voluntary contraction of a flexor, facilitation of interneurones mediating non-reciprocal group I inhibition to extensors, together with other mechanisms (cf. Chapter 11, pp. 519–20), would help prevent a stretch reflex in these muscles.

Changes in Ib inhibition during walking

An important finding concerning transmission in Ib pathways has been the demonstration of a switch from Ib inhibition in the quiescent cat to di- and polysynaptic excitation during fictive locomotion (see p. 248). This indicates that the pathway of Ib inhibition can be suppressed during locomotion, allowing activation of alternative excitatory pathways, not open at rest. Evidence for a similar Ib excitation of homonymous and synergistic motoneurones has been sought in human subjects during walking.

Ib pathways to extensors

Transmission in the pathway of Ib inhibition from gastrocnemius medialis to soleus

Transmission in this pathway has been compared at rest, during a voluntary contraction of triceps surae at 20% MVC and in the middle of the stance phase of walking on a treadmill (Stephens & Yang, 1996). Ib inhibition of the soleus H reflex was reduced during walking but not reversed to excitation. The overall reduction of the inhibition was not more pronounced than during voluntary contractions of triceps surae, a result similar to that reported by Faist *et al.* (1995). However, in 4 of 15 subjects, in whom voluntary contraction merely resulted in decreased Ib inhibition, the inhibition was reversed to excitation during walking, and this occurred at a latency consistent with an oligosynaptic Ib excitatory pathway. Overall, these effects are disappointingly modest compared to the reversal from Ib inhibition of ankle extensors to Ib excitation observed consistently in the decerebrate cat (see p. 248). This may be due to (i) the different preparation (normal awake humans versus decerebrate cats), though a clear example of reflex reversal has been obtained in intact humans in another paradigm (see below), (ii) the weak strength of the conditioning stimulus, necessary to avoid recurrent inhibition, or (iii) the different role of the triceps surae in feline and human walking (see below).

Different roles of the triceps surae in quadrupedal and bipedal locomotion

In the cat, during the stance phase of walking, the triceps surae and quadriceps have the same functional

role (i.e. to support the body weight) and, accordingly, EMG activities of the two muscles and movements of the ankle and the knee are remarkably similar (Engberg & Lundberg, 1969). In contrast, in humans, (i) the knee and ankle movements are out of phase (Brandell, 1977), and (ii) the quadriceps contraction occurs in early stance when it supports the body weight during the yield of the knee. However the triceps surae contraction resists the passive ankle dorsiflexion produced by the resultant of the extrinsic forces (kinetic force, gravity), and progressively increases during the stance phase. It has been suggested that the differential cutaneous suppressive control of Ib pathways to quadriceps and soleus motoneurones observed in the absence of voluntary contraction (see p. 261; Fig 6.4(*e*), (*g*)) might be related to the different roles of the two muscles during walking (Pierrot-Deseilligny, Bergego & Mazières, 1983). Suppression of Ib inhibition to quadriceps motoneurones by the cutaneous volley created by the foot contacting the ground would bring a safety margin to the quadriceps contraction. In contrast, it is important that soleus activity be overcome by dorsiflexion forces if the body is to be brought forward and, together with other mechanisms, the absence of cutaneous depression of Ib inhibition to soleus motoneurones would be expedient (see Chapter 11, pp. 546–7).

Ib pathways to flexors

Changes in Ib inhibition from pretibial flexors to biceps femoris have been compared during human standing and walking (Marchand-Pauvert & Nielsen, 2002).

Peroneal-induced changes in excitability of biceps motoneurones during standing

At rest a group I volley to the deep peroneal nerve elicits in the biceps H reflex an early monosynaptic Ia excitation and a subsequent Ib inhibition, both of which are modest (Pierrot-Deseilligny *et al.*, 1981b; Fig. 6.9(*b*)). During a tonic voluntary co-contraction of biceps and tibialis anterior while standing, a deep peroneal volley produces an early suppression followed by a late excitation in the on-going EMG activity of biceps femoris (Fig. 6.9(*c*)). The early inhibition is group I in origin, since its threshold is below that of group II afferents. It starts 4 ms after the expected time of arrival at motoneuronal level of the fastest Ia afferents in the conditioning volley. However, the central delay of this inhibition is difficult to establish precisely because: (i) Ib inhibition is depressed during voluntary activation of the target motoneurones (see above), (ii) summation of the effects evoked by slower group I afferents is probably necessary to allow it to appear, and (iii) the suppression may be superimposed on a preceding small excitation. The latency of the early suppression in the on-going EMG is therefore compatible with, but not evidence for oligosynaptic Ib inhibition (vertical dotted line in Fig. 6.9(*c*)).

Changes in peroneal-induced effects during walking

At the end of the swing phase of walking, the early suppression of peroneal group I inhibition is similar to that observed during voluntary contractions at equivalent levels of EMG activity and is again preceded by a questionable Ia excitation (Fig. 6.9(*d*)). In striking contrast, in the beginning of the stance phase, the suppression is replaced by facilitation occurring at the same latency as the inhibition in the swing phase (Fig. 6.9(*e*)). The facilitation, found in most of the subjects, is of group I origin, since it is observed with stimuli below group II threshold, and cannot be reproduced by cutaneous stimuli. The latency of the facilitation is compatible with an oligosynaptic group I effect. The observed reflex reversal presumably results from the opening of an excitatory group I pathway in the early stance of walking with a concomitant shut-down of heteronymous group I inhibition.

Functional implications

In early stance there is a lengthening contraction from pretibial flexors and this results in a significant

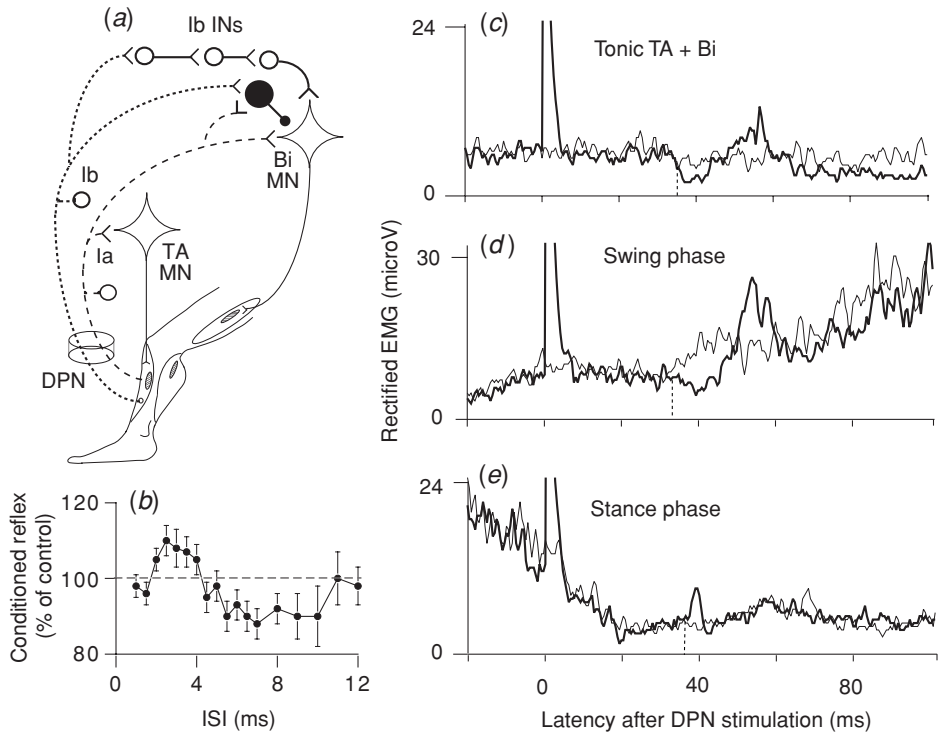


Fig. 6.9. Reversal of Ib inhibition to facilitation during gait. (*a*) Sketch of the presumed pathways mediating disynaptic Ib inhibition and oligosynaptic Ib excitation from tibialis anterior (TA) to biceps femoris (Bi) motoneurones (MN). (*b*) The amplitude of the biceps H reflex (expressed as a percentage of its unconditioned value) conditioned by stimulation of the deep peroneal nerve (DPN, 0.95 × MT) plotted against the interstimulus interval (ISI) at rest. Each symbol represents the mean of 20 measurements. Vertical bars, ±1 SEM. (*c*)–(*e*) Averaged (50 traces) rectified on-going EMG of the biceps, with (thick line) and without (thin line) stimulation of the DPN, plotted against the latency after DPN stimulation during voluntary co-contraction of the TA and biceps in standing (*c*), during the swing phase of gait ((*d*) 950 ms after heel strike) and during the stance phase ((*e*), 15 ms after heel strike) when walking on a treadmill (4 km.h^{-1}). Vertical dotted lines indicate the onset of the EMG suppression ((*c*), (*d*)) or facilitation (*e*). Modified from Pierrot-Deseilligny *et al.* (1981b) (*b*), and Marchand-Pauvert & Nielsen (2002), ((*c*)–(*e*)), with permission.

group I-group II afferent discharge from these muscles (Chapter 3, p. 137). At this time of the gait cycle, the group I discharge facilitates biceps motoneurones. Quadriceps motoneurones would also be facilitated by the group I–group II discharges (cf. Chapter 7, pp. 318–19). Facilitation of the two antagonistic muscles operating at knee level by afferent discharges from ankle dorsiflexors would contribute to the co-contraction, and help ensure maximal stability of the knee joint in early stance (see Chapter 11, p. 547).

Studies in patients and clinical implications

Ib inhibition

Methodology

So far, changes in transmission in Ib inhibitory pathways in patients have been investigated only by assessing the inhibition of the soleus H reflex produced by stimulation of the gastrocnemius medialis

nerve. This is, indeed, the best method because changes in Ib inhibition are not contaminated by possible changes in presynaptic inhibition of Ia terminals. However, it is necessary to keep the conditioning stimulus below 1 × MT to avoid recurrent inhibition, and few group I afferent fibres will be recruited by conditioning volleys of such weak intensity. As a result, in normal subjects, the inhibition of the reflex is inconstant and modest, when present (see p. 256). This makes it difficult to determine the significance of a reduction of the inhibition in patients.

Stroke patients

Modulation of the soleus H reflex by a conditioning volley to the gastrocnemius medialis nerve (0.95 × MT) has been studied in six hemiplegic spastic patients following a stroke (Delwaide & Olivier, 1988). On the unaffected side of these patients, there was, as in normal subjects, inhibition of the reflex, maximal at the 6 ms ISI, by on average ∼15% of the control reflex value. In contrast, on the hemiplegic side, the inhibition was replaced by facilitation, occurring with a similar central delay, compatible with an oligosynaptic group I effect. The amount of facilitation was moderately correlated with the degree of spasticity assessed by the Ashworth scale ($r = 0.6$). These results have since been confirmed in a larger number of patients (Delwaide, 1993). The suppression of the inhibition in patients with corticospinal lesions might suggest that there is normally tonic corticospinal facilitation of Ib interneurones. However, because the inhibition tends to be replaced by facilitation, a reduction of the inhibition does not necessarily mean that transmission in the Ib inhibitory pathway is suppressed (see below).

Patients with spinal cord lesions

Gastrocnemius medialis-induced inhibition of the soleus H reflex has been investigated in patients with well-defined (essentially traumatic) chronic spinal cord lesions (Downes, Ashby & Bugaresti, 1995). In normal subjects, the inhibition could be obtained with stimulus intensities as low as 0.7 × MT, and peaked at the 6 ms ISI. When using an intensity of 1 × MT, it was quite weak (on average, reducing the test reflex to 93.5% of the control). In patients with spinal cord lesions, the amount of inhibition of the soleus H reflex was not significantly different from normal subjects (96.3% on average).

Hyperekplexia

Five patients with hyperekplexia (startle disease) have been investigated, three of whom had a defined mutation in glycine receptors (Floeter *et al.*, 1996). Reciprocal Ia inhibition (known to be mediated through a glycinergic inhibitory system; Chapter 5, p. 233) was reduced, but Ib inhibition was not modified with respect to normal subjects. However, the results were so variable that they have to be interpreted with caution.

Parkinson's disease

In 19 patients with Parkinson's disease, gastrocnemius medialis-induced inhibition of the soleus H reflex was found to be reduced or even replaced by facilitation occurring with the same central delay, consistent with transmission through an oligosynaptic group I pathway (Delwaide, Pepin & Maertens de Noordhout, 1991). The departures from normal values correlated with the intensity of rigidity assessed by the Webster scale: increased rigidity was associated, first, with a reduction of inhibition and, from a score of 2 or more, with facilitation replacing the normal inhibition. In *de novo* patients treated with L-dopa, the decrease in facilitation paralleled the reduction of the rigidity. High-frequency stimulation in the subthalamic nucleus has also recently been shown to produce a restoration of the inhibition, paralleling the reduction of the axial symptoms and gait disorders (Pöter *et al.*, 2004). Because of the strong correlation between the decreased Ib inhibition and the increased reciprocal Ia inhibition, a common mechanism for these two abnormalities has been put forward (increased reticulospinal activation;

Delwaide, Pepin & Maertens de Noordhout, 1993). However, again, the reduction of the gastrocnemius medialis-induced inhibition of the soleus H reflex does not necessarily mean that the transmission in the Ib inhibitory pathway is suppressed (see below).

Patients with progressive supranuclear palsy

Gastrocnemius medialis-induced inhibition of the soleus H reflex is greater in such patients (Fine *et al.*, 1998). This could be related to a loss of inhibition of Ib interneurones through degeneration of the medullary reticulospinal pathway.

Mechanisms underlying changes in Ib inhibition in patients

The decrease in the gastrocnemius medialis-induced Ib inhibition of the soleus H reflex in spastic or Parkinsonian patients does not necessarily imply decreased transmission across the Ib inhibitory pathway. The inhibition tends to be replaced by a facilitation, and this could indicate that facilitated group I excitation overwhelms the Ib inhibition, with or without decreased Ib inhibition. Two oligosynaptic pathways are possible candidates for the facilitation. (i) Facilitation of transmission in lumbar propriospinal neurones, for which there is independent evidence in spastic patients (see Marque *et al.*, 2001; Chapter 10, pp. 503–4). The finding that this facilitation of the soleus H reflex does not occur in patients with spinal cord lesions indicates that it probably requires the presence of other descending controls in the spinal cord. The increased amplitude and decreased threshold of the MEP elicited by TMS in the quadriceps of patients with Parkinson's disease have also been attributed to hyperexcitability of the relevant lumbar propriospinal neurones (Trembley & Trembley, 2002). (ii) Opening of the pathway of oligosynaptic group I excitation disclosed in some normal subjects during the stance phase of walking (cf. pp. 273–4).

Ib excitation in spastic patients

Peroneal-induced group I facilitation

Disynaptic peroneal-induced reciprocal Ia inhibition of soleus can be replaced by group I facilitation in patients with spasticity, whether due to stroke (Yanagisawa, Tanaka & Ito, 1976; Crone *et al.*, 2003), spinal cord injury (Okuma, Mizuno & Lee, 2002; Crone *et al.*, 2003) or multiple sclerosis (Crone *et al.*, 1994). Delwaide (1985) also mentioned an early peroneal-induced facilitation in a few spastic patients, but gave no details of the lesions causing the spasticity. Pooled data illustrating the time course of the effects of deep peroneal stimulation on the soleus H reflex show that the disynaptic reciprocal Ia inhibition seen in normal subjects is replaced by a facilitation in patients with spinal cord injury and on the affected side of hemiplegic patients (Fig. 6.10(*b*)). The facilitation has the same central delay as reciprocal Ia inhibition and peaks at the 3–4 ms ISI. In individual subjects, the facilitation was seen in two of four patients with incomplete spinal cord injury, four of seven patients with a complete lesion, and all six stroke patients (Crone *et al.*, 2003). A follow-up study performed in hemiplegic patients revealed that the short-latency facilitation was present the first time the patients were tested (as early as 2 weeks after the onset of disease) or appeared with the development of hyperactive Achilles tendon jerks.

Increased group I facilitation or decreased reciprocal Ia inhibition?

Similar disynaptic facilitation has been described in the cat when transmission in the glycinergic reciprocal Ia inhibitory pathway was blocked by strychnine (Bradley, Easton & Eccles, 1953), and it is therefore possible that the findings in spastic patients could be due to the fact that a normal Ib excitation is more easily disclosed because of the decreased reciprocal Ia inhibition (see Chapter 5, pp. 229–32). However, Crone *et al.* (2003) have provided arguments favouring increased (facilitated) group I excitation:

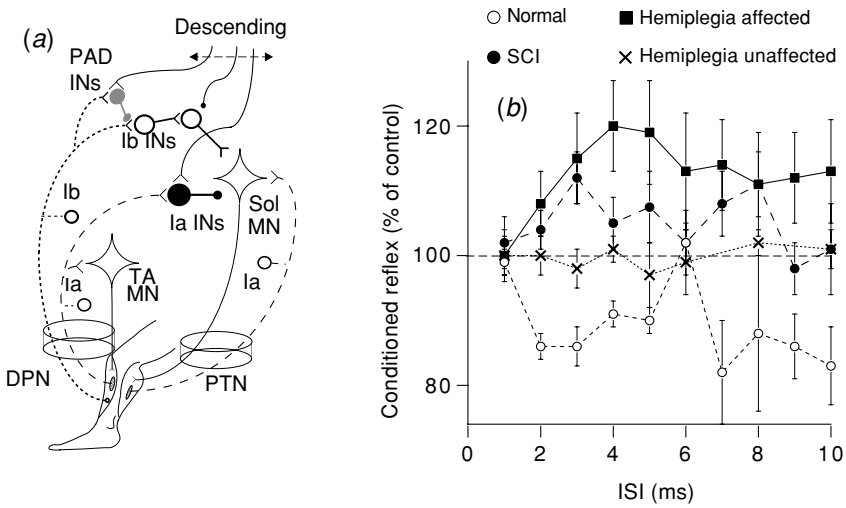


Fig. 6.10. Changes in peroneal-induced Ib excitation of ankle extensors in spastic patients. (*a*) Sketch of the presumed pathway of reciprocal Ia inhibition and Ib excitation from ankle flexors to ankle extensors. The descending facilitation of Ia inhibitory interneurones (IN) and the descending inhibition of Ib excitatory INs and/or the descending facilitation of PAD INs mediating presynaptic of Ib afferents are presumed to be interrupted in spastic patients (horizontal double-headed dashed arrow). (*b*) Time course of the changes in the soleus H reflex induced by deep peroneal stimulation (1 × MT). The size of the conditioned H reflex (expressed as a percentage of its unconditioned value) is plotted against the interstimulus interval (ISI). Average data from 15 normal subjects (○), 11 patients with spinal cord injury (SCI) between C2 and T8 (●), and the affected (■) and unaffected (×) sides of 6 patients with hemiplegia. Vertical bars ±1 SEM. Modified from Crone *et al.* (2003), with permission.

(i) a short-latency facilitation has not been seen in those normal subjects in whom no or very little disynaptic reciprocal Ia inhibition can be demonstrated; (ii) in the hemiplegic patients, it was not seen on the non-spastic side where the disynaptic reciprocal Ia inhibition was also absent (Fig. 6.10(*b*)); (iii) in normal subjects, it has not been seen during plantar flexion of the ankle or co-contraction of ankle flexors and extensors, manoeuvres in which the deep peroneal-induced reciprocal Ia inhibition decreases considerably or disappears (cf. Chapter 5, pp. 223–7).

Origin of the facilitation of the Ib excitation

Because of its short latency and low threshold, the early facilitation seen in spastic patients has been considered to be due to Ib excitation (Yanagisawa, Tanaka & Ito, 1976; Crone *et al.*, 2003). The finding that this excitation is not seen in normal subjects (p. 258) would indicate that the activity in the pathway is normally strongly inhibited by a supraspinal inhibitory control that is interrupted in the patients. This facilitation would then be a 'release phenomenon' (cf. Yanagisawa, 1980), due to either suppression of a descending tonic inhibitory control on Ib excitatory interneurones or, alternatively, of a facilitatory control on PAD interneurones mediating presynaptic inhibition of Ib afferents. However, here again, an alternative possibility would be a facilitated oligosynaptic group I excitation due to enhanced transmission in lumbar propriospinal neurones (see above).

Contribution to pathophysiology of spasticity

Reciprocal Ib facilitation appeared in parallel with the development of hyperactive Achilles tendon

reflexes, the only clinical finding correlated with the facilitation. The correlation suggests that the facilitation may contribute to the development of spasticity (see Chapter 12, p. 569). It also seems likely that the reciprocal facilitation may contribute to adverse co-contraction of antagonistic muscles during voluntary movement in spastic patients (Crone *et al.*, 2003).

Conclusions

Role of changes in Ib inhibition during motor tasks

During voluntary contractions, the essential finding is that Ib inhibition to voluntarily activated motoneurones is suppressed. This suppression would prevent Ib inhibition evoked by the discharge from Golgi tendon organs from dampening the discharge of active motoneurones and interfering with the recruitment of new units when the effort has to be increased. However, Ib inhibition can be restored during certain phases of movement by the convergence of other afferents (cutaneous, joint) onto Ib interneurones, and this could help to curtail a movement when the moving limb meets an obstacle or when joint afferents are activated at the extremes of joint movement. Ib inhibition to inactive synergistic motoneurones is increased, and this probably contributes to the selective activation of muscles in discrete movements. Increased Ib inhibition to motoneurones supplying muscles antagonistic to those involved in the voluntary contraction is one of the mechanisms contributing to the relaxation of those antagonists.

During the stance phase of walking, the pathway of Ib inhibition from pretibial flexors to biceps is suppressed, and an opposite excitatory pathway, not open at rest, is then revealed. This reflex reversal contributes to stabilising the knee during early stance.

Changes in Ib pathways and the pathophysiology of movement disorders

Gastrocnemius medialis-induced Ib inhibition of the soleus H reflex may be replaced by facilitation in *spastic stroke* patients and *Parkinsonian* patients. This facilitation could reflect the existence of enhanced group I excitation overwhelming Ib inhibition, with or without decreased Ib inhibition.

Peroneal-induced reciprocal Ia inhibition of the soleus H reflex is replaced by an early facilitation in patients with spasticity whether due to stroke or spinal cord injury. There is evidence that this facilitation is due to a release of Ib excitation.

Résumé

Background from animal experiments

Ib afferents originate from Golgi tendon organs, and their adequate stimulus is muscle contraction. They are fast-conducting afferents, and their diameters largely overlap those of Ia afferents. This explains why it is difficult to separate Ib from Ia afferents on the basis of their electrical threshold, except when the threshold of Ia afferents has been raised by a long-lasting vibration, to which tendon organs are relatively insensitive. Projections of Ib afferents are widely distributed to motor pools of the ipsilateral limb, with typically disynaptic (and trisynaptic) inhibition of homonymous and synergistic motoneurones and trisynaptic excitation of antagonistic motoneurones. In the low spinal cat, these effects are potent from extensors and almost completely missing from flexors, but effects from flexors can be demonstrated after stimulation of the red nucleus. There is extensive excitatory convergence from virtually all peripheral afferents on Ib interneurones. Interneurones intercalated in Ib pathways receive corticospinal and rubrospinal excitation and are inhibited by reticulospinal systems. Alternative

patterns (e.g. corticospinal inhibition of Ib interneurones) can occur through mutual inhibition of Ib interneurones. Ib volleys produce potent presynaptic inhibition of Ib afferents, and this is facilitated by the corticospinal tract. During fictive locomotion in the decerebrate cat there may be a reflex reversal, involving a switch from Ib inhibition to di- and polysynaptic excitation mediated through alternative Ib excitatory pathways.

Methodology

Underlying principle

Ib effects can be assessed in motoneurones by testing the effects on the modulation of the H reflex or the PSTHs of single units produced by electrically induced group I volleys applied to nerves but, to avoid recurrent inhibition, the conditioning volleys must be below the threshold for any H and M response. As a result, few Ib afferents are activated and the strength of the Ib effects is underestimated.

Evidence for Ib effects

Ib inhibition

Ib inhibition is most easily disclosed when investigating the modulation of the H reflex of a relaxed muscle. Given the extensive distribution of heteronymous monosynaptic Ia excitation in the human lower limb, Ib inhibition is usually preceded by an early facilitation of the test H reflex. However, in some situations (gastrocnemius medialis nerve to soleus in the lower limb; musculo-cutaneous or triceps brachii nerves to wrist muscles) group I volleys produce isolated inhibition without any preceding excitation. Evidence for Ib inhibition relies on: the low electrical threshold of the effect (close to that of Ia excitation); the finding that it is not evoked by a tendon tap; a central delay compatible with disynaptic transmission; a short duration (less than 10 ms); and a distribution to homonymous and synergistic motoneurones.

Oligosynaptic group I excitation

Oligosynaptic group I excitation between strict antagonists has the same characteristics (low electrical threshold, non-elicitation by a tendon tap, short central delay).

Critique of the tests to reveal Ib effects

When there is monosynaptic Ia excitation, the size of the test reflex (or of the peak of Ia excitation in the PSTH) depends on the balance of superimposed Ib inhibition and Ia excitation (the latter varying with the degree of presynaptic inhibition of Ia terminals). Ib inhibition from gastrocnemius medialis to soleus is not contaminated by Ia excitation, but the resulting reflex suppression is inconstant and, when present, weak.

Organisation and pattern of connections

Ib effects

Ib inhibition

It is generally impossible to investigate homonymous actions for technical reasons. However, with the soleus and quadriceps, there are particular conditions that make such studies possible. Evidence for heteronymous Ib inhibition has been found in all muscle–nerve combinations tested, except between strict antagonists. The inhibition is generally relatively weak, but this is because: (i) the inhibition is usually superimposed on monosynaptic Ia excitation, which prevents its full exposure, and (ii) stimulation subthreshold for the H and M responses, in order to avoid recurrent inhibition, recruits few group I afferents. Ib interneurones are organised in subsets with regard to the target motoneurones. Convergence of group I afferents from different muscles onto common inhibitory interneurones has been found only rarely, possibly because of occlusion at interneuronal level and/or mutual inhibition of Ib interneurones.

Oligosynaptic group Ib excitation

Ib excitation has been found only between strict antagonists operating at the same joint. It is more frequent at the elbow than at other joints. Low-threshold group I excitation from pretibial muscles to quadriceps motoneurones is mediated via propriospinal interneurones, not a segmental Ib pathway.

Convergence on Ib interneurones

(i) Convergence of Ia afferents onto Ib interneurones is suggested by the significant reduction of the inhibition produced by an electrically induced group I volley when the threshold of Ia afferents has been raised by long-lasting vibration, or the Ia inflow has been reduced by presynaptic inhibition of Ia afferents.

(ii) At rest, cutaneous volleys from the sole of the foot suppress homonymous Ib inhibition of quadriceps, and heteronymous Ib inhibition from triceps surae to quadriceps and biceps. The same cutaneous volleys do not modify Ib inhibition of soleus motoneurones. A possible mechanism would be a cutaneous activation of Ib interneurones producing, through mutual inhibition of Ib interneurones, inhibition of other Ib interneurones.

(iii) Cutaneous facilitation of Ib inhibition is more frequently observed. Cutaneous facilitation of Ib inhibition of knee muscle motoneurones can be demonstrated even at rest, where it follows the initial cutaneous suppression. During a voluntary contraction of triceps surae, Ib inhibition from triceps surae to soleus and quadriceps motoneurones is facilitated by cutaneous afferents from the anterior part of the sole. During strong quadriceps contractions autogenetic Ib inhibition of quadriceps motoneurones is facilitated by cutaneous afferents from the anterior part of the leg. Radial-induced Ib excitation to FCR is facilitated by afferents from the skin of the dorsal side of the fingers.

(iv) Facilitation of Ib inhibition to quadriceps by joint afferents: the facilitation of the quadriceps H reflex by stimulation of the lateral articular nerve of the knee joint during weak contractions of quadriceps is reversed to inhibition during strong contractions, but the on-going EMG activity remains facilitated. This discrepancy indicates an inhibitory mechanism gating the afferent volley of the test reflex. PSTHs of single units have shown that this gating is due to convergence of joint afferents and group I afferents in the test volley for the H reflex onto interneurones mediating disynaptic Ib inhibition to quadriceps motoneurones.

(v) Tonic stimulation of nociceptive afferents alters the transmission of Ib inhibition from gastrocnemius medialis to soleus and quadriceps, enhancing transmission in Ib pathways when afferents from the skin of the dorsum of the foot are stimulated, and inhibiting it when afferents inside the extensor digitorum brevis are activated.

(vi) Stimulation of both the motor cortex and the vestibular apparatus facilitates Ib inhibition from gastrocnemius medialis to soleus when the conditioning volleys are weak, and suppresses it (due to occlusion and/or mutual inhibition of interneurones) when the conditioning volleys are strong.

(vii) Multiple convergence. Group I afferents in the femoral nerve converge with various conditioning joint and cutaneous volleys onto Ib interneurones projecting to quadriceps motoneurones. At rest or during weak contractions, this convergence can only be revealed when two conditioning volleys, articular and cutaneous, are combined with the femoral volley. However, during strong contractions, a single conditioning input (articular or cutaneous) can facilitate the Ib inhibition elicited by the femoral volley, probably because there is a descending facilitation of the first-order interneurones mediating the conditioning cutaneous or articular input.

Motor tasks and physiological implications

Suppression of Ib inhibition to voluntarily activated motoneurones

(i) There is a suppression of Ib inhibition to soleus motoneurones during tonic contractions, and at the

onset of and within the 50 ms preceding a voluntary contraction of triceps surae. Transmission in all Ib inhibitory pathways (homonymous and heteronymous) is depressed, and the depression is more marked during tonic contractions than at the onset of contractions. This suppression may be due to increased presynaptic inhibition of Ib afferents. PAD interneurones would be activated by a focused corticospinal drive before the group I feedback from the contracting muscle reaches the spinal cord, and later their activation would be maintained by the natural contraction-induced group I discharge. Suppression of autogenetic group I inhibition to active motoneurones is appropriate because, otherwise, Ib inhibition evoked by the discharge from Golgi tendon organs would dampen the firing of active motoneurones and interfere with the recruitment of new units when the effort has to be increased. This view is supported by the finding that the suppression of autogenetic Ib inhibition increases along with an increase in the contraction force.

(ii) Although suppressed during homonymous contractions, Ib inhibition may reappear when transmission in Ib pathways is facilitated during certain phases of movement or by inputs from other peripheral afferents. Thus, cutaneous facilitation of transmission in Ib pathways could be used to curtail an exploratory movement meeting an obstacle. This view is supported by the finding that cutaneous facilitation has a precise local sign: it is produced only by the skin field that would come into contact with an obstacle during the contraction of the corresponding muscle. Similarly, facilitation of Ib inhibition from joint receptors activated at the extremes of joint movement will increase Ib inhibition and automatically contribute to curtailing the movement.

Ib inhibition directed to motoneurones not involved in the voluntary contraction

(i) Group I inhibition from soleus to inactive quadriceps motoneurones is increased during selective voluntary contractions of soleus. Focused presynaptic inhibition of Ib terminals on soleus-coupled Ib interneurones might account for this finding. This gating would filter the peripheral input to soleus-coupled Ib interneurones but not that to quadriceps-coupled Ib interneurones. The differential control of Ib pathways to active soleus and inactive quadriceps motoneurones would help focus the motor command for tasks requiring discrete contractions.

(ii) Ib inhibition is increased at the onset of a voluntary contraction of the antagonistic muscle. This effect appears only during very weak contractions, and disappears with small increases in contraction strength, probably because of occlusion in Ib interneurones. Such an occlusion would imply that some of the Ib interneurones are facilitated sufficiently to be fired by the descending command. This is one mechanism contributing to the relaxation of the antagonists during a voluntary contraction.

Changes in Ib inhibition during gait

(i) Reversal of Ib inhibition of soleus from gastrocnemius medialis to facilitation has been found only rarely in human subjects. This contrasts with findings during fictive locomotion in the decerebrate cat. The discrepancy might be related to the different roles played by the triceps surae during walking in the two species.

(ii) Ib inhibition from tibialis anterior to biceps is consistently reversed to facilitation during the stance phase of walking, and this could contribute to stabilising the knee in early stance.

Studies in patients and clinical implications

Ib inhibition

The gastrocnemius medialis-induced Ib inhibition of the soleus H reflex is the best method for assessing inhibitory Ib effects.

(i) In stroke patients, Ib inhibition of soleus motoneurones is normal on the unaffected side, but may be replaced on the hemiplegic side by a

facilitation occurring with a latency compatible with transmission through an oligosynaptic pathway.

(ii) In contrast there is no such change in patients with spinal cord lesions.

(iii) In Parkinsonian patients, Ib inhibition is replaced by a trend to facilitation, and this change is correlated with the degree of rigidity.

The results observed in stroke and Parkinsonian patients may not result from a true change in Ib inhibition. They could reflect the existence of a facilitated group I excitation overwhelming Ib inhibition, with or without decreased Ib inhibition. In this respect, there is independent evidence for facilitation of transmission in lumbar propriospinal neurones in spastic patients.

Ib excitation

In spastic patients, whatever the lesion (stroke, spinal cord injury or multiple sclerosis), the disynaptic peroneal-induced reciprocal Ia inhibition of the soleus H reflex is often obscured by an early group I excitation, which is correlated with hyperactive Achilles tendon jerks. This could reflect the release of Ib excitation normally strongly inhibited by supraspinal centres.

REFERENCES

Alstermark, B., Lundberg, A. & Sasaki, S. (1984). Integration in descending motor pathways controlling the forelimb in the cat. 11. Inhibitory pathways from higher motor centres and forelimb afferents to C3–C4 propriospinal neurones. *Experimental Brain Research*, **56**, 293–307.

Araki, T., Eccles, J. C. & Ito, M. (1960). Correlation of the inhibitory post-synaptic potential of motoneurones with the latency and time course of inhibition of monosynaptic reflexes. *Journal of Physiology (London)*, **154**, 354–77.

Aymard, C., Chia, L., Katz, R., Lafitte, C. & Pénicaud, A. (1995). Reciprocal inhibition between wrist flexors and extensors in man: a new set of interneurones? *Journal of Physiology (London)*, **487**, 221–35.

Bergmans, J., Delwaide, P. J. & Gadea-Ciria, M. (1978). Short-latency effects of low-threshold muscular afferent fibers on different motoneuronal pools of the lower limb in man. *Experimental Neurology*, **60**, 380–5.

Bradley, K., Easton, D. M. & Eccles, J.C. (1953). An investigation of primary or direct inhibition. *Journal of Physiology (London)*, **122**, 474–88.

Brandell, B. R. (1977). Functional roles of the calf and vastus muscles in locomotion. *American Journal of Physical Medicine*, **56**, 59–74.

Brink, E., Jankowska, E., McCrea, D. & Skoog, B. (1983). Inhibitory interactions between interneurones in reflex pathways from group Ia and group Ib afferents in the cat. *Journal of Physiology (London)*, **343**, 361–79.

Brooke, J. D. & McIlroy, W. E. (1989). Effect of knee joint angle on a heteronymous Ib reflex in the human lower limb. *The Canadian Journal of Neurological Sciences*, **16**, 58–61.

Burke, D., Knowles, L., Andrews, C. & Ashby, P. (1972). Spasticity, decerebrate rigidity and the clasp-knife phenomenon: an experimental study in the cat. *Brain*, **95**, 31–48.

Burke, D., Hagbarth, K.-E. & Löfstedt, L. (1978). Muscle spindle activity in man during shortening and lengthening contractions. *Journal of Physiology (London)*, **277**, 131–42.

Burke, D., Gandevia, S. C. & Macefield, G. (1988). Responses to passive movement of receptors in joint, skin and muscle of the human hand. *Journal of Physiology (London)*, **402**, 347–61.

Burne, J. A. & Lippold, O. C. J. (1996). Reflex inhibition following electrical stimulation over muscle tendons in man. *Brain*, **119**, 1107–14.

Cavallari, P. & Katz, R. (1989). Pattern of projections of group I afferents from forearm muscles to motoneurones supplying biceps and triceps muscles in man. *Experimental Brain Research*, **78**, 465–78.

Cavallari, P., Fournier, E., Katz, R., Malmgren, K., Pierrot-Deseilligny, E. & Shindo, M. (1985). Cutaneous facilitation of transmission in Ib reflex pathways in the human upper limb. *Experimental Brain Research*, **60**, 197–9.

Cavallari, P., Katz, R. & Pénicaud, A. (1992). Pattern of projections of group I afferents from elbow muscles to motoneurones supplying wrist muscles in man. *Experimental Brain Research*, **91**, 311–19.

Coppin, C. M. C., Jack, J. J. B. & MacLennan, C. R. (1970). A method for the selective electrical stimulation of tendon organ afferent fibres from the cat soleus muscle. *Journal of Physiology (London)*, **210**, 18*P*–20*P*.

Crone, C., Hultborn, H., Jespersen, B. & Nielsen, J. (1987). Reciprocal Ia inhibition between ankle flexors and extensors in man. *Journal of Physiology (London)*, **389**, 163–85.

Crone, C., Nielsen, J., Petersen, N., Ballegaard, M. & Hultborn, H. (1994). Disynaptic reciprocal inhibition of ankle extensors in spastic patients. *Brain*, **117**, 1161–8.

Crone, C., Johnsen, L. L., Biering-Sørensen, F. & Nielsen, J.B. (2003). Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury. *Brain*, **126**, 495–507.

Delwaide, P. J. (1985). Electrophysiological testing of spastic patients: its potential usefulness and limitation. In *Clinical Neurophysiology in Spasticity*, ed. P. J. Delwaide & R. R. Young, pp. 185–203. Amsterdam: Elsevier.

Delwaide, P. J. (1993). Pathophysiological mechanisms of spasticity at the spinal cord level. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 296–308. Berlin: Springers.

Delwaide, P. J. & Olivier, E. (1988). Short-latency autogenetic inhibition (Ib inhibition) in human spasticity. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 1546–50.

Delwaide, P. J., Pepin, J. L. & Maertens de Noordhout, A. (1991). Short-latency autogenic inhibition in patients with Parkinsonian rigidity. *Annals of Neurology*, **30**, 83–9.

(1993). Contribution of reticular nuclei to the pathophysiology of parkinsonian rigidity. *Advances in Neurology*, **60**, 381–5.

Downes, L., Ashby, P. & Bugaresti, J. (1995). Reflex effects from Golgi tendon organ (Ib) afferents are unchanged after spinal cord lesion in humans. *Neurology*, **45**, 1720–4.

Duysens, J., Clarac, F. & Cruse H. (2000). Load-regulating mechanisms in gait and posture: comparative aspects. *Physiological Reviews*, **80**, 83–133.

Eccles, J. C., Eccles, R. M. & Lundberg, A. (1957). Synaptic actions of motoneurones caused by impulses in Golgi tendon organ afferents. *Journal of Physiology (London)*, **138**, 227–52.

Engberg, I. & Lundberg, A. (1969). An electromyographic analysis of muscular activity in the hindlimb of the cat during unrestrained locomotion. *Acta Physiologica Scandinavica*, **75**, 105–22.

Enriquez-Denton, M., Nielsen, J., Perreault, M. C., Morita, H., Petersen, N. & Hultborn, H. (2000). Presynaptic control of transmission along the pathways mediating disynaptic reciprocal inhibition in the cat. *Journal of Physiology (London)*, **526**, 623–37.

Faist, M., Hoefer, C., Duysens, J., Berger, W. & Dietz, V. (1995). Decrease in Ib-inhibition during human standing and walking (abstract). *Electroencephalography and Clinical Neurophysiology*, **97**, 178.

Ferrell, W. R. (1980). The adequacy of stretch receptors in the cat knee joint for signalling joint angle throughout a full range of movement. *Journal of Physiology (London)*, **299**, 85–100.

Fetz, E. E., Jankowska, E., Johannisson, T. & Lipski, J. (1979). Autogenetic inhibition of motoneurones by impulses in group Ia muscle spindle afferents. *Journal of Physiology (London)*, **293**, 173–95.

Fine, E. J., Hallett, M., Litvan, I., Tresser, N. & Katz, D. (1998). Dysfunction of Ib (autogenic) spinal inhibition in patients with progressive supranuclear palsy. *Movement Disorders*, **13**, 668–72.

Floeter, M. K., Andermann, F., Andermann, E., Nigro, M. & Hallett, M. (1996). Physiological studies of spinal inhibitory pathways in patients with hereditary hyperekplexia. *Neurology*, **46**, 766–72.

Forget, R., Pantieri, R., Pierrot-Deseilligny, E., Shindo, M. & Tanaka, R. (1989). Facilitation of quadriceps motoneurones by group I afferents from pretibial flexors in man. 1. Possible interneuronal pathway. *Experimental Brain Research*, **78**, 10–20.

Fournier, E., Katz, R. & Pierrot-Deseilligny, E. (1983). Descending control of reflex pathways in the production of voluntary isolated movements in man. *Brain Research*, **288**, 375–7.

(1984). A re-evaluation of the pattern of group I fibre projections in the human lower limb on using randomly alternated stimulations. *Experimental Brain Research*, **56**, 193–6.

Gossard, J. P., Brownstone, R. M., Barjon, I. & Hultborn, H. (1994). Transmission in a locomotor-related group Ib pathway from hindlimb extensor muscles in the cat. *Experimental Brain Research*, **98**, 213–28.

Granit, R. (1950). Reflex self-regulation of muscle contraction and autogenetic inhibition. *Journal of Neurophysiology*, **13**, 351–72.

Hammar, I., Slawinska, U. & Jankowska, E. (2002). A comparison of postactivation depression of synaptic actions evoked by different afferents and at different locations in the feline spinal cord. *Experimental Brain Research*, **145**, 126–9.

Harrison, P. J. & Jankowska, E. (1985). Source of input to interneurones mediating group I non-reciprocal inhibition of motoneurones in the cat. *Journal of Physiology (London)*, **361**, 379–401.

Hongo, T., Jankowska, E. & Lundberg, A. (1969). The rubrospinal tract. Facilitation of interneuronal transmission of reflex paths to motoneurones. *Experimental Brain Research*, **7**, 365–91.

Houk, J. C. & Henneman, E. (1967). Responses of Golgi tendon organs to active contractions of the soleus muscle in the cat. *Journal of Neurophysiology*, **30**, 466–81.

Hultborn, H., Meunier, S., Morin, C. & Pierrot-Deseilligny, E. (1987). Assessing changes in presynaptic inhibition of Ia fibres: a study in man and the cat. *Journal of Physiology (London)*, **389**, 729–56.

Hultborn, H., Conway, B. A., Gossard, J. P. *et al.* (1998). How do we approach the locomotor network in the mammalian spinal cord. *Annals of the New York Academy of Sciences*, **860**, 70–82.

Iles, J. F. & Pisini, J. V. (1992a). Vestibular-evoked postural reactions in man and modulation of transmission in spinal reflex pathways. *Journal of Physiology (London)*, **455**, 407–24.

(1992b). Cortical modulation of transmission in spinal reflex pathways of man. *Journal of Physiology (London)*, **455**, 425–46.

Iles, J. F., Stokes, M. & Young, A. (1990). Reflex actions of knee joint afferents during contraction of the human quadriceps. *Clinical Physiology*, **10**, 489–500.

Illert, M., Lundberg, A. & Tanaka, R. (1976). Integration in descending motor pathways controlling the forelimb in the cat. 2. Convergence on neurones mediating disynaptic cortico-motoneuronal excitation. *Experimental Brain Research*, **26**, 521–40.

Jami, L. (1992). Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. *Physiological Reviews*, **72**, 623–66.

Jankowska, E. (1992). Interneuronal relay in spinal pathways from proprioceptors. *Progress in Neurobiology*, **38**, 335–78.

Jankowska, E. & Lundberg, A. (1981). Interneurones in the spinal cord. *Trends in Neurosciences* **4**, 230–3.

Jankowska, E., McCrea, D. & Mackel, R. (1981). Pattern of 'non reciprocal' inhibition of motoneurones by impulses in group Ia muscle spindle afferents. *Journal of Physiology (London)*, **316**, 393–409.

Katz, R., Pénicaud, A. & Rossi, A. (1991). Reciprocal Ia inhibition between elbow flexors and extensors in the human. *Journal of Physiology (London)*, **437**, 269–86.

Lafleur, J., Zytnicki, D., Horcholle-Bossavit, G. & Jami, L. (1992). Depolarization of Ib afferent axons in the cat spinal cord during homonymous muscle contraction. *Journal of Physiology (London)*, **445**, 345–54.

(1993). Declining inhibition in ipsi-and contralateral lumbar motoneurons during contractions of an ankle extensor in the cat. *Journal of Neurophysiology*, **70**, 1797–804.

Laporte, Y. & Lloyd, D. P. C. (1952). Nature and significance of the reflex connections established by large afferent fibers of muscular origin. *American Journal of Physiology*, **169**, 609–21.

Lundberg, A., & Malmgren, K. (1988). The dynamic sensitivity of Ib inhibition. *Acta Physiologica Scandinavica*, **133**, 123–4.

Lundberg, A. & Voorhoeve, P. (1962). Effects from the pyramidal tract on spinal reflex arcs. *Acta Physiologica Scandinavica*, **56**, 201–19.

Lundberg, A., Malmgren, K. & Schomburg, E. D. (1977). Cutaneous facilitation of transmission in reflex pathways from Ib afferents to motoneurones. *Journal of Physiology (London)*, **265**, 763–80.

(1978). Role of joint afferents in motor control exemplified by effects on reflex pathways from Ib afferents. *Journal of Physiology (London)*, **284**, 327–43.

McCrea, D. (1998). Neuronal basis of afferent-evoked enhancement of locomotor activity. *Annals of the New York Academy of Sciences*, **802**, 216–25.

McCrea, D. A., Shefchyk, S. J., Stephens, M. J. & Pearson, K. G. (1995). Disynaptic group I excitation of synergist ankle extensor motoneurones during fictive locomotion in the cat. *Journal of Physiology (London)*, **487**, 385–401.

McIntyre, A. K., Proske, U. & Rawson, J. A. (1984). Cortical projection of afferent information from tendon organs in the cat. *Journal of Physiology (London)*, **354**, 395–406.

(1985). Pathway to the cerebral cortex for impulses from tendon organs in the cat's hind limb. *Journal of Physiology (London)*, **369**, 115–26.

Mao, C. C., Ashby, P., Wang, M. & McCrea, D. (1984). Synaptic connections from large muscle afferents to the motoneurones of various leg muscles in man. *Experimental Brain Research*, **56**, 341–50.

Marchand-Pauvert, V. & Nielsen, J. B. (2002). Modulation of heteronymous reflexes from ankle dorsiflexors to hamstring muscles during human walking. *Experimental Brain Research*, **142**, 402–8.

Marchand-Pauvert, V., Nicolas, G. & Pierrot-Deseilligny, E. (2000). Monosynaptic Ia projections from intrinsic hand muscles to forearm motoneurones in humans. *Journal of Physiology (London)*, **525**, 241–52.

Marchand-Pauvert, V., Nicolas, G., Burke, D. & Pierrot-Deseilligny, E. (2002). Suppression of the H reflex by disynaptic autogenetic inhibitory pathways activated by the test volley. *Journal of Physiology (London)*, **542**, 963–76.

Marque, P., Nicolas, G., Marchand-Pauvert, V., Gautier, J., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (2001a). Group I projections from intrinsic foot muscles to motoneurones of leg and thigh muscles in humans. *Journal of Physiology (London)*, **536**, 313–27.

Marque, P., Simonetta-Moreau, M., Maupas, E. & Roques, C. F. (2001b). Facilitation of transmission in heteronymous

group II pathways in spastic hemiplegic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 36–42.

Matthews, B. H. C. (1933). Nerve endings in mammalian muscle. *Journal of Physiology (London)*, **78**, 1–33.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and their Central Action*, 630 pp. London: Arnold.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta, M. (1993). Pattern of monosynaptic heteronymous Ia connections in the human lower limb. *Experimental Brain Research*, **96**, 533–44.

Nicolas, G., Marchand-Pauvert, V., Lassere, V., Guihenneuc, C., Pierrot-Deseilligny, E. & Jami, L. (2005). Perception of non-voluntary brief contractions in normal subjects and in a deafferented patient. *Experimental Brain Research*, **161**, 2056–61.

Okuma, Y., Mizuno, Y. & Lee, R. G. (2002). Reciprocal Ia inhibition in patients with asymmetric spinal spasticity. *Clinical Neurophysiology*, **113**, 292–7.

Pierrot-Deseilligny, E., Katz, R. & Morin, C. (1979). Evidence for Ib inhibition in human subjects. *Brain Research*, **166**, 176–9.

Pierrot-Deseilligny, E., Bergego, C., Katz, R. & Morin, C. (1981a). Cutaneous depression of Ib reflex pathways to motoneurones in man. *Experimental Brain Research*, **42**, 351–61.

Pierrot-Deseilligny, E., Morin, C., Bergego, C. & Tankov, N. (1981b). Pattern of group I fibre projections from ankle flexor and extensor muscles in man. *Experimental Brain Research*, **42**, 337–50.

Pierrot-Deseilligny, E., Bergego, C. & Katz, R. (1982). Reversal in cutaneous control of Ib pathways during human voluntary contraction. *Brain Research*, **233**, 400–3.

Pierrot-Deseilligny, E., Bergego, C. & Mazières, L. (1983). Reflex control of bipedal gait in man. In *Motor Control Mechanisms in Health and Disease*, ed. J. E. Desmedt, pp. 699–716. New York: Raven Press.

Pierrot-Deseilligny, E. & Fournier, E. (1986). Control of transmission in spinal pathways during movement in man – functional significance. In *Sensorimotor Plasticity: Theoretical, Experimental and Clinical Aspects*, ed. S. Ron, R. Schmid & M. Jeannerod, pp. 385–95. Paris: Les Editions INSERM.

Pötter, M., Illert, M., Wenzelburger, R., Deuschl, G. & Volkmann, J. (2004). The effect of subthalamic stimulation on autogenetic inhibition in Parkinson's disease. *Neurology*, **63**, 1234–9.

Priori, A., Berardelli, A., Inghilleri, M., Pedace, F., Giovannelli, M. & Manfredi, M. (1998). Electrical stimulation over muscle tendons in humans. Evidence favouring presynaptic inhibition of Ia fibres due to the activation of group III tendon afferents. *Brain*, **121**, 373–80.

Proske, U. (1981). The Golgi tendon organ. Properties of the receptor and reflex action of impulses arising from tendon organs. *International Review of Physiology*, **25**, 127–71.

Quevedo, J., Fedirchuk, B., Gosgnach, S. & McCrea, D. A. (2000). Group I disynaptic excitation of cat hindlimb flexor and bifunctional motoneurones during fictive locomotion. *Journal of Physiology (London)*, **525**, 549–64.

Rossi, A. & Decchi, B. (1995). Cutaneous nociceptive facilitation of Ib heteronymous pathways to lower limb motoneurones in humans. *Brain Research*, **700**, 164–72.

(1997). Changes in Ib heteronymous inhibition to soleus motoneurones during cutaneous and muscle nociceptive stimulation in humans. *Brain Research*, **774**, 55–61.

Rossi, A., Decchi, B., Dami, S., Della Volpe, R. & Groccia, V. (1999a). On the effect of chemically activated fine muscle afferents of interneurones mediating group I nonreciprocal inhibition of extensor ankle and knee muscles in humans. *Brain Research*, **815**, 106–10.

Rossi, A., Decchi, B. & Ginanneschi, F. (1999b). Presynaptic excitability of group Ia fibres to muscle nociceptive stimulation in humans. *Brain Research*, **818**, 12–22.

Rudomin, P. & Schmidt, R. F. (1999). Presynaptic inhibition in the vertebrate spinal cord revisited. *Experimental Brain Research*, **129**, 1–37.

Rymer, W. Z., Houk, J. C. & Crago, P. E. (1979). Mechanisms of the clasp-knife reflex studied in an animal model. *Experimental Brain Research*, **37**, 93–113.

Schieppati, M., Romano, C. & Gritti, I. (1990). Convergence of Ia fibres from synergistic and antagonistic muscles onto interneurones inhibitory to soleus in humans. *Journal of Physiology (London)*, **431**, 365–77.

Sherrington, C. (1909). On plastic tonus and proprioceptive reflexes. *Quarterly Journal of Experimental Physiology*, **2**, 109–56.

Stephens, M. J. & Yang, J. F. (1996). Short latency, non-reciprocal group I inhibition is reduced during the stance phase of walking in humans. *Brain Research*, **743**, 24–31.

Trembley, F. & Trembley, L. (2002). Cortico-motor excitability of the lower limb motor representation: a comparative study in Parkinson's disease and healthy controls. *Clinical Neurophysiology*, **113**, 2006–12.

Wargon, I., Lamy, J. C., Baret, M., Aymard, C., Pénicaud, A. & Katz, R. (2005). The disynaptic inhibition between wrist flexor and extensor muscles revisited in humans. *Experimental Brain Research*, submitted.

Yanagawa, S., Shindo, M. & Nakagawa, S. (1991). Increase in Ib inhibition on voluntary contraction of antagonistic muscles in man. *Journal of Physiology (London)*, **440**, 311–23.

Yanagisawa, N. (1980). Reciprocal reflex connections in motor disorders in man. In *Spinal and Supraspinal Mechanisms of Voluntary Motor Control and Locomotion*, ed. J. E. Desmedt, pp. 129–41. Basel: Karger.

Yanagisawa, N., Tanaka, R. & Ito, Z. (1976). Reciprocal Ia inhibition in spastic hemiplegia of man. *Brain*, **99**, 555–74.

Zytnicki, D. & Jami, L. (1998). Presynaptic inhibition can act as a filter of input from tendon organs during muscle contraction. In *Presynaptic Inhibition and Neural Control*, ed. P. Rudomin, R. Romo & L. Mendell, pp. 303–14. Oxford: Oxford University Press.

Zytnicki, D., Lafleur, J., Horscholle-Bossavit, G., Lamy, F. & Jami, L. (1990). Reduction of Ib autogenetic inhibition in motoneurons during contractions of an ankle extensor muscle in the cat. *Journal of Neurophysiology*, **64**, 1380–9.

7

Group II pathways

Although group II afferents from muscle spindles are more numerous than Ia afferents, the role of secondary spindle afferents in spinal motor control was originally largely neglected and then vigorously debated. There are two reasons for this difference in the treatment of the pathways fed by the two types of spindle afferent. First, Ia effects are easier to investigate because they appear first in motoneurones after peripheral nerve stimulation and do so at lower threshold. It is therefore impossible to stimulate group II afferents selectively: (i) group I and group II fibres travel along the same nerve trunks and electrical stimulation of any muscle nerve will necessarily activate low-threshold group I afferents first; and (ii) it is not possible to activate spindle secondary endings by their specific stimulus, i.e. muscle stretch, without also activating the primary endings. Secondly, the asymmetry of group II actions with dominant flexor excitation and extensor inhibition found in investigations performed in the 1940s–1950s in anaesthetised low spinal cats led to their assignment to the 'flexor reflex afferents' (FRA) group. Only recently has it become possible to investigate group II pathways in human subjects. Most of the group II effects investigated so far appear superimposed on group I effects, and this has required special attention to identifying criteria. Nevertheless, these investigations have led to the view that they play a major role in the normal control of posture and gait and in pathophysiology of movement disorders.

Background from animal experiments

Initial findings

The investigation of the reflex effects of group II muscle afferents started with the documentation of the actions of muscle afferents of smaller diameter than group I afferents (Lloyd, 1943, 1946). Electrical stimulation of group II afferents from both flexors and extensors was shown to facilitate monosynaptic reflexes of flexors and to inhibit those of extensors (Lloyd, 1946; Laporte & Lloyd, 1952). Adequate stimulation of muscle receptors demonstrated that these effects resulted mainly from stimulation of secondary spindle afferents (Laporte & Bessou, 1959). The asymmetry in favour of flexors in anaesthetised low spinal cats was confirmed with intracellular recording techniques (R. M. Eccles & Lundberg, 1959). However, alternative pathways with activation of extensors were also revealed by a low pontine lesion in the decerebrate animal (Holmqvist & Lundberg, 1961) and, in their seminal paper, R. M. Eccles & Lundberg (1959) postulated that group II muscle afferents '*may* evoke the flexion reflex', not that they *must* evoke stereotyped flexor actions (see Schomburg, 1990). The complex spinal organisation of group II pathways was revisited in the 1980s by Jankowska and colleagues (see Jankowska, 1992). In parallel, Matthews (1989) developed a method now widely used to demonstrate

group II excitation in humans (cooling of peripheral nerves, see p. 297; though when first using it looking for a group II reflex in hand muscles, Matthews failed to find such evidence). The following description of group II pathways is based on comprehensive reviews by Schomburg (1990) and Jankowska (1992).

Muscle spindle secondary endings and group II afferents

Muscle spindle secondary endings

Secondary endings are located on either side of the central region of the muscle spindle, mainly on chain fibres and occasionally on one of the bag fibres (the static bag_2 fibre). A spindle contains 0–5 secondary endings, each of which gives rise to a group II afferent. Secondary and primary endings are similarly sensitive to the static component of stretch, but the secondary endings are much less sensitive to the dynamic component (see Matthews, 1972). The bag_2 fibre and chain fibres are innervated by static fusimotor (γ_s) axons which increase the static sensitivity of the primary and secondary endings. Secondary endings are much less sensitive to vibration than primary endings, but human secondary endings may respond to vibration as it must be applied in intact human volunteers (see Chapter 3, p. 130).

Group II afferents

Group II afferents have axons of 4–12 μm diameter and conduction velocities of 24–72 m s^{-1} in the cat (though some group II afferents conduct at higher velocities). In muscle nerves, most arise from spindle secondary endings and their electrical threshold is about twice that of Ia afferents. Their conduction velocity is significantly slower in humans than in cats, but the ratios found for conduction velocity and electrical threshold of group II/Ia afferents are probably similar in the two species (cf. p. 303). Calculations of the synaptic linkage from latency measurements in spinal neurones must take into account that conduction in secondary spindle afferents may slow down more than in Ia afferents within the spinal cord, and this can add up to 1.2 ms to the central conduction time (see Schomburg, 1990).

Synaptic linkage

Monosynaptic excitatory projections

A monosynaptic excitatory projection from secondary spindle afferents to homonymous motoneurones has been demonstrated in thoracic and triceps surae motoneurones (Kirkwood & Sears, 1975; Stauffer *et al.*, 1976). However, the monosynaptic connections from group II muscle afferents are weak, and the major effects from secondary spindle afferents on motoneurones are exerted via interneuronal pathways (Lundberg, Malmgren & Schomburg, 1977). The most direct linkage in both excitatory and inhibitory interneuronal pathways is disynaptic (see below, and Fig. 7.1(*a*), (*b*)).

Group II interneurones

Interneurones on which group II afferents synapse have been found in two main locations: in the dorsal horn (laminae IV–V) and in the intermediate zone/ventral horn (laminae VI–VIII). Only the intermediate zone interneurones synapse on ipsilateral motoneurones and are, accordingly, referred to as 'group II interneurones' in the following (see Jankowska, 1992). Because their concentration is particularly high in midlumbar (L3–L4–L5) segments, where they constitute a major component of the ventromedial lumbar propriospinal system (see Chapter 10, p. 491), they are also referred to as 'lumbar propriospinal neurones' in the following (Fig. 7.1(*a*), (*b*)). However, many group II interneurones have also been found caudal to L6 (Cavallari & Pettersson, 1991; Riddell & Hadian, 2000). Finally, more ventrally located interneurones with group II input appear to be primarily commissural interneurones which synapse with contralateral motoneurones (Jankowska, Slawinska & Hammar, 2002).

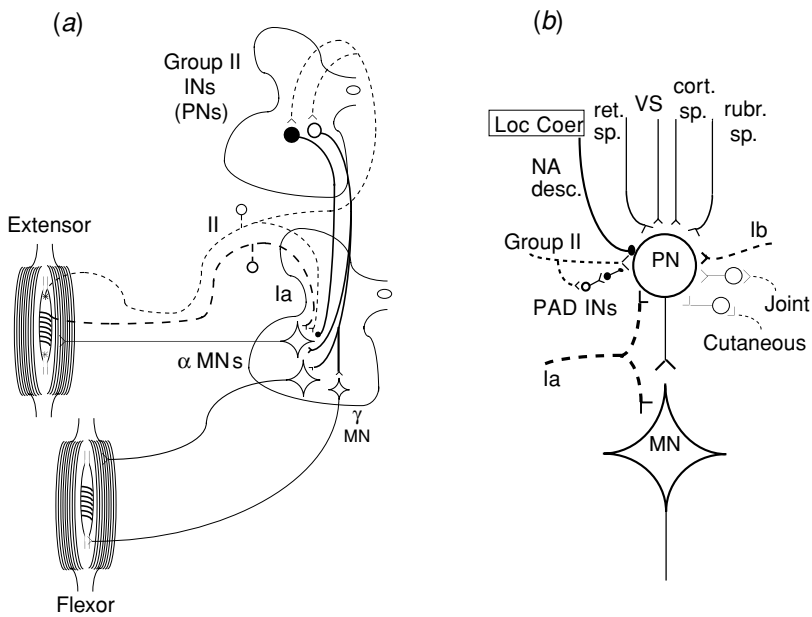


Fig. 7.1. Wiring diagram of the connections of group II pathways. (*a*), (*b*) In this and subsequent figures, excitatory synapses are represented by Y-shaped bars and inhibitory synapses by small filled circles, excitatory interneurones by open circles and inhibitory interneurones by filled circles, group II afferents by dotted lines, Ia afferents by dashed lines, cutaneous and joint afferents by thin dotted lines. (*a*) Projections of group II afferents originating from a muscle spindle secondary ending of an extensor muscle have weak homonymous monosynaptic projections, disynaptic excitatory and inhibitory projections on homonymous α motoneurones (MN), and disynaptic excitatory projections on α MNs of flexors (inhibitory projections on flexor MNs have been omitted). Projections on γ MNs of flexors are also represented. Interneurones (IN) mediating these disynaptic effects are 'propriospinal neurones' (PN) located rostral to MNs. (*b*) Extensive convergence onto a group II IN (PN) of various afferents and descending tracts, with excitatory projections from group II, Ia, Ib and, via interposed INs, cutaneous and joint afferents, and from descending tracts: corticospinal (cort.sp.), rubrospinal (rubr.sp.), vestibulo-spinal (VS) and reticulospinal (ref.sp.). (In fact, separate subsets of group II INs are excited by cortico- and rubro-spinal tracts on the one hand, and by vestibulo- and reticulo-spinal tracts on the other hand). Transmission of group II effects to INs are gated by presynaptic inhibition with primary afferent depolarisation (through PAD INs) and by a noradrenergic descending (NA desc.) system from the locus coeruleus (Loc Coer). The gating may be pre- and/or post-synaptic but, for simplicity sake, it is represented as acting presynaptically in the following sketches. The PN is sketched to mediate excitatory effects on MNs, because so far there is only evidence for group II excitation in humans.

Transmission through group II pathways

Transmission through group II interneurones is very effective, with large unitary EPSPs in interneurones and little or no opportunity for spatial and temporal summation. It is likely that these EPSPs are sufficient to discharge the interneurone even though evoked from a single afferent. Thus, the disynaptic linkage may function almost like a monosynaptic linkage, if the interneurones are provided with some background activity from peripheral or descending sources (Lundberg, Malmgren & Schomburg, 1987b, c).

Conclusions

It can be stated that 'intermediate zone/ventral horn interneurones may be activated by group II afferents both directly and via dorsal horn interneurones,

and that synaptic action of group II afferents upon these interneurones, and their subsequent actions upon α motoneurones, may be modulated in parallel at the level of intermediate zone/ventral horn and dorsal horn interneurones' (Jankowska, Slawinska & Hammar, 2002).

Projections from group II interneurones

α motoneurones

In anaesthetised low spinal cats, there is an asymmetry of group II projections to ipsilateral α motoneurones, with a dominant pattern of flexor excitation and extensor inhibition, whatever the muscle of origin. This led to the view that group II actions form a component of flexor reflexes and that group II afferents are exclusively 'FRA'. However, in the decerebrate animal, alternative pathways may be revealed by a low pontine lesion (Holmqvist & Lundberg, 1961), and group II EPSPs in extensor motoneurones are more common in unanaesthetized high and low spinal cats (Wilson & Kato, 1965; Hongo & Pettersson, 1988). It has been suggested that the group II IPSPs evoked in feline motoneurones by electrical stimuli in the group II range are produced by non-spindle group II afferents (Rymer, Houk & Crago, 1979), but there is convincing evidence for spindle group II IPSPs in cat motoneurones (Lundberg, Malmgren & Schomburg, 1987a).

γ motoneurones

γ motoneurones receive strong excitation from group II interneurones and weaker monosynaptic excitation from group II afferents (Gladden, Jankowska & Czarkowska-Bauch, 1998). Most γ motoneurones are excited by group II afferents from several muscles, both flexors and extensors. Excitation of γ motoneurones by the homonymous mono- and non-monosynaptic actions of group II afferents would create a positive-feedback loop, which would be self-reinforcing but potentially unstable.

Mutual inhibition of group II interneurones

Group II afferents evoke disynaptic IPSPs in group II interneurones, with or without monosynaptic group II EPSPs, a finding which indicates that subgroups of group II interneurones mutually inhibit each other (Edgley & Jankowska, 1987).

Excitatory inputs to group II interneurones

Group II afferents

Interneurones in different segments differ greatly in the muscle of origin of their group II input: interneurones in the L3–L5 segments are excited primarily by group II afferents from quadriceps, sartorius, gracilis, peroneus and flexor digitorum longus (Edgley & Jankowska, 1987), while group II afferents from other muscles provide input only to interneurones of more caudal segments (Fukushima & Kato, 1975; Lundberg, Malmgren & Schomburg, 1987b; Riddell & Hadian, 2000). There is wide convergence and divergence in group II pathways. Through interneuronal connections group II afferents from one muscle may reach different motoneurone pools of the limb, and correspondingly each motoneurone receives input from group II afferents from different muscles of the limb, both flexors and extensors. This convergence takes place partly at the motoneuronal level and partly at the interneuronal level. Recordings from single interneurones have revealed monosynaptic group II EPSPs only from afferents of a few different muscles, and there are many subgroups of group II interneurones, with a different convergent input from different muscles (Lundberg, Malmgren & Schomburg, 1987b, c).

Other peripheral afferents

Group Ia and Ib afferents constitute the other major source of peripheral input to group II interneurones, present in >60% of group II interneurones (Edgley & Jankowska, 1987; Fig. 7.11(*b*)). Other afferents (low-threshold afferents in cutaneous, joint

and interosseous nerves, and some higher-threshold afferents belonging to the FRA) excite smaller proportions of group II interneurones (cf. Jankowska, 1992).

Descending tracts

Most midlumbar group II interneurones receive monosynaptic excitation from descending motor pathways. Separate subpopulations of group II interneurones are excited by cortico- and rubrospinal tracts on the one hand, and by vestibulo- and reticulo-spinal tracts on the other hand (Davies & Edgley, 1994; Fig. 7.11(*b*)).

Crossed input

Contrary to input from Ia afferents, which is almost exclusively ipsilateral (Harrison & Zytnicki, 1984), both ipsilateral and contralateral group II afferents provide input to group II interneurones. The most direct excitatory actions of contralateral group II afferents are disynaptic (Bajwa, Edgley & Harrison, 1992).

Inhibitory control systems

Post-synaptic inhibition

Mutual inhibition of group II interneurones may be evoked by group II volleys and by volleys in group I, cutaneous and joint afferents. Group II interneurones are also inhibited by interneurones mediating non-reciprocal group I inhibition.

Presynaptic inhibition with PAD

Group II afferent terminals are strongly depolarised by group II muscle afferents and by cutaneous and joint afferents, but only weakly and occasionally by group I muscle afferents (see Jankowska & Riddell, 1998). Since group II interneurones may modify the sensitivity of muscle spindles via γ-motoneurones (see above), it has been proposed that presynaptic inhibition of group II terminals on group II interneurones provides a negative feedback preventing the instability that positive feedback could cause. PAD interneurones projecting to group II terminals are activated by stimulation of the reticular formation, locus coeruleus and raphe nuclei in the medulla. Thus, presynaptic inhibition may also contribute to the feed-forward control of the activity of group II interneurones.

Monoaminergic modulation

The second main system of inhibitory control of group II interneurones is that of noradrenergic descending tract neurones arising from the locus coeruleus/subcoeruleus in the brainstem. Both local application of noradrenaline and stimulation within the region of the locus coeruleus selectively depress the synaptic actions of group II afferents (see Jankowska & Riddell, 1998). Synaptic actions of group I afferents are then not influenced or even enhanced (Jankowska *et al.*, 2000). Tizanidine, an α_2 adrenergic receptor agonist, appears to be particularly effective in producing selective blockade of transmission from group II afferents (Bras *et al.*, 1990). Group II excitatory effects onto γ motoneurones are also strongly depressed by noradrenergic agonists (Jankowska, Gladden & Czarkowska-Bauch, 1998). Note that 5-HT-releasing raphe-spinal neurones may have opposite actions on group II interneurones, facilitating their activation by group II afferents (Jankowska *et al.*, 2000). The monoamines may act pre- and/or post-synaptically, but the mechanisms of their differential action on transmission from group I and group II afferents are not yet resolved. In any event, the selective noradrenergic gating of group II excitation of motoneurones provides the unique possibility in human studies of producing pharmacological evidence for transmission through the pathway.

Post-activation depression

Post-activation depression of transmission to interneurones of the feline intermediate zone fed by group I and group II afferents is marginal, much

weaker than with dorsal horn interneurones fed by group II afferents (Hammar, Slawinska & Jankowska, 2002).

Methodology

Underlying principles

Group II afferents may be activated by stretching the receptor-bearing muscle or by electrical stimulation. However, such stimuli also activate group I afferents, and group II excitation is always superimposed on group I effects. Several criteria may be used to attribute a response to the activation of group II pathways: (i) longer latency than that of the monosynaptic Ia excitation due to the slower conduction velocity of the afferent fibres, (ii) electrical threshold about twice that of group Ia excitation, and (iii) suppression by tizanidine.

Stretch-induced homonymous group II excitation of leg and foot muscles

This technique has been used extensively by Schieppati and colleagues (Nardone *et al.*, 1990b; Schieppati *et al.*, 1995; Schieppati & Nardone, 1999). Subjects stand at ease, eyes open and arms by their sides on a rotating platform, and the averaged rectified on-going EMG activity of leg and foot muscles is recorded during rotation of the platform around an axis parallel to the ankle (Fig. 7.2(*b*)). Toe-up rotation of the platform produces a biphasic EMG response in soleus and flexor digitorum brevis, with short- and medium-latency responses (Fig. 7.2(*c*), (*d*) and its legend). The mean latency of the short-latency response (SLR) is compatible with a monosynaptic Ia response. Medium-latency responses (MLR) occur ~35 and 40 ms later in soleus and flexor digitorum brevis, respectively. Toe-down rotation of the platform elicits only a medium-latency response in tibialis anterior (Fig. 7.2(*m*)), not preceded by a short-latency response (unless the perturbation is very fast, cf. Chapter 2, p. 90).

Electrically induced heteronymous group II excitation

Group II excitation produced by electrically induced muscle group II volleys can be assessed in heteronymous motoneurones using the modulation of the H reflex, the PSTHs of single units, or the on-going EMG. The latency of the late excitation is compared to the expected time of arrival of a group I volley in the 'conditioning nerve' at the tested motoneurone pool (estimated as explained in Chapter 2, pp. 70–2).

Late high-threshold facilitation of the H reflex

(i) Stimulation of the gastrocnemius medialis nerve at 2 × MT produces a huge facilitation of the semitendinosus H reflex (Simonetta-Moreau *et al.*, 1999). The facilitation has a relatively high threshold, between 1.2 and 1.3 × MT (Fig. 7.3(*d*)), and appears 12 ms later than the expected arrival of the conditioning group I volley at the motoneurone (Fig. 7.3(*e*)). In this experimental paradigm, group II excitation is not contaminated significantly by a preceding group I effect. However, the H reflex can be recorded easily in semitendinosus only in thin subjects.

(ii) Stimuli to the common peroneal nerve produce more complex effects on the quadriceps H reflex, because the late high-threshold reflex facilitation observed with a stimulation at 2–3 × MT is superimposed on earlier group I effects (Fig. 7.4(*b*); Marque, Pierrot-Deseilligny & Simonetta-Moreau, 1996). An early excitation is the only effect obtained with stimuli <1 × MT. It starts 3 ms after the expected arrival of the group I volley at the motoneurone pool, peaks 1–2 ms later and then progressively declines (see Forget *et al.*, 1989; Chapter 10, p. 493). The late peak requires higher stimulus intensities, >1.2–1.5 × MT, and appears ~6 ms later.

(iii) Stimuli to the tibial nerve at 2 × MT also produce complex effects on the quadriceps H reflex with, successively, monosynaptic Ia excitation, subsequent group I inhibition mediated by inhibitory interneurones located at a different

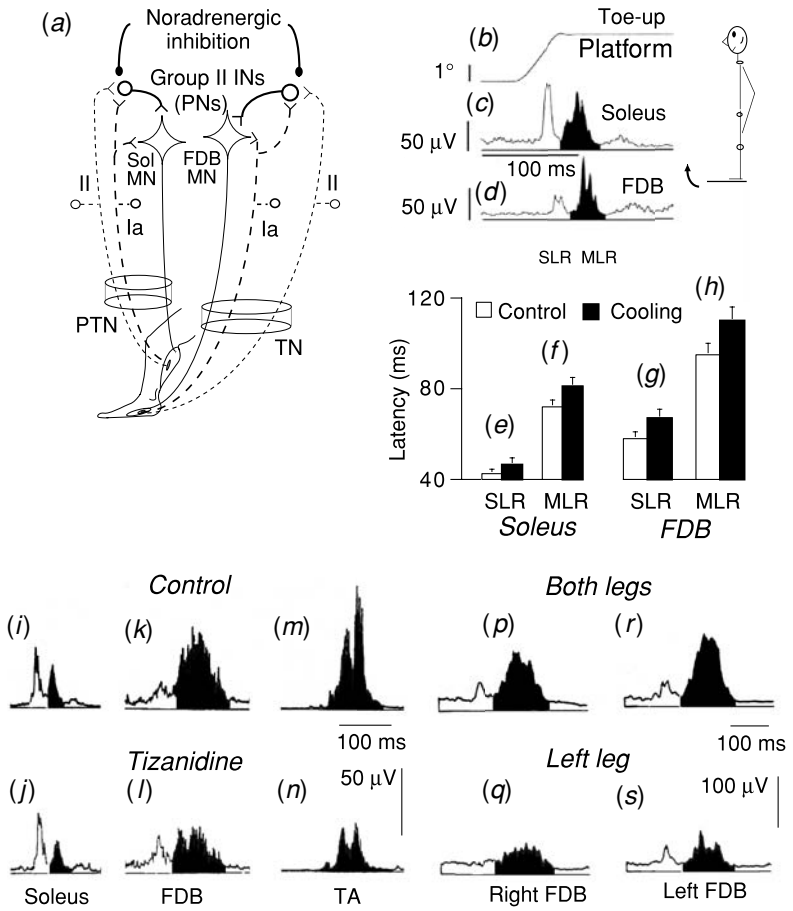


Fig. 7.2. Homonymous early- and medium-latency responses to stretch in leg and foot muscles. (*a*) Sketch of the presumed pathways, with monosynaptic projections on motoneurones (MN) of Ia afferents, convergence of Ia and group II afferents onto group II excitatory interneurones (IN or PN) projecting on soleus (Sol) and flexor digitorum brevis (FDB) motoneurones (MN), and noradrenergic descending inhibition of the transmission of group II excitation. (*b*) Toe-up rotation of the platform (3° from the initial position, at a velocity of 50° s^{-1}) stretched Sol and FDB and produced in the rectified EMG of the Sol ((*c*), (*i*), (*j*)) and FDB ((*d*), (*k*), (*l*), (*p*)–(*s*)) a short-latency (SLR, mean latencies 44.6 and 61.3 ms, respectively) and a medium-latency (MLR, black area, mean latencies 80 and 102 ms, respectively) response, averaged over 30 ((*c*), (*d*), (*p*)–(*s*)) or 15 ((*i*)–(*n*)) trials, whereas a toe-down rotation of the platform produced the MLR in the tibialis anterior (TA) ((*m*), (*n*)), mean latency 79.7 ms). (*e*)–(*h*) Effect of cooling the leg (for 20–40 minutes) on the latency of the SLR ((*e*), (*g*)) and MLR ((*f*), (*h*)) in the Sol ((*e*), (*f*)) and FDB ((*g*), (*h*)); latencies are compared in the control situation (□) and during cooling (■). On average, the increases in latencies were 4.6 and 8.4 ms for the SLR and 10.3 and 14.6 ms for the MLR in the Sol and FDB, respectively. (*i*)–(*n*) Comparison of the responses in soleus ((*i*), (*j*)) and FDB ((*k*), (*l*)) after toe-up rotation and in TA after toe-down rotation ((*m*), (*n*)) in the control situation ((*i*) (*k*) (*m*)) and 145 min after oral intake of tizanidine 150 μg kg^{-1} ((*j*), (*l*), (*n*)). MLR (black area) is reduced after tizanidine in all three muscles. (*p*)–(*s*) Responses in the right ((*p*), (*q*)) and left ((*r*), (*s*)) FDB are compared when both legs ((*p*), (*r*)) or only the left leg ((*q*), (*s*)) were on the supporting platform. After unilateral stretch of the left leg, the MLR is decreased and delayed by 5 ms in the left leg (*s*), but persists in the right leg, although further decreased and delayed with respect to the left leg (*q*). (*i*)–(*s*) The onset of the perturbation corresponds to the onset of the trace. Modified from Schieppati & Nardone (1999) ((*b*)–(*h*)), Corna *et al.* (1995) ((*i*)–(*n*)), and Corna *et al.* (1996) ((*p*)–(*s*)), with permission.

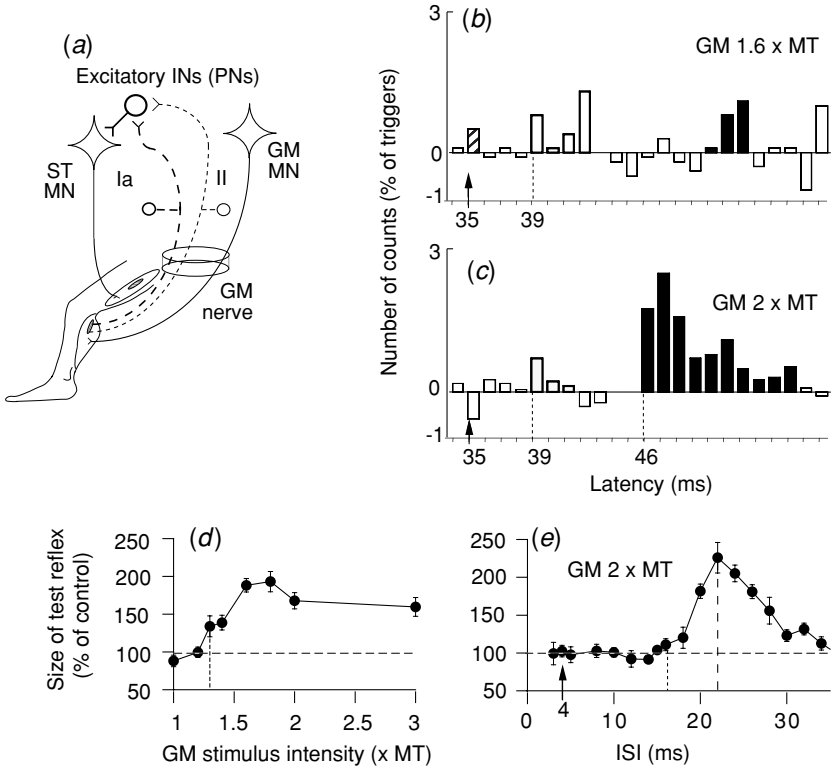


Fig. 7.3. Heteronymous group II excitation from gastrocnemius medialis to semitendinosus. (*a*) Sketch of the presumed pathways, with convergence of Ia and group II afferents from the gastrocnemius medialis (GM) onto excitatory interneurones (IN or PN) projecting onto semitendinosus (ST) motoneurones (MN). (*b*), (*c*) PSTHs (after subtraction of the background firing, 1 ms bin width) of a ST unit after stimulation of the GM nerve ((*b*), 1.6 × MT; (*c*), 2 × MT). Vertical dotted lines indicate the onset of the early non-monosynaptic group I (□) and late group II (■) peaks, with their latencies. The small dashed column in (*b*) occurs at monosynaptic Ia latency. The non-monosynaptic group I excitation observed at 1.6 × MT decreased when the stimulus intensity was increased to 2 × MT. (*d*), (*e*) Changes in the ST H reflex (as a percentage of its unconditioned value) elicited by a volley to the GM nerve are plotted against the interstimulus interval (ISI) ((*e*), GM nerve intensity at 2 × MT) and the intensity of the conditioning stimulus ((*d*), 22 ms ISI) (unconditioned H reflex 19% of M_{max}). Each symbol in (*d*), (*e*) is the mean of 20 measurements; vertical bars ±1 SEM. The arrows in (*b*), (*c*), (*e*) indicate the expected time of arrival of the GM Ia volley at the segmental level of ST MNs (4 ms ISI in (*e*)). Vertical lines highlight, in (*d*), the threshold of the group II excitation, between 1.2 and 1.3 × MT, and, in (*e*), the onset (dotted line, 16 ms) and the peak (dashed line, 22 ms) of the reflex facilitation. Modified from Simonetta-Moreau *et al.* (1999), with permission.

segmental level than motoneurones (see Marque *et al.*, 2001a; Chapter 10, p. 497), and a large facilitation at long interstimulus intervals (ISIs) (Fig. 7.6(*b*)). Again, the threshold for the late facilitation is relatively high (1.3 × MT, Fig. 7.6(*c*), Marque *et al.*, 2005).

PSTHs

PSTHs of single motor units have provided an invaluable tool for investigating the distribution of group II excitation (Simonetta-Moreau *et al.*, 1999; Marque *et al.*, 2005). Results in several nerve–muscle

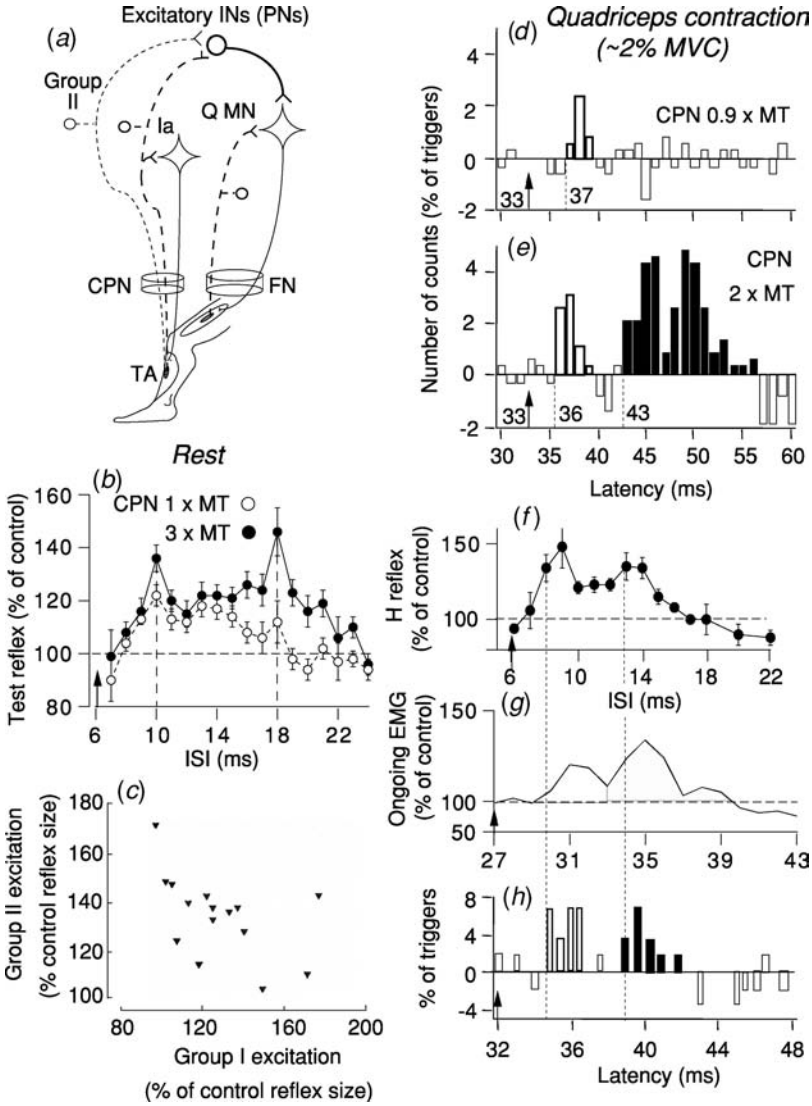


Fig. 7.4. Heteronymous group I–group II excitation from pretibial flexors to quadriceps. (*a*) Sketch of the presumed pathways with convergence of Ia and group II afferents from the tibialis anterior (TA) onto excitatory interneurones (IN or PN) projecting onto quadriceps (Q) motoneurones (MN). (*b*) Changes in the Q H reflex (as a percentage of its control value) produced by a stimulus to the common peroneal nerve (CPN) at 1 (○) and 3 (●) × MT plotted against the interstimulus interval (ISI) (unconditioned H reflex 20% of M_{max}). (*c*) Group II CPN-induced facilitation of the Q H reflex plotted against the group I facilitation (each point represents one subject, CPN at 3–4 × MT), both effects measured at their peak (vertical dashed lines in (*b*)) and expressed as a percentage of the control reflex. (*d*), (*e*) PSTHs (after subtraction of the background firing, 1 ms bin width) of a vastus lateralis (VL) unit after CPN stimulation ((*d*), 0.9 × MT; (*e*), 2 × MT), with early (□) and late (■) peaks. (*f*)–(*h*) Changes induced by a CPN volley (1.5 × MT) in different recordings from the VL: H reflex (*f*), rectified on-going EMG ((*g*), 150 sweeps) and PSTH (0.5 ms bin width) of a single unit (*h*) during the same experiment with a weak (2% MVC) Q voluntary contraction. Each symbol in (*b*), (*f*) is the mean of 20 measurements; vertical bars ±1 SEM. Arrows in (*b*) and (*d*)–(*h*), expected time of arrival of the CPN Ia volley at the segmental level of Q MNs (i.e. the 6 ms ISI in (*b*), (*f*) is the zero central delay for Ia effects). Vertical dotted lines in (*d*)–(*h*) highlight the onset of the early and late peaks (with their latencies in the PSTHs in (*d*), (*e*)). Note that the differences in latencies of the early and late responses in (*f*)–(*h*) are the same. Modified from Marque, Pierrot-Deseilligny & Simonetta-Moreau (1996) (*b*), Chaix *et al.* (1997) (*c*), Simonetta-Moreau *et al.* (1999) ((*d*), (*e*)), and Marchand-Pauvert *et al.* (2005), with permission.

combinations have revealed the existence of a peak of late high-threshold excitation, and two examples are shown below. In the semitendinosus unit illustrated in Fig. 7.3(*b*), (*c*), the large late excitation, occurring 11 ms after the expected arrival of the gastrocnemius medialis group I conditioning volley at motoneurone level, was present with a stimulus intensity of 2 × MT, but not 1.6 × MT. In Fig. 7.4(*d*), (*e*), stimuli to the common peroneal nerve <1 × MT produced an early peak of non-monosynaptic group I excitation with a central delay of 3–4 ms in this vastus lateralis unit. However, increasing the stimulus intensity above 1.5–2 × MT caused a second, larger peak to appear 5–7 ms later, i.e. 9–11 ms after the expected arrival of the group I conditioning volley at motoneurone level.

Modulation of the on-going EMG

Modulation of the on-going EMG is a suitable method to compare the amount of group II excitation in two motor tasks, at equivalent levels of background EMG activity (during, e.g. gait and voluntary contraction, see Fig. 7.12(*b*)–(*c*)). The experiment illustrated in Fig. 7.4(*f*)–(*h*) shows that, during a weak quadriceps voluntary contraction, deep peroneal stimulation at 1.5 × MT produced a similar biphasic facilitation of the H reflex, of the rectified on-going EMG, and in the PSTH of a single motor unit of the quadriceps. The differences in latencies of the early and late responses are much the same with the three methods (Marchand-Pauvert *et al.*, 2005).

Evidence for muscle group II excitation

Evidence that the late excitation is not due to fusimotor axon stimulation

Because the conditioning volley evokes Ia excitation (mono- and/or non-monosynaptic) in the same motoneurones, it is conceivable that late peaks produced by electrical stimuli >1 × MT may result from a motor- or fusimotor-induced Ia discharge (as explained in the legend of Fig. 7.5(*a*)). However, the difference in latencies of the early and late peaks is longer after more distal stimulation, a finding that is not consistent with this possibility (cf. Fig. 7.5(*a*) and its legend; Fig. 7.5(*b*), (*c*); Simonetta-Moreau *et al.*, 1999).

Evidence for slowly conducting afferents

Underlying principle behind cooling experiments

The longer latency of the stretch-induced medium-latency excitation or of the late response evoked by electrical stimulation might be produced by either slower conduction in the peripheral afferent pathway or by a longer central pathway fed by Ia afferents. To distinguish between these two possibilities, Matthews (1989) developed a technique of cooling the limb. The rationale behind this technique is that cooling a nerve decreases conduction velocity proportionally in large and small fibres (Paintal, 1965; Franz & Iggo, 1968), thereby leading to a longer absolute delay in the transmission over a fixed distance of impulses travelling along group II fibres than for those travelling along Ia afferents.

Responses to stretch

During cooling, the increases in latency of the medium-latency responses were significantly greater than those of the short-latency Ia-mediated responses in both the soleus and the flexor digitorum brevis (Fig. 7.2(*e*)–(*h*); Schieppati & Nardone, 1997). In addition, the finding that the taller the subject the greater the difference between the latencies of the early and late responses provided further evidence for a slower conduction velocity of the afferent fibres responsible for the medium-latency response (Nardone *et al.*, 1996). However, in hand muscles, the late response is mediated through a long-loop pathway fed by the same Ia input as the early response (cf. Chapter 2, p. 92), and the difference in latencies of the two responses is independent of height (Noth *et al.*, 1991).

Electrically induced responses

Cooling the peroneal nerve increased the latency of the heteronymous late excitation more than that of the early group I non-monosynaptic excitation

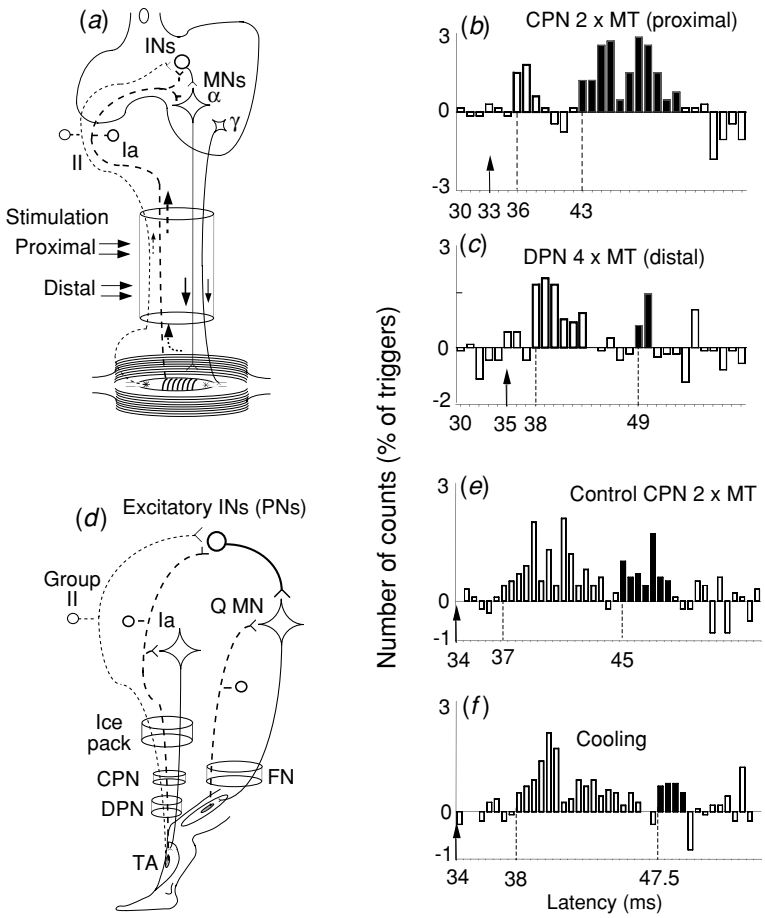


Fig. 7.5. Evidence that the late excitation is mediated through group II afferents. (*a*) Sketch illustrating the differentiation between late fusimotor-induced Ia effects and effects due to slow afferents. Stimulation >1 × MT elicits a discharge in Ia (upward thick dashed arrow) and group II (upward thin dotted arrow) afferents, but also in α (downward thick continuous arrow) and β-γ (downward thin continuous arrow) efferents. The efferent volley could produce a late Ia discharge (upward bent dotted arrow), due to an early discharge (Hunt & Kuffler, 1951) associated with the α volley and/or an activation of primary endings by the fusimotor volley. If this were the case, distal stimulation should decrease the latency difference between early and late peaks, because the conduction distance along motor axons (from stimulation site to muscle spindles) would then be decreased. In contrast, with slow afferent fibres, the latency difference for a late excitation should be increased. (*b*), (*c*) PSTHs (after subtraction of the background firing, 1 ms bin width) of a vastus lateralis (VL) unit after stimulation of the common peroneal nerve (CPN, (*b*), 2 × MT) and deep peroneal nerve (DPN, (*c*), 4 × MT, stimulated 12 cm more distally than the CPN). The latencies of both peaks were longer after more distal stimulation: 38 vs. 36 ms for the early peak and 49 vs. 43 ms for the late peak, suggesting that the latter is mediated via afferents with a slower conduction velocity than Ia afferents. (*d*) Sketch of the presumed pathways with convergence of Ia and group II afferents from the tibialis anterior (TA) onto excitatory interneurones (IN or PN) projecting to quadriceps (Q) MNs. ((*e*), (*f*)) PSTHs (after subtraction of the background firing, 0.5 ms bin width) of another VL unit after stimulation of the CPN (2 × MT) in a control situation (*e*), and during cooling of the CPN ((*f*), 20–40 minutes). Cooling increased more the latency of the late excitation (2.5 ms, from 45 to 47.5 ms) than that of the early peak (1 ms, from 37 to 38 ms). After rewarming, the latencies of the responses recovered towards control values (not illustrated). (*b*), (*c*), (*e*), (*f*) Arrows indicate the expected time of arrival of the CPN Ia volley at the level of Q MNs. Vertical dotted lines highlight the onset of the early (□) and late (■) peaks, with their latencies. Modified from Simonetta-Moreau *et al.* (1999), with permission.

in the PSTHs of quadriceps units (Fig. 7.5(*e*), (*f*); Simonetta-Moreau *et al.*, 1999). This differential effect of cooling provides evidence that the longer latency of the late responses is not due to a longer central pathway fed by Ia afferents, but to the activation of peripheral afferents of slower conduction velocity.

Pharmacological validation

Oral intake of tizanidine (150 μg kg^{-1}) suppresses medium-latency responses produced by stretch in foot and leg muscles, while short-latency responses in the soleus and flexor digitorum brevis are not modified (Fig. 7.2(*i*)–(*n*); Corna *et al.*, 1995). Similarly, tizanidine reduces the late peak produced in the on-going EMG of the peroneus brevis by stimulation of the tibial nerve at 1.5 × MT, but does not modify the early peak due to non-monosynaptic group I excitation (Fig. 7.6(*d*); Marque *et al.*, 2005). Selective suppression by tizanidine of the late excitation, whether elicited by stretch or electrical stimulation, supports the view that it is mediated through muscle group II afferents (cf. p. 292).

Origin of group II afferents

Do cutaneous afferents contribute to group II excitation?

A significant contribution of cutaneous afferents to the stretch-induced medium-latency response was ruled out by experiments in which it was shown that blocking the cutaneous input from the sole of the foot did not modify the medium-latency responses (see Diener *et al.*, 1984; Schieppati & Nardone, 1999). In addition, it had been shown previously that electrical stimulation of the digital nerves of the foot did not induce detectable changes in the on-going EMG of the soleus and flexor digitorum brevis at a latency compatible with the medium-latency response (Abbruzzese, Rubino & Schieppati, 1996). Similarly, innocuous cutaneous stimuli mimicking the sensation elicited by electrically induced mixed nerve volleys failed to produce late excitation (Marque *et al.*, 1996, 2005; Simonetta-Moreau *et al.*, 1999, e.g. see Fig. 7.6(*b*)). This is consistent with animal data that tizanidine depresses responses of dorsal horn neurones to noxious stimuli, but does not modify responses to innocuous skin stimuli (Davies *et al.*, 1984). It is therefore likely that the late excitation suppressed by tizanidine was not related to an effect transmitted by cutaneous afferents mediating non-painful tactile sensations.

Contribution from joint afferents?

A contribution from joint afferents to the excitation produced by the small (3°) rotation of the platform is probably small, given that the vast majority of joint afferents are activated as the joint approaches the extremes of movement (see Chapter 6, p. 272). In addition, in the cat, a few non-spindle group II afferents can be activated by stimulation of the gastrocnemius medialis nerve, but they are in the high-threshold range (Lundberg, Malmgren & Schomburg, 1987a). It is therefore likely that the effects of stimuli applied to the nerve branch to the gastrocnemius medialis at intensities corresponding to the threshold of group II afferents activate mainly spindle afferents (1.3 × MT in Fig. 7.3(*d*)).

Conclusions

There are several independent lines of evidence indicating that late responses evoked by stretch of the receptor-bearing muscle or by electrical stimulation at intensities ~1.3–2 × MT are mediated through a spinal pathway fed by group II muscle afferents.

Critique of the tests used to reveal group II actions

Contamination by group I effects

Stretch responses produced by rotation of the platform may contain a monosynaptic Ia response, due to the activation of spindle primary endings, before the medium-latency response. This monosynaptic Ia

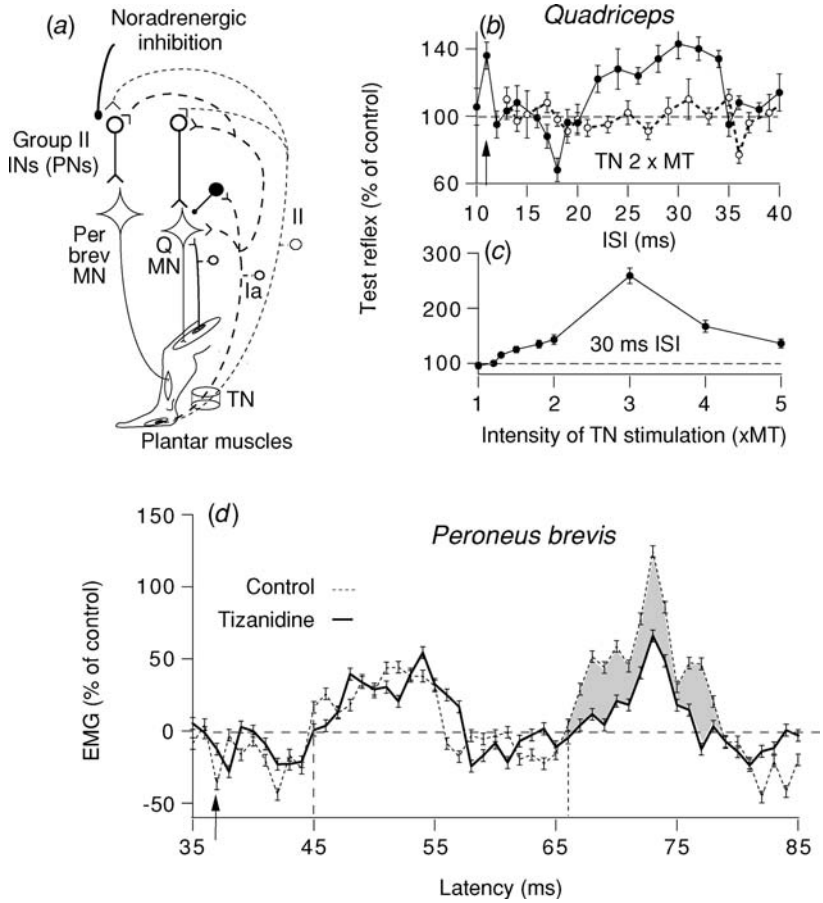


Fig. 7.6. Heteronymous group II excitation from plantar muscles to quadriceps and peroneus brevis. (*a*) Sketch of the presumed pathways with convergence of Ia and group II afferents from plantar muscles onto excitatory interneurones (IN or PN) projecting to quadriceps (Q) and peroneus brevis (Per brev) motoneurones (MN) (group I inhibition of Q MNs is also represented, Chapter 10, p. 497). Noradrenergic descending inhibition of the transmission of group II excitation to Per brev MNs is represented. (*b*), (*c*) Changes in the Q H reflex (as a percentage of its control value) elicited by a tibial nerve (TN) volley plotted against the interstimulus interval (ISI) ((*b*), ●, TN at 2 × MT; ○, effects of cutaneous stimulation mimicking the sensation evoked by TN stimulation, after allowance for the extra peripheral conduction time), and the intensity of the conditioning stimulus ((*c*), 30 ms ISI). Each symbol mean of 20 measurements. Vertical bars in (*b*)–(*d*) ±1 SEM. (*d*) On-going rectified EMG (100 sweeps, expressed as a percentage of control EMG) recorded in the Per brev after TN stimulation (1.5 × MT) in a control situation (thin dotted line), and 60 minutes after oral intake of tizanidine 150 $\mu g\,kg^{-1}$ (thick continuous line). Tizanidine suppressed the late excitation (pale grey area highlights the difference between the situations). Dashed and dotted vertical lines highlight the latencies of the non-monosynaptic group I and group II excitations. Arrows in (*b*) and (*d*) indicate the expected time of arrival of the TN Ia volley at the segmental level of the tested MNs. Modified from Marque *et al.* (2005), with permission.

response is well developed in the soleus and smaller in the flexor digitorum brevis. Similarly, it is impossible with electrical stimulation to produce a group II volley that is not preceded by a group I volley, because group II afferents have a smaller diameter and a higher electrical threshold than group I afferents. The problem is particularly relevant in the human lower limb, where (i) heteronymous Ia excitation between the different muscles is almost the rule (see Table 2.1), and (ii) non-monosynaptic group I excitation is widespread (cf. Chapter 10, p. 494).

Overlapping group II and group I excitations

Homonymous medium-latency responses to stretch in soleus and flexor digitorum brevis often overlap with short-latency responses (e.g. Figs. 7.2(*i*), (*k*), 7.11(*e*)). This overlap does not argue against the existence of the group II excitation, but it makes an accurate assessment of the onset difficult, and this led Grey *et al.* (2001) to distinguish the two responses by the latencies of their peaks, not their onsets (Fig. 7.11(*e*)). With common peroneal stimulation, there is a similar overlap between early group I and late group II excitations in the H reflex and the on-going EMG of quadriceps (Fig. 7.3(*f*), (*g*)). The more proximal the muscle (i.e. the shorter the distance to the spinal cord), the more prominent will be the overlap between the peaks.

Interactions with group I inhibitory effects

Figure 7.6(*b*) shows that the onset of the late tibial nerve-induced excitation of the quadriceps H reflex cannot be determined precisely because of the overlap of the excitation and the preceding long-latency group I inhibition.

Interactions between the effects of the two volleys at motoneuronal level

In experiments performed on discharging motoneurones, post-spike afterhyperpolarisation (AHP) and recurrent inhibition following the firing of the tested motoneurone(s) by the group I discharge may interfere with motoneurone recruitment by the subsequent group II volley (cf. p. 28). This would reduce the size of the group II-induced peak and delay its appearance. Such problems do not arise in experiments performed at rest with the H reflex. On the other hand, whichever method is used, summation of group II EPSPs with preceding subliminal group I EPSPs would enhance the group II excitation (and advance its appearance).

Interactions between the two volleys at interneuronal level

Non-monosynaptic group I and group II excitations are probably mediated through common interneurones (see pp. 305–6). Here again, this might have two opposite effects: facilitation if group I EPSPs are subliminal (it will be shown below that ischaemic blockade of group I afferents may reduce the group II excitation), but occlusion if the interneurones are fired by group I EPSPs (see p. 306; Fig. 7.4(*c*)). The question is further complicated by the fact that group I volleys can also evoke IPSPs in interneurones co-activated by group I and group II afferents (see Chapter 10, pp. 496–7).

Other limitations

Stretch-induced homonymous group II excitation

This excitation occurs only while the subject maintains an active upright stance, and is suppressed when holding onto a stable frame (see p. 313; Schieppati & Nardone, 1999). This technique for producing group II responses cannot be used to investigate transmission in group II pathways at rest or the changes from rest to voluntary movement.

Electrically induced group II excitation

Facilitation of the H reflex by group II afferents is a suitable method for investigating group II excitation at rest in patients. However, contraction of the target muscle can suppress the H reflex, due to the

Table 7.1. Conduction velocity of group II muscle afferents

1	2	3	4	5	6	7	8	9	10	11
Nerve–muscle combination	Distance	Ia CV	Ia ACT	Extra time II vs. Ia	Spinal latency group II	Group I central delay	Group II central delay	II ACT	CV Group II	II CV/Ia CV
Bi – VL	40	68	5.9	8.2	14.1	3.9	4.9	9.2	**43**	*0.64*
CP – VL	70	68	10.3	9.0	19.3	3.9	4.9	14.4	**48**	*0.68*
GM – ST	70	65	10.8	9.7	20.5	5.0	6.0	15.5	**45**	*0.64*
DP – VL	75	68	11.0	11.7	22.7	3.9	4.9	17.8	**42**	*0.62*
DP – Bi	75	68	11.0	11.5	22.5	5.0	6.0	16.5	**45**	*0.66*
SP – ST	80	68	11.7	12.7	24.5	5.0	6.0	18.5	**43**	*0.63*

1: Nerve–muscle combination; Bi (biceps femoris), VL (vastus lateralis), ST (semitendinosus), GM (gastrocnemius medialis), CP (common peroneal), DP (deep peroneal), SP (superficial peroneal). 2: Distance (cm) between stimulation site and L2 vertebra. 3: Conduction velocity (CV) in Ia afferents (m s^{-1}) (from Meunier, Pierrot-Deseilligny & Simonetta, 1993). 4: Afferent conduction time (ACT, ms) in Ia afferents (col. 2/col. 3). 5: Extra time of group II excitation over and above the time of arrival of the Ia volley at the motoneurone pool (ms). 6: Spinal latency of group II excitation (col. 4 + col. 5) (ms). 7: Central delay of non-monosynaptic group I excitation (cf. Table 10.2 in Chapter 10) (ms). 8: Central delay of group II excitation (col. 7 + 1 ms, see below). 9: ACT of group II volleys (col. 6 – col. 8) (ms). 10: CV of group II afferents (col. 2/col. 9) (m s^{-1}). 11: Ratio group II CV to Ia CV (col. 10/col. 3). From Simonetta-Moreau *et al.* (1999). Results obtained in a subject 1.68 m tall.

Calculations involve: (i) estimating the peripheral afferent conduction time of the Ia volley in the same nerve-muscle combination (col. 4); (ii) calculating the extra time of group II excitation over and above the time of arrival of the Ia volley at the motoneurone pool, by subtracting the peripheral afferent conduction time of the Ia volley from the latency of the group II excitation in the PSTH (col. 5); (iii) adding these two values, to obtain the spinal latency of group II excitation, which includes the peripheral ACT and the central delay of group II excitation (col. 6); (iv) assuming that non-monosynaptic group I and group II excitations are mediated through a common interneuronal pathway (see p. 306), and deducting the group II central delay from the previously calculated central delays of group I non-monosynaptic actions (Chaix *et al.*, 1997) (col. 7); (v) adding 1 ms to this value to take into account a longer conduction time along intraspinal collaterals of group II than of Ia afferents (cf. p. 289) (col. 8); (vi) subtracting from the spinal latency of group II excitation the central delay so estimated to obtain the peripheral ACT (col. 9); (vii) dividing the distance between stimulation site and spinal level by the peripheral ACT to obtain the conduction velocity of group II afferents (col. 10).

convergence between conditioning and test volleys onto interneurones mediating autogenetic Ib inhibition, and this constitutes an important limitation of the method (see pp. 310–12).

Organisation and pattern of connections

Peripheral pathway

Homonymous group II excitation

The conduction velocities of afferents mediating the stretch-induced responses in the human flexor digitorum brevis and soleus have been estimated at ~51 m s^{-1} and 21.4 m s^{-1} for Ia and group II afferents, respectively (Nardone & Schieppati, 1998).

Heteronymous group II excitation from leg muscles to thigh motoneurones

The peripheral afferent conduction time of group II afferent volleys from leg muscles has been inferred from comparisons of the latency of the group II excitation in the PSTHs of single units with the expected time of arrival at motoneuronal level of the Ia volley in the same 'conditioning nerve' (Simonetta-Moreau *et al.*, 1999). Results obtained in one subject in different nerve–muscle combinations are shown in Table 7.1. The legend gives details of the relevant

calculations. Column 10 shows that the conduction velocity of group II afferents was similar (~45 m s^{-1}, range 42–48 m s^{-1}) for the different nerve-motoneurone combinations.

Heteronymous group II excitation from plantar muscles

Group II conduction velocities have been estimated independent of the central delay, by comparing the latencies of the non-monosynaptic group I and group II excitations produced by tibial nerve stimulation in PSTHs from the same tibialis anterior units (Marque *et al.*, 2005). The conduction velocity for group II afferents from plantar muscles so estimated was ~39 m s^{-1}.

Conclusions: Group II–Ia ratio

The values found for the conduction velocities of Ia and group II fibres are higher with electrical stimulation of leg nerves than with stretch-induced responses. This is not surprising, given that (i) electrical stimulation activates preferentially the fastest fibres within the afferent population, while this is not necessarily true with muscle stretch; and (ii) conduction velocities measured over distal nerve segments are lower because of axon tapering and, particularly, lower temperature. Accordingly, after electrical stimulation, conduction velocities are slower for afferents in the distal tibial nerve than in nerves of leg muscles (see above). Thus, the values of 60–70 m s^{-1} and 40–50 m s^{-1} found in PSTH measurements after electrical stimulation for the fastest group Ia and group II afferents, respectively, are appropriate, given that measurements of latencies in the PSTHs of single units have an excellent time resolution. In leg muscles, the conduction velocity of the fastest afferents evoking the late excitation is ~45 m s^{-1} vs. ~68 m s^{-1} for the fastest Ia afferents (cf. columns 10 and 3 in Table 7.1). This indicates that the conduction velocity of these afferents is ~65% of that of Ia afferents in the nerves investigated (column 11 in Table 7.1). Similarly, the conduction velocity of group II afferents in the tibial nerve is ~67% of that of Ia afferents (Marque *et al.*, 2005). The electrical threshold (~1.2–1.3 × MT, Figs. 7.3(*d*) and 7.6(*c*)) is about 2.1 times that of Ia afferents (0.5–0.6 × MT; cf. Chapter 2, p. 75). These ratios, are similar to those found for group II/Ia afferents in the cat (see Matthews, 1972).

Central pathway of group II excitation

Estimates of the central delay

The central delay of the homonymous group II medium-latency response has been inferred from the distance between the flexor digitorum brevis and the spinal cord and from the sum of afferent and efferent conduction times. A value of 6.7 ms was reported (Nardone & Schieppati, 1998). Tibial nerve stimulation produces heteronymous monosynaptic Ia excitation and a high-threshold late group II excitation in the PSTHs of motor units belonging to different motoneurone pools (cf. Table 2.1 in Chapter 2, and Table 7.3). The central delay of tibial-induced group II excitation in these motor pools could then be calculated by subtracting the difference in peripheral afferent conduction times for the two volleys from the difference in latencies between group II and monosynaptic Ia excitations (Marque *et al.*, 2005). Although the stretch- and electrically induced responses involved different methods, similar values (~7 ms) have been found for the central delay of group II excitation in sacral motoneurones.

Rostral location of the interneurones mediating group II excitation

The medium-latency group II excitation produced by stretch has an onset as abrupt as that of the monosynaptic Ia response (Fig. 7.2(*b*), (*c*)). Group II responses evoked in the PSTHs of semitendinosus or quadriceps units also have an abrupt onset (Figs. 7.3(*c*), 7.4(*e*)), and they often appear at the

Table 7.2. Central delay of tibial nerve-induced group II excitation (Marque *et al.*, 2005)

1	2	3
Motor nucleus	Segmental location	Central delay
Vastus lateralis	L2–L4	3.8
Tibialis anterior	L4–L5	4.9
Peroneus brevis	L5–S1	5.7
Semitendinosus	L5–S1	7.5
Biceps	L5–S2	8.6

Table 7.3. Distribution of heteronymous group II excitation

Nerve / MN	CP	DP	SP	TN	BI	GM	FN
Q	90% 22	71% 4	25% 3	69% 7	60% 25	NE	NE
ST	NE	0	63% 29	47% 6	NE	100% 39	NE
Bi	NE	44% 27	NE	36% 18	NE	NE	NE
TA	NE	NE	NE	47% 13	NE	0	NE
Per brev	NE	NE	NE	95% 14	NE	NE	NE
GM	0	0	NE	NE	NE	NE	NE

Columns: nerve stimulated: CP (common peroneal), DP (deep peroneal), SP (superficial peroneal), TN (tibial nerve at the ankle), BI (nerve to the biceps), GM (nerve to the gastrocnemius medialis), FN (femoral nerve). Rows: motoneurone pools (MN) investigated with the PSTH method: Q (quadriceps), ST (semitendinosus), Bi (biceps femoris), TA (tibialis anterior), Per Brev (peroneus brevis), GM (gastrocnemius medialis). In each cell, the upper value indicates the percentage of motor units with a significant group II excitation (as a percentage of the number of tested MUs), and the lower value the mean magnitude of the effect expressed as a percentage of the number of triggers. 0: no effect. NE: not explored. Grey cells: not explored because of recurrent inhibition. From Simonetta-Moreau *et al.* (1999) and Marque *et al.* (2005). Note, however, that effects on ankle extensors could not be investigated because the twitch produced by stimuli $> 1 \times$ MT in plantar muscles produced a stretch-induced Ia discharge in the triceps surae, and this contaminated any effect due to the afferent volley elicited by stimuli to the tibial nerve (Bussel & Pierrot-Deseilligny, 1977).

threshold of group II excitation, thereby suggesting an oligosynaptic pathway. The long latency would then be explained by a long conduction time to and from interneurones located at different spinal segments than the motoneurones. Accordingly, Table 7.2 shows that the more caudal the motoneurone pool, the longer the central delay of the tibial nerve-induced group II excitation. For this finding to be explicable by a segmental interneuronal pathway, one would have to postulate more interneurones in the pathway the more caudal the motoneurone pool. A more parsimonious explanation is that there is a longer intraspinal pathway for caudal motoneurones, and this implicates interneurones located rostral to the motoneurones (Marque *et al.*, 2005).

Distribution of group II excitation

Homonymous responses to stretch

These responses are regularly found in subjects standing on a movable platform, but their amplitude is larger in tibialis anterior than in flexor digitorum brevis or soleus (Schieppati *et al.*, 1995).

Heteronymous group II excitation

Table 7.3 shows the distribution of heteronymous group II excitation in the human lower limb (Simonetta-Moreau *et al.*, 1999; Marque *et al.*, 2005). Because group II effects are elicited by volleys $>1 \times$ MT, the resulting antidromically conducted volleys in motor axons activate Renshaw cells and evoke recurrent inhibition, which is strong and widely distributed to motoneurones in the human lower limb (Meunier, Pierrot-Deseilligny & Simonetta-Moreau, 1994; Table 4.1). The combinations in which heteronymous recurrent inhibition might have complicated the interpretation, in particular the projections from quadriceps to leg muscles, were therefore not explored (grey cells in Table 7.3). The strongest connections, inferred from both the frequency of occurrence and the mean magnitude of the excitation, are from the gastrocnemius medialis

nerve to semitendinosus motoneurones (found in 100% of the units, with a mean magnitude of 39% of the triggers), and from the common peroneal nerve to quadriceps motoneurones. There was no evidence for group II excitation between muscles operating at the ankle. Such a discrepancy between the group II excitatory projections from ankle muscles to motoneurones of muscles operating at knee and ankle levels does not exist in the cat (Lundberg, Malmgren & Schomburg, 1987a) and could reflect an evolutionary change related to bipedal stance and gait. However, the pathways underlying group II excitation between GM and tibialis anterior exist in humans, and can be disclosed when the relevant interneurones are facilitated by corticospinal volleys (Lourenço *et al.*, 2005). Group II excitation from the tibial nerve at the ankle has been found in all tested proximal motor nuclei, the strongest projection being onto peroneus brevis motoneurones (Marque *et al.*, 2005).

Bilateral group II projections

Bilateral projections have been demonstrated in experiments using unilateral stretch. On the non-perturbed side, a short-latency response is not apparent, but the medium-latency response is present in the flexor digitorum brevis, although decreased and delayed (Fig. 7.2(*p*)–(*q*); Corna *et al.*, 1996). Unilateral toe-down tilt also elicits a medium-latency response in the contralateral tibialis anterior, but of smaller amplitude than in the stretched tibialis anterior. These bilateral responses are in keeping with the fact that, in the cat, group II afferents have crossed actions (cf. p. 292). There is no such projection for group I afferents, and this is further evidence that different afferents are responsible for the short- and medium-latency responses.

Upper limb

There are as yet no published data concerning group II afferent projections in the human upper limb. Long-latency responses to stretch of human hand muscles have been shown to be due to transcortical Ia reflexes (see Chapter 2, p. 92). However, current experiments indicate that electrical stimulation of group II afferents travelling in the ulnar nerve at the wrist produce potent excitation in motoneurones of flexors in the forearm. This effect has a long latency, is more delayed by cooling than the Ia excitation, and is suppressed by tizanidine, suggesting involvement of group II afferents (G. Lourenço, C. Iglesias, E. Pierrot-Deseilligny, P. Cavallari & V. Marchand-Pauvert, unpublished data).

Convergence with other peripheral afferents

Group I afferents

Absence of direct evidence

Because intermediate zone/ventral horn midlumbar interneurones in the cat are co-activated by group I and group II afferents (see Jankowska, 1992; p. 291, Fig. 7.1(*b*)), convergence of group I afferents onto interneurones mediating group II excitation has been carefully sought. Studies using spatial facilitation of the quadriceps H reflex have provided no direct evidence for convergence of group II and group I afferents onto common interneurones (Chaix *et al.*, 1997). However, absence of evidence is not conclusive. Two mechanisms could have prevented convergence from manifesting itself: (i) lateral inhibition between two pathways fed by two different nerves (cf. Chapter 10, pp. 496–7), and (ii) at the long ISIs required because of the slower conduction velocity of group II afferents, conditioning volleys applied to the common peroneal nerve or its branches at rest can evoke presynaptic inhibition of the test Ia volley in the femoral nerve (Forget *et al.*, 1989; Marque, Pierrot-Deseilligny & Simonetta-Moreau, 1996). In addition, in the cat, the convergence of group I and group II afferents onto common interneurones is weak when tested with spatial facilitation in motoneurones, and more marked for inhibitory than for excitatory group II effects (Jankowska, Perfilieva & Riddell, 1996).

Indirect evidence

Despite the absence of direct evidence, several indirect arguments suggest that group I and group II afferents do converge onto common excitatory interneurones.

(i) The smaller the early non-monosynaptic peroneal-induced group I excitation of the quadriceps H reflex, the larger the late excitation (Fig. 7.4(*c*); Chaix *et al.*, 1997). This negative correlation is consistent with mediation of the two facilitatory effects through common interneurones: when the group I-facilitation was small, many interneurones would be available for the following group II volley, the effects of which would be facilitated by the subliminal group I EPSPs; in contrast, a large reflex facilitation produced by the group I volley would involve many interneurones which might then be less responsive to the following group II volley. In this respect, it is relevant that little spatial or temporal facilitation of transmission has been found in group II excitatory pathways in the cat (see p. 290).

(ii) Group II excitation is delayed when group I excitation is inhibited. Deep peroneal group I volleys activate both excitatory interneurones projecting onto quadriceps motoneurones and feedback inhibitory interneurones inhibiting them (see Chapter 10, p. 496). When feedback inhibitory interneurones are facilitated by corticospinal volleys (see p. 310), the difference in the latencies of group I and group II excitations is greater. This would be expected if excitation evoked by group I and group II afferents was mediated through common interneurones (Marchand-Pauvert, Pierrot-Deseilligny & Simonetta-Moreau, 1999).

(iii) During gait, the suppression of group II excitation by ischaemic blockade of group I afferents is best explained by convergence of group I and group II afferents onto common lumbar propriospinal neurones (see pp. 316, 318, 320). In this connection, it has been reported that the medium-latency response evoked by stretch in the voluntarily activated triceps surae is suppressed by ischaemic blockade of Ia afferents (Fellows *et al.*, 1993). This suppression might simply indicate that in this particular situation (voluntary contraction) the depolarisation of propriospinal neurones by the group I afferent discharge is required for the group II excitation to manifest itself.

(iv) There is similar corticospinal facilitation of interneurones mediating non-monosynaptic group I and group II excitations and of inhibitory interneurones inhibiting them (cf. pp. 307–10 and pp. 498–500).

(v) Non-monosynaptic group I excitation is mediated through lumbar propriospinal neurones which are located rostral to motoneurones, much as are interneurones mediating group II excitation (cf. Chapter 10, pp. 493–4).

Conclusions

Overall, these arguments suggest that, as in the cat, non-monosynaptic group I and group II excitations are mediated through common lumbar propriospinal neurones, rostral to motoneurones. This is consistent with findings in the cat where the concentration of interneurones co-activated by group I and group II afferents is particularly high in mid-lumbar (L3–L4–L5) segments (cf. Jankowska, 1992; p. 289). It should be noted that the segmental location within the lumbar spinal cord is different in humans (who have five lumbar segments) and the cat (which has seven lumbar segments). Thus, lumbar propriospinal neurones in L3–L5 in the cat should be above L1–L2 in human subjects (see Chapter 10, pp. 493–4).

Absence of evidence for cutaneous projections

Cutaneous volleys are insufficient by themselves to produce excitation resembling that from group II afferents (cf. p. 299). This finding by no means eliminates the possibility that cutaneous (and/or joint) afferents converge onto group II interneurones, much as in the cat (Jankowska, 1992). It is, however, possible that in awake human subjects strong descending control exerted on

transmission in cutaneous pathways completely abolishes the effects of cutaneous stimuli observed in the spinal animal (see Holmqvist & Lundberg, 1961).

Peripheral inhibitory input to interneurones co-activated by group I and II afferents

Group I suppression of the excitation

There is evidence that group I volleys also excite feedback inhibitory interneurones inhibiting lumbar propriospinal neurones (cf. Chapter 10, pp. 496–7).

Group II inhibition of excitatory interneurones

In contrast to the ease with which heteronymous group II excitation is disclosed in semitendinosus motoneurones, the only evidence for a suppressive effect induced by group II muscle afferents is the small decrease in the gastrocnemius medialis-induced excitation of semitendinosus motoneurones observed in both H reflex and PSTHs when the gastrocnemius medialis stimulus intensity is increased above 2 × MT (e.g. Fig. 7.3(*d*); Simonetta-Moreau *et al.*, 1999). That this depression has not been found in combinations without group II excitation and appears only as a suppression of the excitation suggests that it results from inhibition of interneurones mediating group II excitation.

High-threshold decrease in excitation

A decrease in tibial nerve-induced excitation of the quadriceps H reflex appears at intensities above 3 × MT (Fig. 7.6(*c*); Marque *et al.*, 2005). Such a threshold is far above that of group II afferents (1.2 × MT) and could correspond to the recruitment of smaller afferents.

Absence of inhibition of motoneurones

The absence of evidence for group II inhibition of motoneurones of pure extensor muscles in humans, whether in homonymous soleus pathways (Schieppati & Nardone, 1999) or heteronymous pathways to vastus lateralis (Simonetta-Moreau *et al.*, 1999), is the most striking difference from animal data (see Jankowska, 1992; p. 291).

Corticospinal control of peripheral facilitation

There is evidence for convergence of peripheral and corticospinal volleys onto common interneurones (Marchand-Pauvert, Pierrot-Deseilligny & Simonetta-Moreau, 1999).

Corticospinal facilitation of group II excitation

Figure 7.7(*b*) shows that the MEP evoked in semitendinosus is facilitated by gastrocnemius medialis stimulation, and this facilitation appears only at long ISIs and with a threshold >1.2 × MT (Fig. 7.7(*d*), (*c*)), indicating that it is mediated by slowly conducting high-threshold (group II) afferents. Experiments using the common peroneal-quadriceps paradigm allow a more precise identification of the responsible pathway. Stimulation of the common peroneal nerve produces biphasic facilitation of the quadriceps MEP, with early low-threshold (0.8 × MT) and late high-threshold (1.5 × MT) components (Fig. 7.8(*b*)). The differences in latency and threshold of the two effects suggest that they are mediated by group I and group II afferents, respectively. That the difference in latencies of the early and late facilitations of the quadriceps MEP was positively correlated with the height of the subject further supports the view that the late facilitation is mediated by slower (group II) afferents (see p. 297). The finding that, at late ISIs, the group II facilitation of the MEP was much greater than that of the H reflex suggests convergence of group II and corticospinal volleys on to interneurones projecting to quadriceps motoneurones

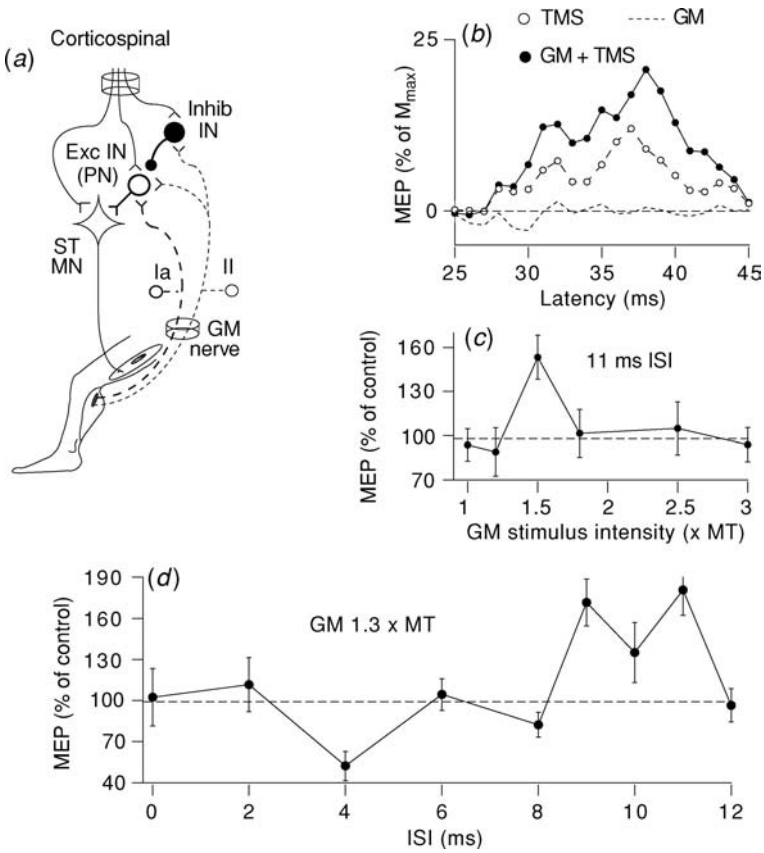


Fig. 7.7. Corticospinal projections to interneurones mediating gastrocnemius medialis group I–group II excitation to semitendinosus motoneurones. (*a*) Sketch of the presumed pathways, with corticospinal projections to semitendinosus (ST) motoneurones (MN), excitatory interneurones (Exc IN or PN) fed by groups I and II afferents in the gastrocnemius medialis (GM) nerve, and to inhibitory interneurones (Inhib IN) inhibiting them (group I projections onto inhibitory INs have been omitted). (*b*) Average (10 trials) of the rectified motor evoked potential (MEP, after subtraction of the control EMG, weak contraction at ~5% MVC), expressed as a percentage of the maximal M wave, plotted against the latency after the conditioning stimulus. Effects of separate GM stimulation (1.3 × MT, dotted line), separate transcranial magnetic stimulation (TMS, 33% of the maximal stimulator output, ○) or combined TMS and GM stimulation at the 9 ms ISI (●) (note that the abscissa is relative to TMS, even for separate GM stimulation). (*c*), (*d*) The conditioned MEP (expressed as a percentage of its unconditioned value) is plotted against the conditioning stimulus intensity ((*c*), 11 ms interstimulus interval [ISI]) or ISI ((*d*), GM intensity at 1.3 × MT). Each symbol is the mean of 20 measurements; vertical bars ±1 SEM. Modified from Marchand-Pauvert, Simonetta-Moreau & Pierrot-Deseilligny (1999), with permission.

(Fig. 7.8(*b*) and its legend). Extra facilitation on combined stimulation in the PSTHs of single quadriceps units supports this view. Indeed, the effect on combined stimulation is greater than the sum of the effects of separate stimuli (Fig. 7.8(*c*), (*d*)), indicating summation of EPSPs produced by corticospinal and group II volleys in premotoneurones. Convergence of corticospinal and group II volleys onto interneurones is further supported by the absence of extra facilitation in the initial 0.8 ms of the corticospinal

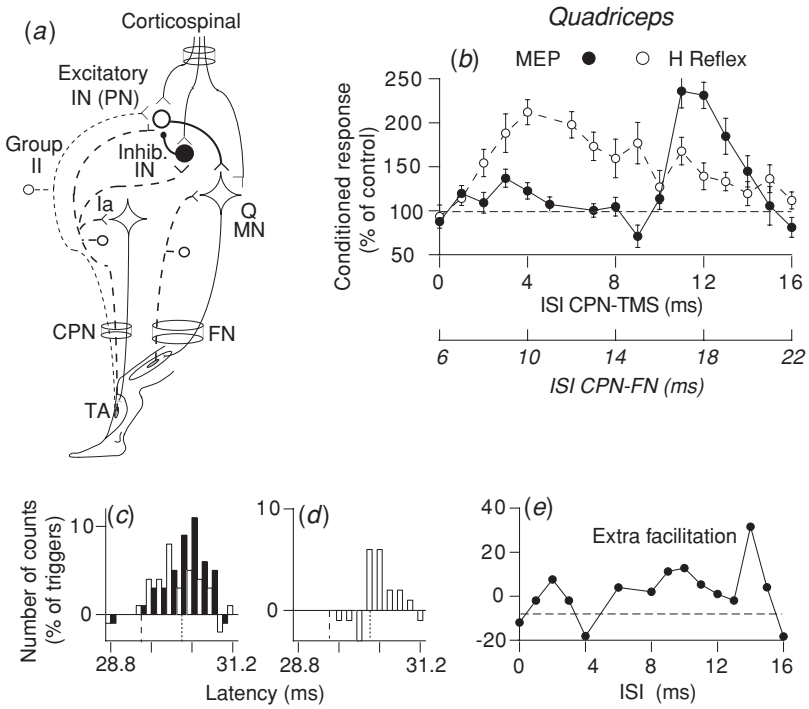


Fig. 7.8. Corticospinal projections to interneurones mediating peroneal group I–group II excitation to quadriceps motoneurones. (*a*) Sketch of the presumed pathways with corticospinal projections to quadriceps (Q) motoneurones (MN), excitatory interneurones (IN or PN) fed by group I and II afferents in the common peroneal nerve (CPN), and inhibitory INs (Inhib. IN) inhibiting them (group II projections onto Inhib. INs have been omitted). FN, femoral nerve. (*b*) The motor evoked potential (MEP, ●) and the H reflex (○) of the Q (as a percentage of the control responses) during a weak Q voluntary contraction (~2 % MVC) conditioned by a CPN volley (2 × MT) plotted against the interstimulus interval (ISI) CPN-TMS (upper abscissa) and CPN-FN (lower abscissa, in italics), the two abscissae being aligned to start at the simultaneous arrival of conditioning and test volleys at the Q MN pool. Each symbol, mean of 20 measurements; vertical bars ±1 SEM. Because convergence of peroneal and corticospinal volleys onto MNs should have modified the H and MEP responses to the same extent, the differential effect (larger late group II excitation) observed on the two responses indicates a convergence onto INs. (*c*), (*d*) PSTHs of a vastus lateralis (VL) unit (after subtraction of the background firing, 0.2 ms bin width). (*c*) The algebraic sum (□) of effects elicited by separate CPN (2 × MT) and cortical stimuli is compared to the effect on combined stimulation (9 ms ISI, ■). (*d*) Extra facilitation on combined stimulation, i.e. the difference (■ – □) in (*c*). Dashed and dotted lines in (*c*), (*d*) highlight the onset of the corticospinal peak and of the extra facilitation on combined stimulation, respectively. (*e*) The amount of extra facilitation on combined stimulation (calculated as in (*d*), same unit as in (*c*), (*d*) plotted against the ISI. Extra facilitation peaked at 14 and 10 ms ISIs corresponding to the synchronous arrival of the group II volley with successive corticospinal (D and I waves) volleys at relevant interneurones. Modified from Marchand-Pauvert, Simonetta-Moreau & Pierrot-Deseilligny (1999), with permission.

peak (Fig. 7.8(*c*), (*d*)). Sparing of the initial 0.8 ms corresponds to the delay required for transmission across one interneurone in human pathways, and this sparing is what would be expected if the two volleys converged onto common interneurones rather than directly onto the motoneurone (see Chapter 1, pp. 46–7). Overall, these findings suggest that part of the corticospinal volley is transmitted to motoneurones by lumbar propriospinal neurones (cf. the sketch in Fig. 7.8(*a*) and Chapter 10, pp. 498–500).

Corticospinal control of interneurones inhibiting lumbar propriospinal neurones

Inhibition from low-threshold afferents

Corticospinal and peripheral group I (and possibly cutaneous) volleys converge onto inhibitory interneurones projecting to lumbar propriospinal neurones (see Chapter 10, p. 500). This convergence accounts for the early GM-induced inhibition of the semitendinosus MEP at the 4 ms ISI (Fig. 7.7(*d*)), observed in all subjects. It also accounts for (i) the finding that, in the quadriceps, common peroneal stimulation elicits a smaller early facilitation of the MEP than of the H reflex (Fig. 7.8(*b*)), and (ii) the early peroneal-induced inhibition of the corticospinal peak in the PSTHs of quadriceps units (4 ms ISI in Fig. 7.8(*e*)).

Convergence of corticospinal and group II volleys onto inhibitory interneurones

When increasing the gastrocnemius medialis stimulus intensity above 1.5 × MT, there is complete suppression of the group II facilitation of the semitendinosus MEP (Fig. 7.7(*c*)). This contrasts with the weak decrease in the group II facilitation of the H reflex in this muscle in the absence of cortical stimulation (Fig. 7.3(*d*)). Thus, group II volleys, which cannot activate the inhibitory interneurones in the absence of TMS, become very effective when their synaptic actions are combined with corticospinal volleys. This suggests that inhibitory interneurones also receive corticospinal excitation. Group II volleys in the common peroneal nerve also suppress the corticospinal peak in quadriceps units, and the group II facilitation is consistently followed by an inhibition (as at the 16 ms ISI in Fig. 7.8(*e*)).

Conclusions

Corticospinal volleys facilitate lumbar propriospinal neurones co-activated by group I and group II afferents. However, they also facilitate inhibitory interneurones mediating feedback inhibition to lumbar propriospinal neurones. Overall the dominant effect of corticospinal volleys on the lumbar propriospinal system seems to be excitation of feedback inhibition, particularly in the pathway of propriospinal excitation to semitendinosus motoneurones.

Motor tasks and physiological implications

There is no evidence for post-activation depression of group I inputs to human lumbar propriospinal neurones co-activated by group I and group II afferents (Lamy *et al.*, 2005). This finding is in keeping with the absence of post-activation depression in feline interneurones of the intermediate zone fed by group I and group II afferents (see pp. 292–3). Thus, contrary to Ia inputs at the Ia-motoneurone synapse (cf. Chapter 2, pp. 96–9), the synaptic efficacy of group I and group II excitatory inputs to lumbar propriospinal neurones would not be held at a low level during motor tasks by post-activation depression.

Voluntary contractions

Voluntary contraction of the quadriceps

Modulation of the H reflex appears *a priori* to be the best method to investigate how transmission in spinal pathways is changed by motor tasks, because it enables a comparison of the results obtained at rest and during movement. The biphasic facilitation of the quadriceps H reflex produced by common peroneal stimulation at 2 × MT is unchanged with respect to rest during weak tonic quadriceps contractions (Marchand-Pauvert *et al.*, 2002, their Fig. 7.1(*a*)). However, during relatively strong contractions of quadriceps at ~10% of MVC, the early peroneal group I facilitation of the quadriceps H reflex is truncated by a suppression that also abolishes the late group II facilitation (Figs 1.12(*c*) and Fig. 7.9(*g*)). This suppression is due to the convergence of joint and/or cutaneous inputs in the conditioning peroneal volley and group I input in

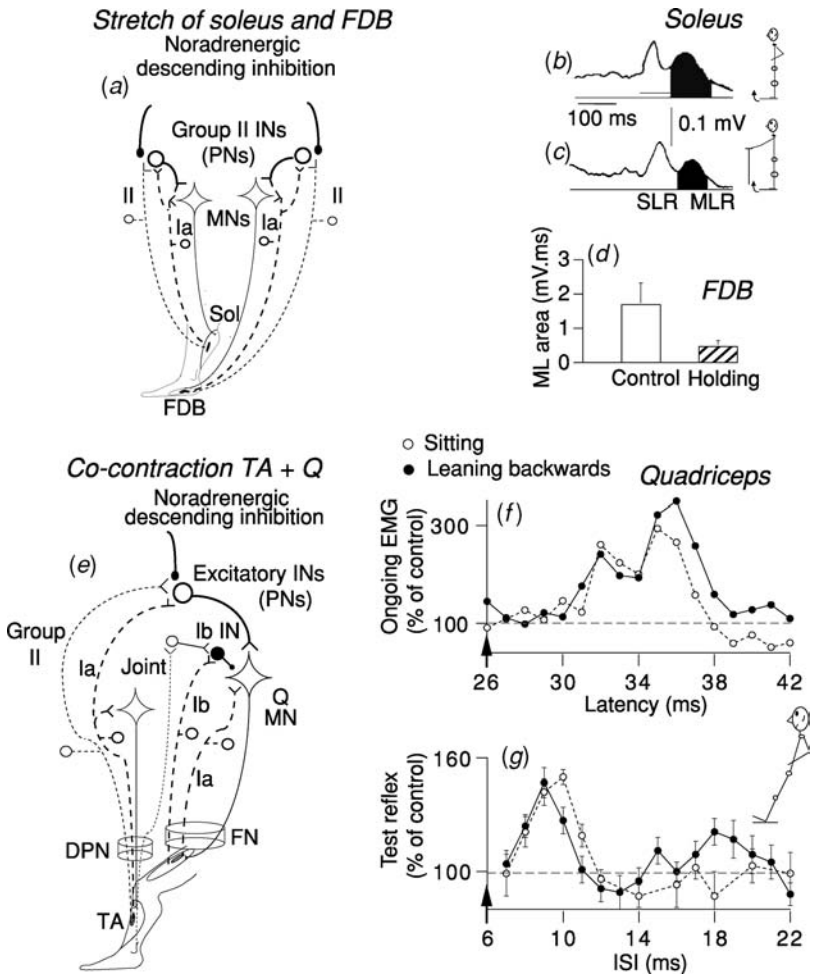


Fig. 7.9. Changes in group II excitation during postural tasks. (*a*) and (*e*) Sketches of the presumed pathways of homonymous group I–group II excitation to soleus (Sol) and flexor digitorum brevis (FDB) motoneurones (MN) (*a*), and heteronymous group I–group II excitation from tibialis anterior (TA) to quadriceps (Q) MNs (*e*). Noradrenergic descending gating of group II excitation is represented. Sketches of the posture on the right of (*b*), (*c*), (*g*). (*a*) Monosynaptic projections on MNs of Ia afferents, and convergence of Ia and group II afferents onto group II excitatory interneurones (IN or PN). (*b*), (*c*) Short-latency (SLR) and medium-latency (MLR) responses (average of 10 trials) elicited in the Sol by upward tilt during free stance (*b*) and while holding onto a stable frame (*c*). The MLR (black area) is suppressed, but the SLR is not influenced by the 'postural set'. (*d*) Average area (mV ms, 6 subjects) of the FDB MLR during free stance (□) and while holding onto a stable frame (dashed column). (*e*) Sketch with the convergence of Ia and group II afferents from TA onto INs (PN) exciting Q MNs, and the convergence of joint afferents in the deep peroneal (DPN) conditioning volley and Ib afferents in the femoral (FN) test volley on Ib INs projecting to Q MNs. (*f*), (*g*) DPN (2 × MT) modulation of the on-going EMG ((*f*), 200 sweeps, as a percentage of control EMG) and of the H reflex ((*g*), as a percentage of its unconditioned value, mean of 20 measurements, vertical bars ±1 SEM) of the Q when leaning backwards (●) and during voluntary co-contraction of TA and Q (○) at equivalent levels of EMG activity (21% MVC). Vertical arrows indicate the expected time of arrival of the peroneal Ia volley at Q MN level ((*f*), 26 ms; (*g*), 6 ms interstimulus interval [ISI]). Early group I and late group II facilitations measured within the windows 29–34, and 35–38 ms for the on-going EMG, and at the 8–10, and 17–21 ms ISIs for the H reflex, respectively. Modified from Schieppati & Nardone (1991) (*b*), (*c*), Schieppati & Nardone (1999) (*d*), and Marchand-Pauvert *et al.* (2005) ((*f*), (*g*)), with permission.

the test femoral volley onto interneurones mediating the autogenetic 'Ib inhibition' to quadriceps motoneurones (see the sketch in Fig. 7.9(*e*); Marchand-Pauvert *et al.*, 2002; Chapter 1, pp. 14–16). It complicates the use of the H reflex to assess the changes in peroneal-induced group II excitation during voluntary movement, whether the voluntary contraction involves quadriceps only or both tibialis anterior and quadriceps. Common peroneal group II facilitation of the on-going quadriceps EMG is larger during a strong voluntary contraction at 20% of MVC than during a weak contraction at 5% of MVC (Fig. 1.12(*b*); Marchand-Pauvert *et al.*, 2002). Facilitation of the transmission of heteronymous peroneal group II volleys during a selective contraction of the quadriceps is not surprising, given the convergence of peroneal and femoral volleys onto common propriospinal neurones projecting to quadriceps motoneurones (Forget *et al.*, 1989; Chapter 10, p. 496). Because the greater peroneal-induced facilitation of the on-going EMG during strong contractions involves both early group I and late group II excitations, an increase in the excitability of propriospinal neurones co-activated by the two types of afferents is plausible. This increased excitability might be simply due to the γ-driven Ia and group II inflow from the contracting quadriceps and/or increased corticospinal excitation.

Voluntary contraction of the semitendinosus

The gastrocnemius medialis-induced facilitation of the semitendinosus H reflex observed at rest (cf. Fig. 7.3(*d*), (*e*)) is suppressed during voluntary contraction of the semitendinosus at ~20% of MVC (Marchand-Pauvert *et al.*, 2005). Presumably, this suppression also reflects convergence of afferents in the conditioning volley and group I afferents in the test volley onto interneurones mediating autogenetic 'Ib inhibition' to the semitendinosus motoneurones (convergence of Ib afferents from different muscles onto common Ib interneurones has been demonstrated, cf. Chapter 6, pp. 257–8). Only a weak facilitation of the on-going semitendinosus EMG by group II volleys from the gastrocnemius medialis was observed, whether the voluntary contraction was weak, and involved only hamstrings, or was strong and involved both the triceps surae and hamstrings (Marchand-Pauvert *et al.*, 2005). Despite the strong heteronymous excitatory group II projections from gastrocnemius medialis to semitendinosus neurones (see Table 7.3), there is no evidence that heteronymous group II pathways are significantly implicated in the excitation of motoneurones involved in voluntary co-contractions of these two muscles.

Conclusions

Differences in the changes in transmission of heteronymous group II excitation to quadriceps and semitendinosus motoneurones during contraction of the target muscle could reflect the dominant corticospinal excitation of feedback inhibition in the pathway of propriospinal excitation to semitendinosus motoneurones (see above). In addition, as proposed by Jankowska (1992), group II pathways in the cat may be involved particularly in the control of posture and gait, and this also appears to be so in human subjects (see below).

Postural tasks

Role of homonymous group II pathways in transient perturbations of stance

A sudden displacement of the platform upon which subjects stand produces ankle rotation and stretch-induced responses in triceps surae after toe-up tilt and in tibialis anterior after toe-down tilt (Figs. 7.2, 7.9(*b*), (*c*); Schieppati *et al.*, 1995). These responses help the subject counteract the displacement as it shifts the projection of the centre of mass from its normal position on the foot support base. Note, however, that excessively large responses could destabilise posture (cf. Chapter 11, pp. 540–1). Stretch responses in triceps surae are accompanied and

completed by analogous activities in the flexor digitorum brevis. These latter responses create a background torque anchoring the foot to the platform (Schieppati & Nardone, 1999; Schieppati *et al.*, 2001).

Role of the 'postural set'

Medium-latency stretch responses elicited by toe-up tilt in soleus and flexor digitorum brevis during normal upright stance are considerably reduced when subjects hold onto a stable frame, but the short-latency responses are not altered (Fig. 7.9(*b*)–(*d*); Nardone, Corrà & Schieppati, 1990; Nardone *et al.*, 1990b). This differential effect indicates descending control focused on transmission in the pathways of group II excitation. Similarly, stabilisation of the upright posture considerably reduces the medium-latency response elicited in tibialis anterior by downward tilt (Schieppati & Nardone, 1991). The suppression of the medium-latency response is not triggered by arm motion or contact with the frame. Indeed, it begins about 200 ms before subjects touch the frame, and this suggests that it is related to the transition to a new stabilised 'postural set' (Schieppati & Nardone, 1995).

Bilateral medium-latency responses

Bilateral responses elicited by unilateral perturbations are functionally required, because even a unilateral displacement shifts the centre of mass from its normal position on the foot support base. However, the contralateral responses are then weaker (see p. 305), presumably because when one leg is on firm ground the perturbation is less destabilising, and this could have tuned down the excitability of the pathway in the same way as holding onto a stable frame.

Conclusions

Two lines of evidence indicate that stretch-induced group II-mediated medium-latency responses play a crucial role in compensating for perturbations to upright stance: (i) the responses are considerably reduced if they are not required to ensure equilibrium, such as when the subjects support themselves by holding onto a stable frame; and (ii) patients with Charcot–Marie–Tooth type 1A disease, in whom medium-latency responses are preserved (even if distorted, see Fig. 7.13(*b*)), do not have balance problems, despite the lack of short-latency Ia responses (see p. 320). The role of short-latency Ia-mediated reflex responses in correcting for rapid perturbations to the stance is questionable (see Chapter 11, p. 541). However, because of the convergence of Ia afferents onto propriospinal neurones mediating group II effects, a Ia discharge would contribute to medium-latency responses by depolarising these interneurones.

Role of heteronymous group II pathways in postural tasks

It has been investigated whether heteronymous group II excitation from pretibial flexors to quadriceps and from gastrocnemius medialis to semitendinosus is involved in the maintenance of bipedal stance in postural tasks requiring co-contraction of leg and thigh muscles (Pierrot-Deseilligny, 1999; Marchand-Pauvert *et al.*, 2005).

Peroneal group II facilitation of quadriceps

The modulation of the on-going EMG of quadriceps by deep peroneal stimulation (2 × MT) has been recorded during postural co-contractions of quadriceps and tibialis anterior produced by standing and leaning backwards, and during voluntary co-contraction of these two muscles, at matched levels of EMG activity. While the early group I facilitation was of the same magnitude in the two situations, the late facilitation of the EMG was greater when leaning backwards (Fig. 7.9(*f*)). During the strong quadriceps contraction, the early group I facilitation of the quadriceps H reflex was truncated and the late group II facilitation completely suppressed, because of the

gating effect on the test H reflex of Ib afferents in the test volley (see above). When leaning backwards, the early group I facilitation was similarly truncated but, contrary to voluntary contraction, there was a late excitation attributable to II afferents (Fig. 7.9(*g*)). The finding that the early peak of reflex facilitation was truncated to the same extent with respect to rest in the two situations suggests that, while leaning backwards, there was facilitation of the peroneal-induced group II excitation, superimposed on a suppression of equal magnitude as during voluntary contraction. In the postural task, the group II excitation was greater in the ongoing EMG than in the H reflex, because the former was not affected by changes in transmission of the afferent volley for the test H reflex. The early group I and late group II excitations are probably mediated through common interneurones (see p. 306). The similar magnitude of the early group I excitation in the two tasks therefore suggests that the enhanced group II excitation during the postural task was not due to increased excitability of these interneurones (e.g. due to vestibulospinal facilitation), but to a specific mechanism acting on transmission of group II effects. A good candidate would be a decrease in the monoaminergic gating of transmission in group II pathways exerted from the brainstem (see below).

Gastrocnemius medialis group II facilitation of semitendinosus

During postural co-contractions of triceps surae and hamstrings, as occurs when standing and leaning forwards, gastrocnemius medialis volleys at 1.3–1.5 × MT facilitate the on-going EMG of semitendinosus at central delays compatible with group II excitation. Because there is no equivalent facilitation during voluntary co-contractions of these muscles, here again, the postural task is presumably accompanied by increased group II excitation.

Functional implications

A perturbation to stance produces postural responses in the tibialis anterior and triceps surae due to activation of homonymous group II afferents by stretch (see Schieppati *et al.*, 1995; Fig. 7.2). In the cat, transmission of group II excitation is gated by monoaminergic control from the locus coeruleus/subcoeruleus and from raphe nuclei in the brainstem (cf. p. 292). A descending projection from the locus coeruleus/subcoeruleus probably also exists in human subjects, as shown by the suppression of group II excitation produced by tizanidine (see p. 299). Thus, Nardone, Corna & Schieppati (2001) suggested that, when the medium-latency responses are no longer required to ensure the control of upright quiet stance, there is a reduction in a descending inhibitory control exerted on the locus coeruleus, leading to increased activity from the locus, and thereby to increased gating of group II volleys (see the sketch in Fig. 7.15(*a*)). In contrast, when balance is unstable, transmission in group II pathways would be tuned up by decreased activity in this monoaminergic control system. On the other hand, potent heteronymous group II excitation also exists from tibialis anterior to quadriceps and from gastrocnemius medialis to semitendinosus, i.e. linking leg and thigh muscles involved in the maintenance of posture when leaning backwards and forwards, respectively. Transmission of group II discharges from stretched leg muscles, tuned up by the monoaminergic control system, might also contribute to the co-contraction of leg and thigh muscles required in each postural task. In concluding this section, it should be noted that these findings may shed more light on the corrective mechanisms for destabilising perturbations than they tell us about the control of quiet stance (see Chapter 11, pp. 539–41).

Changes in group II excitation during gait

Group II afferent activity has two actions in the control of human walking: (i) contribution to the activation of the muscles during normal unperturbed walking, and (ii) mediation of some of the reactions to sudden external perturbations.

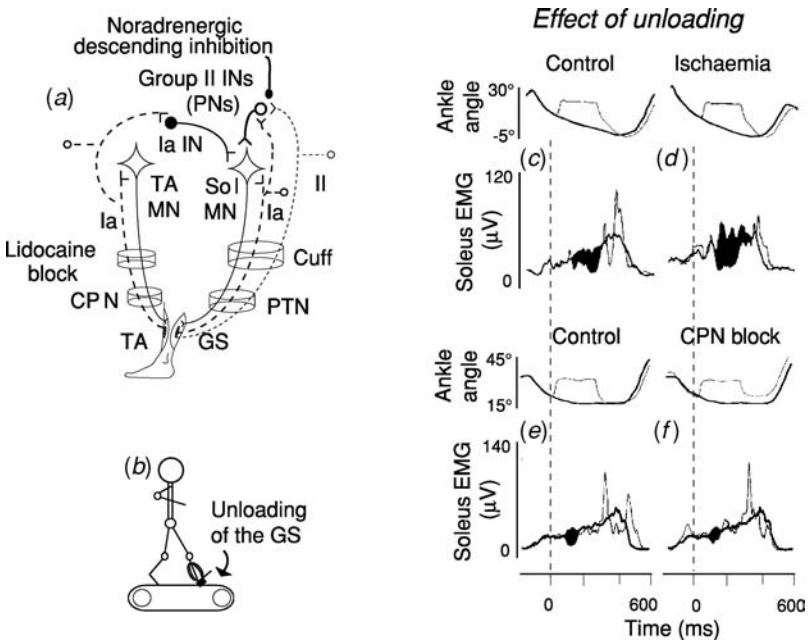


Fig. 7.10. Changes in group II excitation elicited by unloading of ankle extensors during gait. (*a*) Sketch of the presumed pathways of homonymous group I–group II excitation through PNs to soleus (Sol) motoneurones (MN). Reciprocal Ia inhibition from tibialis anterior (TA) to Sol MNs is represented. Ischaemic block of group I afferents in the posterior tibial nerve (PTN) and lidocaine block of the common peroneal nerve (CPN) are sketched. Noradrenergic descending inhibition of the transmission of group II excitation is represented. (*b*) Sketch of the experimental paradigm for unloading gastrocnemius-soleus (GS). (*c*)–(*f*) Effect of unexpected unloading of GS on Sol EMG activity. Unloading: 6° at a velocity of 330° s^{-1}, followed by a hold phase of 210 ms, onset indicated by the zero of the abscissa and the vertical dashed line, triggered 200 ms after heel contact. Upper traces: ankle angle position (0° equals standing position, positive values plantar movement direction). Lower traces: averaged rectified and filtered Sol EMG. Control steps, thick lines; steps with an unloading, thin lines. Sol EMG prior to the unloading matched the Sol EMG activity in the control steps until ~60 ms after perturbation onset. A marked decrease in EMG (black area) was present at this time until ~180 ms after unloading onset. When the unloading was terminated, a peak occurred with a 40 ms latency, reflecting the short-latency Ia stretch reflex. The EMG suppression produced by unloading is compared before (*c*) and 20 min after ischaemia of the thigh blocking group I afferents ((*d*), as shown by the disappearance of the Achilles tendon jerk, while M max was unchanged), and before (*e*) and after (*f*) a total block of transmission in the CPN using lidocaine. Modified from Sinkjær *et al.* (2000) ((*c*)–(*f*)), with permission.

Contribution of homonymous group II afferents to soleus activation

Methodology

Removal of the afferent feedback generated by the movement by suddenly unloading of the active muscle may be a valid approach to the contribution of this feedback to locomotion. To that end, Sinkjær *et al.* (2000) have used a portable stretch device capable of suddenly rotating the ankle joint during walking.

Suppression of the EMG activity by unloading

During the stance phase of walking, the unloading of gastrocnemius-soleus produced by passive ankle plantar flexion decreases soleus EMG activity on average ~64 ms after the onset of the unloading (Fig. 7.10(*c*)). The extent of EMG suppression was generally similar, though sometimes delayed, after an ischaemic block of group I afferents (Fig. 7.10(*d*)), and it is therefore unlikely that an

unloading-related withdrawal of the group I discharge from the gastrocnemius-soleus was the major cause of the suppression. Reciprocal inhibition elicited by the stretch-induced Ia discharge from ankle dorsiflexors was also ruled out, because the amount of suppression was the same before and after complete block of the common peroneal nerve using local anaesthetic (Fig. 7.10(*e*), (*f*)). Withdrawal of group II excitation from gastrocnemius-soleus was the favoured explanation for the EMG suppression. There are other data in favour of or consistent with a group II origin of the unloading response: (i) its onset latency is within the range of the medium-latency response to stretch seen during walking, and this has been demonstrated to be mediated by stretch-sensitive group II afferents (see below); (ii) contraction of the triceps surae during the stance phase of gait is weight-bearing and eccentric, circumstances under which the co-activated γ drive can powerfully excite muscle spindle endings and elicit a potent group II discharge (cf. Chapter 3, p. 135). Because of the convergence of Ia afferents onto interneurones mediating group II effects, Ia discharges may also contribute to the excitation of these interneurones: this would explain why blockade of Ia afferents may delay the unloading response in some subjects.

Conclusions

Unloading reduces by half the on-going EMG activity of soleus, largely due to withdrawal of group II excitation. This does not imply that the group II feedback provides 50% of the excitatory drive to soleus motoneurones. The motoneurone discharge is produced by spatial and temporal summation of combined peripheral and central inputs, and the abrupt removal of either could have a large effect.

Contribution of group II afferents to an unexpected stretch-induced response

Initial findings

Dietz and colleagues first described group II-mediated responses in triceps surae during walking on a treadmill (Berger, Dietz & Quintern, 1984; Dietz, Quintern & Sillem, 1987). Abrupt acceleration of the treadmill stretched triceps surae and produced a large medium-latency response in the gastrocnemius medialis at a latency (~80 ms) consistent with group II mediation. Further evidence for the group II origin of this medium-latency response was provided by the finding that ischaemic blockade of group I afferents did not modify the response (Fig. 7.11(*c*)). Interestingly, this large homonymous response in the triceps surae was accompanied by a small response in hamstrings, in keeping with the strong heteronymous group II projections from gastrocnemius medialis to semitendinosus motoneurones (see Table 7.3). Conversely, stretching the pretibial flexors by abrupt deceleration elicited a medium-latency response in the ipsilateral and contralateral tibialis anterior (Fig. 7.11(*d*)) and in the quadriceps. Here again, the pattern of the response corresponded to that of the heteronymous projections of group II afferents from tibialis anterior: bilateral projections and activation of quadriceps motoneurones (see pp. 304–5). (The reasons for the absence of a monosynaptic Ia response [M1] in this experimental paradigm are discussed in Chapter 2, p. 89).

Further evidence for group II excitation

Further evidence for a group II origin of the stretch-induced responses in soleus has been provided by Grey *et al.* (2001). The same portable device used to unload the triceps surae was used to produce an unexpected dorsiflexion perturbation. Rapid stretch of the ankle extensors evoked both an early (M1) and a later (M2) response at latencies compatible with Ia and group II-mediated responses, respectively (Fig. 7.11(*e*), and its legend). There is strong evidence suggesting that M2 is mediated by group II pathways.

(i) The medium-latency response was not velocity sensitive, contrary to the short-latency response, a finding consistent with the low dynamic sensitivity of muscle spindle secondary endings (cf. p. 289).

(ii) Nerve cooling increased more the latency of the M2 peak than that of the M1 peak (Fig. 7.11(*e*)).

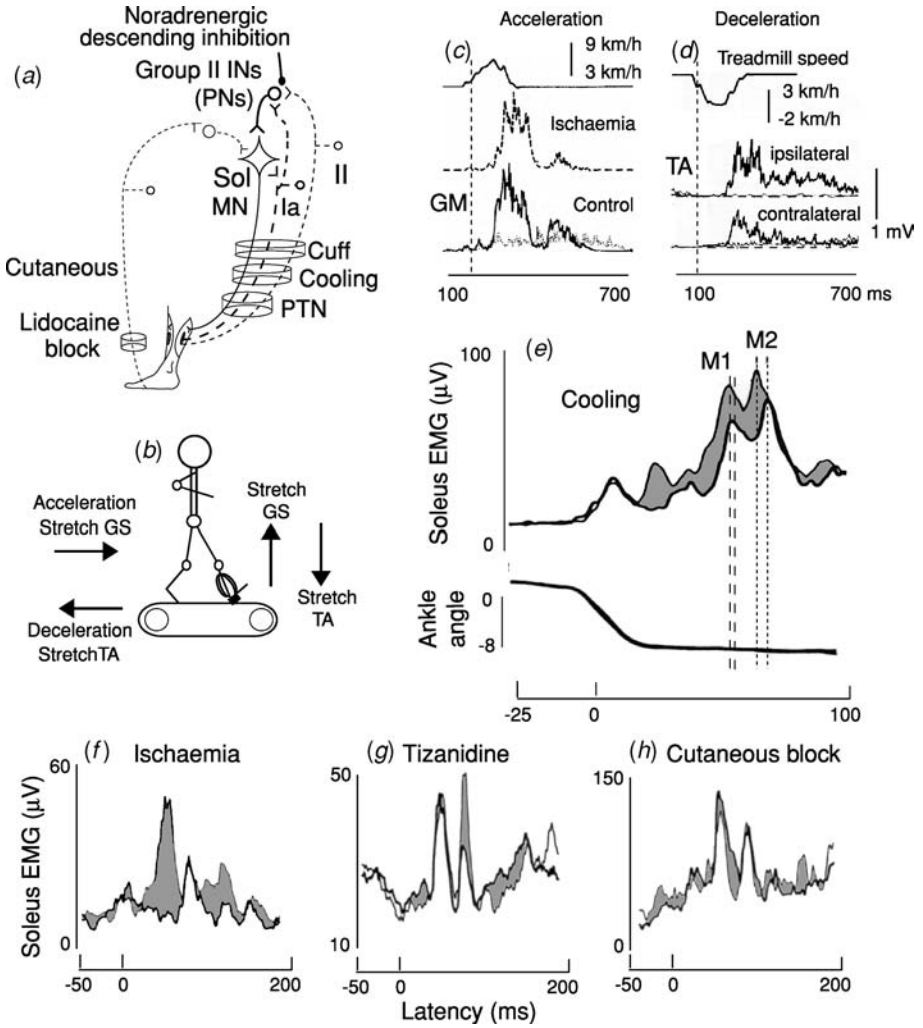


Fig. 7.11. Changes in group II excitation produced by passive stretch of ankle muscles during gait. (*a*) Sketch of the presumed pathways of homonymous group I–group II excitation through propriospinal neurones (PN) to soleus (Sol) motoneurones (MN). Group I–group II pathways to tibialis anterior (TA) MNs have been omitted. Ischaemic block and cooling of afferents in the posterior tibial nerve (PTN), and lidocaine block of cutaneous afferents from the foot are sketched. (*b*) Sketch of the experimental paradigm producing passive stretch of the plantar or dorsiflexors of the ankle during early stance phase of gait, due to either horizontal displacement of the body (horizontal arrows) or ankle rotation (vertical arrows). (*c*), (*d*) A brisk acceleration, stretching the gastrocnemius medialis (GM, (*c*)), or deceleration, stretching the TA (*d*), of the treadmill is triggered 80 ms after heel strike (first row, abscissa is time after heel contact). (*c*) The averaged rectified EMG of the GM is compared in the control situation (third row, conditioned EMG continuous line; unconditioned EMG, dotted line) and after 22 min of ischaemia (second row). (*d*) Results in the ipsilateral (second row) and contralateral TA (third row, conditioned EMG continuous line; unconditioned EMG, dotted line). (*e*)–(*h*) Short-latency (M1) and medium-latency (M2) responses produced in averaged rectified Sol EMG activity, by unexpected ankle dorsiflexion: 8°, at a velocity of 263° s^{-1}, followed by a hold phase of ~200 ms, onset (zero of the abscissa), triggered 200 ms after heel contact. Ankle angle position (0° standing position, negative values = dorsiflexion) is shown in (*e*) (lower trace). Mean latency of M1, 39 ms, and of the *peaks* for M1 and M2 55 and 78 ms, i.e. compatible with monosynaptic Ia and group II-mediated responses, respectively. EMG responses are compared in the control situation (thin line) and after (thick lines): (*e*) cooling of the nerve (dashed and dotted vertical lines highlight cooling-induced differences in latencies for the M1 and M2 responses, respectively); (*f*) ischaemic blockade of group I afferents; (*g*) oral intake of tizanidine 150 μg kg^{-1}; (*h*) Lidocaine block of cutaneous afferents from the foot. Grey areas in (*e*)–(*h*) highlight the differences between the situations. Modified from Berger, Dietz & Quintern (1984) ((*c*), (*d*)), and Grey *et al.* (2001) with permission ((*e*)–(*h*)), with permission.

(iii) Ischaemic blockade of Ia afferents completely suppressed the Ia-mediated short-latency response, but had much less effect on the medium-latency response (Fig. 7.11(*f*)).

(iv) Tizanidine suppressed M2, without affecting M1 (Fig. 7.11(*g*)).

(v) Blocking cutaneous afferents with local anaesthetic did not modify the amplitude of M2 (Fig 7.11(*h*)).

Functional implications

Stretch-induced responses in soleus (whether mediated by Ia or group II afferents) appear particularly in the early stance phase of gait. This suggests that these responses contribute to the stabilisation of the supporting limb during walking rather than to propulsion (see Chapter 11, p. 549).

When the tibialis anterior is active during the swing phase of gait, medium-latency stretch-induced M2 responses are delayed and reduced with respect to tonic voluntary contraction, suggesting depression of transmission in group II pathways. During the stance phase, there was no evidence that vertical displacements of the ankle evoked M2 responses in the tibialis anterior (Christensen *et al.*, 2001). This finding contrasts with the large responses produced by horizontal displacements due to brisk deceleration of the treadmill (see above), and the reasons for this discrepancy are discussed in Chapter 11 (p. 548).

Changes in the peroneal-induced group II excitation of quadriceps motoneurones

Methodology

The averaged, rectified on-going EMG activity of quadriceps was conditioned by stimulation of the deep peroneal nerve (Marchand-Pauvert & Nielsen, 2002a). Results obtained during the early stance phase of walking, where there is a co-contraction of the quadriceps and tibialis anterior, were compared to those found during a tonic voluntary co-contraction of the two muscles when standing, at equivalent levels of EMG activity.

Enhanced peroneal group II excitation of quadriceps

During walking, deep peroneal stimulation produced biphasic facilitation of the on-going EMG of quadriceps, with a large late peak following a weak early peak while, during voluntary contraction, only the early facilitation was present (Fig. 7.12(*b*), (*c*)). Several arguments indicate that the late excitation was due to the activation of muscle group II afferents: (i) the mean latencies of the early and late excitations were 4 and 9 ms in excess of the expected time of arrival of the conditioning Ia volley at motoneuronal level, much as the non-monosynaptic peroneal-induced group I and group II excitations of quadriceps motoneurones, respectively (see pp. 293–7); (ii) the threshold for the early peak was $\sim 1 \times$ MT, and that for the late excitation was $> 1.3 \times$ MT, much as for peroneal-induced excitation of group II afferents; and (iii) cooling the deep peroneal nerve delayed the latency of the late peak more than that of the early peak. However, ischaemic blockade of group I afferents caused both the early and late peaks to disappear. This latter finding might argue against group II excitation, but it could also reflect the transmission of the group I and group II excitations through the same interneuronal pathway (see p. 306), and that depolarisation of lumbar propriospinal neurones by the group I afferent volley was required for the group II excitation to manifest itself.

Possible underlying mechanisms and functional implications

The similar magnitude of the early group I excitation in the two tasks suggests that the enhanced group II excitation during walking was not due to increased excitability of lumbar propriospinal neurones, but

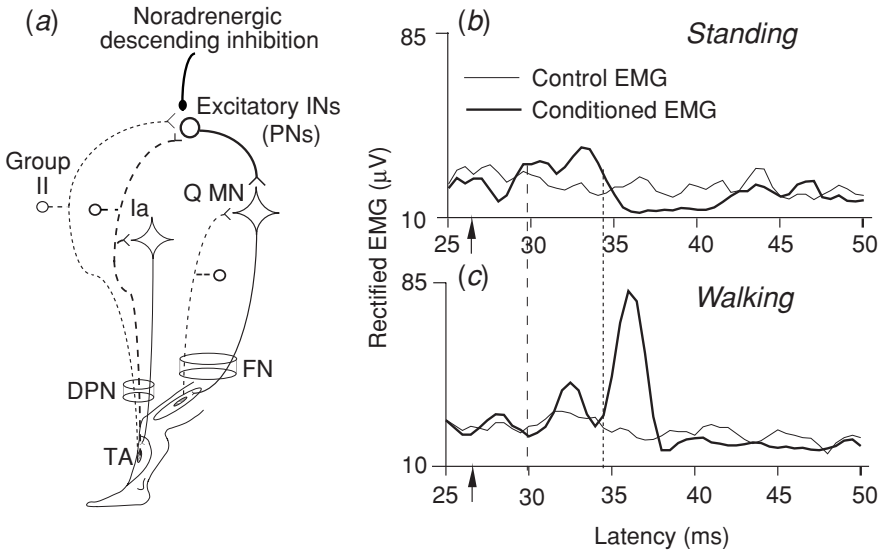


Fig. 7.12. Changes in deep peroneal group II excitation of quadriceps during gait. (*a*) Sketch of the presumed pathways of group I–group II excitation through propriospinal neurones (PN) from tibialis anterior (TA) to quadriceps (Q) motoneurones (MN). Noradrenergic descending inhibition of transmission of group II excitation is represented. (*b*), (*c*) Comparison of the effects of deep peroneal nerve (DPN) stimulation (2.5 × MT) on the averaged rectified EMG of the Q (vastus lateralis) during walking ((*c*) DPN stimulation triggered 30 ms after heel strike) and during voluntary co-contraction of Q and TA while standing (*b*), at equivalent EMG activity. Control (thin line) and conditioned (thick line) on-going EMG traces are plotted against the latency after DPN stimulation. Arrows indicate the expected time of arrival of the DPN group I volley at MN level (27 ms). Dashed and dotted vertical lines highlight the latencies of group I- and group II-mediated responses. Modified from Marchand-Pauvert & Nielsen (2002a), with permission.

to decreased gating of group II pathways from the brainstem. The peroneal group II facilitation was only observed during the early stance phase of walking (0–60 ms after heel strike with a maximum at 30 ms), when there is an eccentric contraction of the tibialis anterior. This would produce strong spindle activation, especially if the contraction was accompanied by enhanced γ_s drive (Chapter 3, p. 135). At this time the weight of the body is shifted to the leg that is about to begin the stance phase, and a strong quadriceps contraction would be required to extend the knee joint to support the body. The feedback carried by Ia and group II spindle discharges from ankle dorsiflexor muscles would help ensure the stabilising contraction of quadriceps. In healthy subjects the early and late peaks of peroneal-induced facilitation observed in early stance while walking at normal speed (3–4 km h^{-1}) are suppressed when walking at 1 km h^{-1}, a walking speed which requires voluntary effort (Marchand-Pauvert & Nielsen, 2002b). This finding could be due to the corticospinal inhibitory control observed on lumbar propriospinal neurones through feedback interneurones (see p. 310), and would indicate that the contribution of group II pathways to the stabilisation of the knee is especially important during natural 'automatic' walking.

Conclusions

Group II pathways play an important role during 'automatic' human walking: (i) homonymous group II discharges from the triceps surae contribute to

the normal activation of soleus motoneurones in the stance phase and, because this contribution can be predicted by the central nervous system, less central drive is necessary to activate the motoneurones in the presence of this feedback (Nielsen & Sinkjær, 2002); (ii) heteronymous group II discharges from pretibial flexors to quadriceps contribute to stabilising the knee in early stance; and (iii) in addition homonymous group II pathways contribute to the reactions to sudden external perturbations. Any group II excitation would be potentiated by group I discharges converging onto the relevant lumbar propriospinal neurones, much as is likely with perturbations to upright stance.

Studies in patients and clinical implications

Peripheral neuropathies

Charcot–Marie–Tooth type 1A disease

In this hereditary peripheral neuropathy, there is loss of large diameter nerve fibres with relative sparing of small-diameter fibres (see Dyck *et al.*, 1993). In such patients, the short-latency responses to stretch in soleus and flexor digitorum brevis are absent or markedly decreased, attesting the loss of Ia afferents, while delayed medium-latency responses (presumably delayed group II responses) are preserved (Fig. 7.13(*b*); Nardone *et al.*, 2000). Despite the absence of Ia stretch reflex responses in leg and foot muscles, the less severely affected patients do not suffer balance problems, and their body sway area is in the same range as in normal subjects (Fig. 7.13(*c*), (*d*)). The delay of the medium-latency responses may be explained by the slow conduction velocity of motor fibres (Nardone *et al.*, 2000).

Neuropathies affecting fibres of all sizes, such as diabetes mellitus

In these neuropathies, not only were the short-latency responses to stretch reduced in the soleus and absent in the flexor digitorum brevis, but the medium-latency responses were delayed in both muscles, and the conduction velocity of group II afferents decreased (Nardone & Schieppati, 2004). It was argued that this alteration of muscle group II afferent feedback was responsible for the increased body sway area and postural ataxia observed in these patients (Fig. 7.13(*e*); Schieppati *et al.*, 2001; Nardone & Schieppati, 2004).

Spasticity

Muscle stretch activates both primary and secondary muscle spindle endings. Hyperexcitability of lumbar propriospinal neurones activated by group II afferents might therefore be one of the causes of the exaggerated stretch reflex characteristic of spasticity, an hypothesis originally proposed on the basis of the selective gating of transmission of group II excitation to motoneurones in animals by monoaminergic agonists, drugs that are effective in depressing spasticity (Jankowska, 1993; Jankowska & Hammar, 2002; cf. p. 299, for evidence for a similar gating in humans). Three questions arise when examining group II excitation in spastic patients.

(i) Does increased group II excitation occur in spastic patients?

(ii) If yes, which is (are) the mechanism(s) underlying it?

(iii) Is increased group II excitation sufficient to cause spasticity?

Methodology

Deep peroneal-induced heteronymous facilitation of the quadriceps H reflex

This appears to be a suitable method to investigate changes in group II pathways in spastic patients, because (i) it can be used at rest; (ii) the group II-mediated excitation will then not be affected by the post-spike afterhyperpolarisation and recurrent inhibition following motoneurone discharge; (iii) the

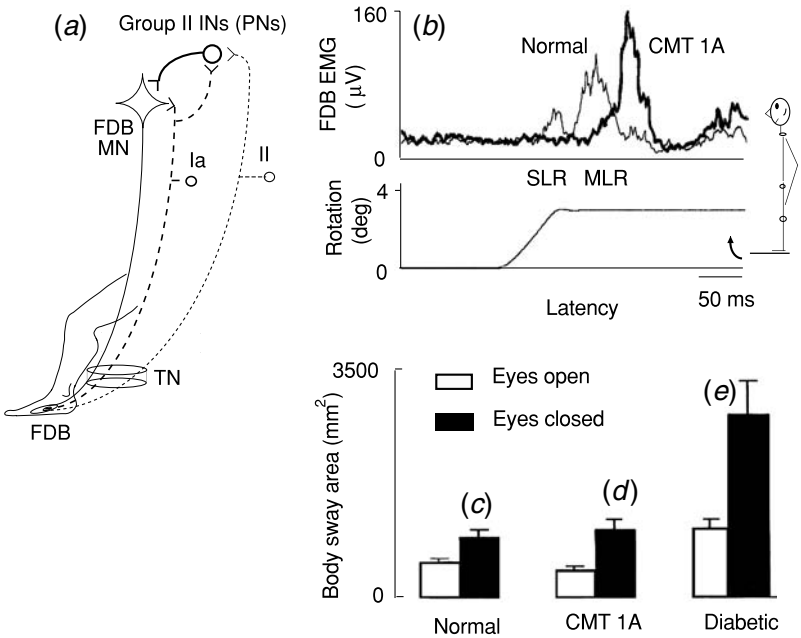


Fig. 7.13. Changes in group II-mediated responses in patients with peripheral neuropathy. (*a*) Presumed pathways mediating short-latency (SLR) and medium-latency (MLR) responses in the flexor digitorum brevis (FDB) muscle. Ia and group II afferents run in the tibial nerve (TN). Ia afferents have monosynaptic projections on FDB motoneurones (MN) and converge with group II afferents onto spinal group II interneurones (IN or PN). (*b*) Toe-up rotation of the platform (lower trace, and sketch on the right) and resulting rectified EMG responses in the FDB (upper traces) in a normal subject (thin line, with both SLR and MLR) and a patient with Charcot–Marie–Tooth type 1A disease (thick line, with an absent SLR and a delayed MLR). (*c*)–(*e*) Body sway area (mm^2) during quiet stance, with feet spaced 10 cm apart, eyes open (□) and closed (■), recorded in 23 normal subjects (*c*), 9 patients with Charcot–Marie–Tooth type 1A (CMT 1A) disease (*d*), and 20 patients affected by diabetic peripheral neuropathy (*e*). Each column is the mean value in the population; vertical bars 1 SEM. Body sway area, with eyes open or closed, is in the same range in normal subjects and in patients with CMT 1A disease, but is increased in patients with diabetic neuropathy. Modified from Nardone *et al.* (2000) (*b*), and Schieppati *et al.* (2001) ((*c*)–(*e*)), with permission.

excitability of the interneurones will not be modified by the 'postural set' (see below); and (iv) there is virtually no heteronymous monosynaptic excitatory Ia projection from pretibial flexors to quadriceps motoneurones. The investigation involves measuring the time course of the changes in the quadriceps H reflex after conditioning stimulation at 2–3 × MT to activate group I and group II afferents in the deep peroneal nerve. To ensure that changes in the deep peroneal facilitation do not simply reflect changes in the excitability of quadriceps motoneurones evoked by an unmodified conditioning group II volley, the H_{max}/M_{max} amplitude and H/M threshold ratios should be recorded in parallel in the quadriceps (Marque *et al.*, 2001b; Maupas *et al.*, 2004).

Monoaminergic gating

If an increase in the late peroneal-induced facilitation of the quadriceps H reflex reflects increased transmission of group II excitation, it should be suppressed by monoamine agonists. Note, however, that monoaminergic suppression is a condition

necessary but insufficient by itself to attribute an increased late facilitation of the reflex to an increased excitation at a premotoneuronal level. A *normal* group II input reaching hyperexcitable α motoneurones would produce an increased reflex response, and this would be similarly suppressed by monoamines. It is therefore important that changes produced by monoamine agonists on the group II excitation have been observed without concomitant changes in α motoneurone excitability (Maupas *et al.*, 2004; Remy-Néris *et al.*, 2003).

Stretch-induced group II-mediated medium-latency responses in leg muscles

During free stance these responses are reduced in spastic patients with supramedullary injuries (Nardone *et al.*, 2001b). However, such responses depend on the 'central set' operating when the subject relies on the group II response to ensure equilibrium (cf. p. 313), and these studies provide limited insight into the excitability of group II pathways under resting conditions (cf. p. 301). Nardone, Corna & Schieppati (2001a) presumed that the *normal* regulation involves inhibitory descending control on the locus coeruleus, leading to decreased monoaminergic gating of group II afferents (cf. p. 314). The loss of this normal descending regulation after stroke could therefore account for the weaker group II excitation during perturbations to stance (cf. the sketch in Fig. 7.14(*a*)).

Evidence for increased propriospinally mediated group I-group II excitation

Stroke patients

The early non-monosynaptic group I and late group II peroneal-induced facilitations of the quadriceps H reflex are increased to a similar extent on the affected side and not modified on the unaffected side when compared with healthy subjects (Figs. 10.17(*b*) and 7.14(*b*); Marque *et al.*, 2001b; Maupas *et al.*, 2004). Oral intake of tizanidine reduced the spasticity and produced, on the affected side, a decrease in the deep peroneal-induced facilitation of the quadriceps H reflex. The decrease was more marked for the late group II excitation than the early non-monosynaptic group I excitation (Fig. 7.14(*b*); Maupas *et al.*, 2004).

Patients with spinal cord lesions

More variable results have been reported in these patients (Remy-Néris *et al.*, 2003). In most patients the group I and II peaks were both significantly enhanced, with a greater increase in the late group II peak (Fig. 7.14(*c*) and Fig. 10.17(*d*)). In some patients, however, the increase was limited to the early group I peak (Fig. 10.17(*c*)). Clonidine (another α_2 noradrenergic agonist injected intrathecally) decreased the spasticity and suppressed both peaks of peroneal-induced facilitation of the quadriceps H reflex, the suppression of the late peak being more prominent (Fig. 7.14(*c*); Remy-Néris *et al.*, 2003). In spinal-injured patients, oral intake of L-dopa (a noradrenaline precursor) also reduced the spasticity and weakened the quadriceps tendon jerk (Fig. 7.14(*d*), (*e*); Eriksson, Olausson & Jankowska, 1996).

Conclusions

There is evidence for increased peroneal-induced group II excitation of quadriceps motoneurones in spastic patients. The finding that monoamine agonists suppress the facilitation produced by group II afferents more than that produced by group I afferents supports this view. The possible mechanisms underlying the suppression of group I-mediated effects are discussed below (cf. p. 324).

Possible mechanisms underlying changes in group II-mediated responses

Stroke patients

Loss of the corticospinal excitation of feedback inhibitory interneurones (cf. p. 310) would produce increased excitability of propriospinal neurones, if the normal control on these inhibitory interneurones were exerted tonically. There is no experimental evidence for tonic corticospinal control of feedback inhibitory interneurones, but this mechanism would provide a simple explanation for why the early group I and late group II peaks of

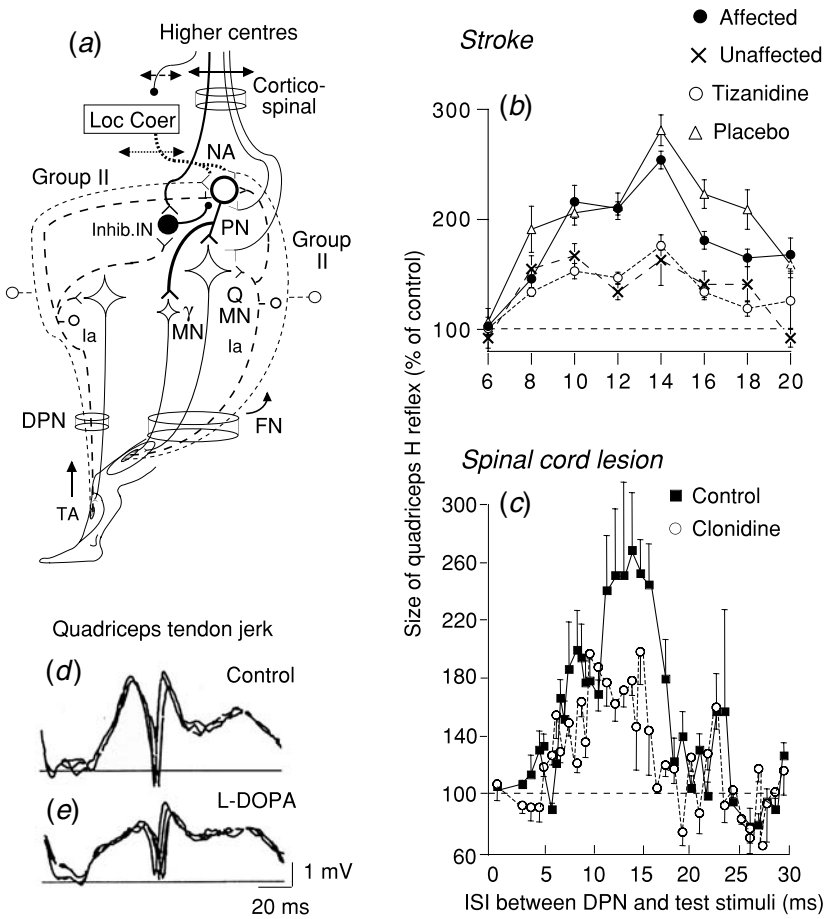


Fig. 7.14. Changes in group II excitation in spastic patients. (*a*) Sketch of the presumed pathways. Group Ia and group II afferents from tibialis anterior (TA) in the deep peroneal nerve (DPN) and from the quadriceps (Q) in the femoral nerve (FN) converge on common propriospinal neurones (PN) projecting to Q motoneurones (MN). PNs are inhibited by feedback inhibitory interneurones (Inhib IN) fed by Ia and group II afferents, and project also to γ motoneurones (positive feedback through the γ loop). Corticospinal projections are more potent (thick line) on inhibitory INs than on PNs and Q MNs. The noradrenergic (NA) gating of group II excitation from the locus coeruleus (Loc Coer) is represented (thick dotted line), and it is assumed that there is descending inhibitory control on the locus coeruleus. Upward vertical arrow represents the tonic group II traffic from TA due to the background stretch on the muscle (see p. 324 in text), and bent upward arrow the spindle discharge produced by quadriceps stretch when assessing Ashworth score. Horizontal double-headed arrows show various lesions interrupting: the corticospinal tract (continuous arrow), the descending tract in the spinal cord from the locus coeruleus (dotted arrow), and the presumed inhibitory higher control of the locus coeruleus (dashed arrow). (*b*), (*c*) Changes in the quadriceps H reflex after DPN stimulation ((*b*), 2 × MT; (*c*), 3 × MT), as a percentage of unconditioned reflex value, are plotted against the interstimulus interval (ISI). (*b*) Results in a stroke patient from the affected side before (●) and 90 min after oral intake of tizanidine 150 μg kg^{-1} (○) or a placebo (△), and from the unaffected side in the control situation (×); vertical bars ±1 SEM. (*c*) Results in a patient with familial spastic paraparesis before (■) and 60 min after intrathecal injection of clonidine 60 μg (○); vertical bars 1 SEM. (*d*), (*e*) In a patient with traumatic spinal cord lesion, four superimposed quadriceps tendon jerks are compared before (*d*) and 50 min after oral intake of L-dopa 200 mg (*e*). Modified from Maupas *et al.* (2004) (*b*), Remy-Néris *et al.* (2003) (*c*) and Eriksson, Olausson & Jankowska (1996) ((*d*), (*e*)), with permission.

facilitation of the quadriceps H reflex are increased to a similar extent in these patients.

Patients with spinal cord injury

The corticospinal lesion might similarly produce hyperexcitability of lumbar propriospinal neurones by the removal of corticospinal inhibition. However, disruption of the normal monoaminergic gating of transmission of group II excitation is the most likely mechanism (see Jankowska & Hammar, 2002). Interruption of the descending noradrenergic suppression would account for the findings that the peroneal-induced group II excitation of the quadriceps H reflex is: (i) generally increased more than the early non-monosynaptic group I excitation; and (ii) always suppressed more by intrathecal clonidine (see above).

Possible mechanisms underlying the changes in non-monosynaptic group I excitation

Tonic group II excitation

Given that the monoaminergic gating is exerted selectively on the transmission of group II excitation (whether at a pre- or post-synaptic level, cf. p. 292), some findings require explanation, namely that: (i) disruption of the normal gating from the brainstem in spinal cord lesions also produces increased non-monosynaptic group I excitation; and (ii) monoaminergic agonists also depress the increased early group I facilitation observed after spinal cord injury or stroke. However, with the ankle plantar flexed at 110–120°, there will be a tonic group I and II discharge from pretibial flexors and, thereby, tonic depolarisation of lumbar propriospinal neurones. Given the convergence of group I and group II afferents on these neurones: (i) the efficacy of group I volleys in activating propriospinal neurones would be increased and, as a result, the non-monosynaptic group I excitation would be enhanced; and (ii) gating of this group II tonic activity by monoaminergic agonists would decrease the excitability of lumbar propriospinal neurones, thereby reducing their response to the conditioning group I volley.

Monoaminergic depression of the tendon jerk by L-dopa

This depression could similarly reflect gating of tonic group II discharges contributing to the excitability of propriospinal neurones. Homonymous Ia excitation of quadriceps motoneurones is partly mediated through propriospinal neurones (Fournier *et al.*, 1986). Because the rising phase of the compound Ia EPSP produced in motoneurones by tendon percussion lasts 5–10 ms (Burke, Gandevia & McKeon, 1984), there is ample time for propriospinally mediated Ia excitation to contribute to the tendon jerk. With the knee semi-flexed (to 120–150°), there would be a tonic group II discharge from quadriceps (and possibly other muscles in the limb), and this could be gated by L-dopa. In any event, a significant part of the tendon jerk exaggeration in spasticity could be due to hyperexcitability of propriospinal neurones, largely maintained by group II inputs. The possibility that propriospinal pathways contribute to the tendon jerk represents a further reason for circumspection in comparing the tendon jerk and H reflex and, in particular, why such comparisons are flawed measures of fusimotor drive (cf. Chapter 3, pp. 117–18).

Is increased group II excitation sufficient to cause spasticity?

There is no definitive answer to this question because spasticity is characterised by an exaggeration of the homonymous stretch reflex, while the excitability of group II excitatory pathways has been assessed at rest only in heteronymous pathways (cf. pp. 320–1). However, indirect arguments suggest that the increased group II excitation is strong enough to cause spasticity.

Exaggerated stretch reflexes are strongly depressed by clonidine and tizanidine

This is so in spastic patients, whether the spasticity is due to stroke or spinal cord injury (e.g. Nance, Shears & Nance, 1985; Steward, Barbeau & Gautier,

1991; Emre, 1993; Delwaide & Pennisi, 1994; Remy-Néris *et al.*, 1999; Maupas *et al.*, 2004). The reduction of spasticity by these monoaminergic agonists is probably due to depression of group II excitation, since they gate transmission of group II excitation to motoneurones and have no effects on pre- or post-synaptic transmission of group I effects (cf. Jankowska & Hammar, 2002). However, the excitability of the stretch reflex is the net result of several mechanisms, and it is conceivable that blockade of any excitatory mechanism would reduce it, even though the primary cause of the exaggeration (spasticity) was another mechanism(s) (cf. Chapter 12, p. 560). Nevertheless, the reduction of spasticity produced by monoaminergic agonists is so complete that a major contribution of increased group II excitation to the stretch reflex exaggeration of spastic patients is probable.

Excessive positive fusimotor feedback

In the cat, there is a potential positive feed-back through the γ-loop, with excitation of γ motoneurones, partly via monosynaptic action of group II afferents but mainly via projections of the propriospinal neurones co-activated by Ia and group II afferents (cf. p. 291). If this occurs in humans, excessive positive feedback might contribute to the exaggeration of stretch reflexes. With the relatively slow muscle stretch used to assess spasticity clinically, group II volleys would have ample time to activate not only propriospinal neurones but also to produce positive feed-back through *hyperexcitable* propriospinal neurones (see the sketch in Fig. 7.14(*a*)). 'A pathological enhancement of reflex actions of not only group II but also of group Ia muscle afferents might then occur because stronger actions of γ motoneurones on muscle spindles would be followed by stronger responses of both primaries and secondaries.' (Gladden, Jankowska & Czarkowska-Bauch, 1998). This amplifying effect of group II actions through a positive feedback loop involving γ_s cannot be revealed by electrically induced volleys, because it requires the conduction time through the γ loop to manifest itself in motoneurones. If this is a factor, the overall contribution of hyperexcitability of lumbar propriospinal neurones to spasticity would be underestimated by electrically induced volleys. Validation of a positive feedback loop involving γ_s motoneurones might be possible with recordings from muscle spindle afferents in response to stretch in spastic patients. As yet, there are no published data for patients with spinal cord injury and the lower-limb data for stroke are from Ia afferents from the triceps surae of only two patients (see Chapter 3, pp. 139–40).

Correlations with disability

The increase in peroneal-induced excitation of quadriceps motoneurones is not correlated with spasticity assessed with the Ashworth score in patients with either cerebral or spinal lesions (Marque *et al.*, 2001b; Remy-Néris *et al.*, 2003). Similarly, after the administration of clonidine to paraplegics or tizanidine to hemiplegics, the decrease in spasticity is poorly correlated with the decrease in the late facilitation of the quadriceps H reflex. There may be several reasons for this absence of correlation: (i) the electrically induced peroneal facilitation of the quadriceps H reflex does not assess group II excitation of γ motoneurones; (ii) the peroneal facilitation of the quadriceps H reflex assesses a heteronymous pathway, whereas spasticity is assessed clinically for the homonymous pathway, and also depends on the exaggeration of the monosynaptic Ia stretch reflex; (iii) spasticity, measured as the resistance to passive stretch, involves changes in the mechanical properties of muscle, and this may be an important factor, in particular in stroke patients (cf. Chapter 12, pp. 572–3); (iv) the exaggeration of the stretch reflex in individual patients depends on several factors which do not necessarily co-vary (cf. Chapter 12, p. 571).

Conclusions

The contribution of increased group II excitation to the exaggeration of the stretch reflex in spastic

patients appears likely. The extent to which it contributes to the motor impairment and limitation of activity in patients is examined in Chapter 12.

Spindle group II afferents are not responsible for the clasp-knife phenomenon

The size of the stretch reflex of the quadriceps muscles of spastic human subjects is inversely proportional to the initial length of the muscle, if the velocity of stretch remains constant (Burke, Gillies & Lance, 1970; Burke & Lance, 1973). This length-dependent suppression of the stretch reflex was attributed to secondary spindle endings, and it was postulated that the underlying inhibition was responsible for the clasp-knife phenomenon. Subsequent studies in the cat have shown that other slowly conducting muscle afferents (non-spindle group II and group III–IV afferents) are probably necessary for the initiation of clasp-knife phenomenon (Rymer, Houk & Crago, 1979). In addition, there is no evidence for group II inhibition of motoneurones of pure extensor muscles in humans, either in homonymous or heteronymous pathways (cf. p. 307). It cannot be excluded that group II inhibitory pathways to extensor motoneurones do exist but are not open in awake intact man. However, the results presented so far for patients with complete spinal cord lesions indicate an increase in group II *excitation* of quadriceps motoneurones (Remy-Néris *et al.*, 2003).

Parkinson's disease

Homonymous group II excitation

The amplitude of medium-latency responses in the soleus and tibialis anterior during active upright stance is normal or slightly increased in parkinsonian patients (Schieppati & Nardone, 1991). The main abnormality is the absence of an influence of 'postural set' on medium-latency responses: the amplitude of medium-latency responses, particularly in the tibialis anterior, does not attenuate normally when standing patients hold onto a stable frame (Fig. 7.15(*d*), (*e*)). This failure to modulate the medium-latency response when stability is assisted correlates significantly with the severity of the disease (as measured using the Webster scale). In normal subjects, when the medium-latency responses are no longer required to ensure the control of upright stance, group II excitation is suppressed, possibly due to increased activity from the locus coeruleus (see p. 314). In parkinsonian patients, there could be failure of this increased monoaminergic gating of group II excitation from the locus coeruleus. Indeed, a role for the locus coeruleus in the control of posture has been proposed by Pompeiano (2001), and there is a significant cell loss in this structure, even in early-stage disease (German *et al.*, 1992).

Peroneal group II excitation of quadriceps

The late group II but not the early group I facilitation of the quadriceps H reflex produced by stimulation of the deep peroneal nerve may be larger in parkinsonian patients than in normal subjects (Fig. 7.15(*f*); Simonetta-Moreau *et al.*, 2002). Interestingly, increased group II excitation is found only in rigid patients, where it is correlated with rigidity score assessed with the Unified Parkinson's Disease Rating Score (Fahn & Elton, 1987). The finding that the group II excitation is selectively increased suggests a failure of the monoaminergic gating of group II excitation from the locus coeruleus (see above).

Conclusions

Role of group II pathways in natural motor tasks

During a voluntary contraction, group II pathways contribute to the excitation of quadriceps motoneurones. However, group II excitatory pathways are mainly involved in postural and locomotor tasks: (i) homonymous stretch-induced responses of leg and foot muscles mediated through group II

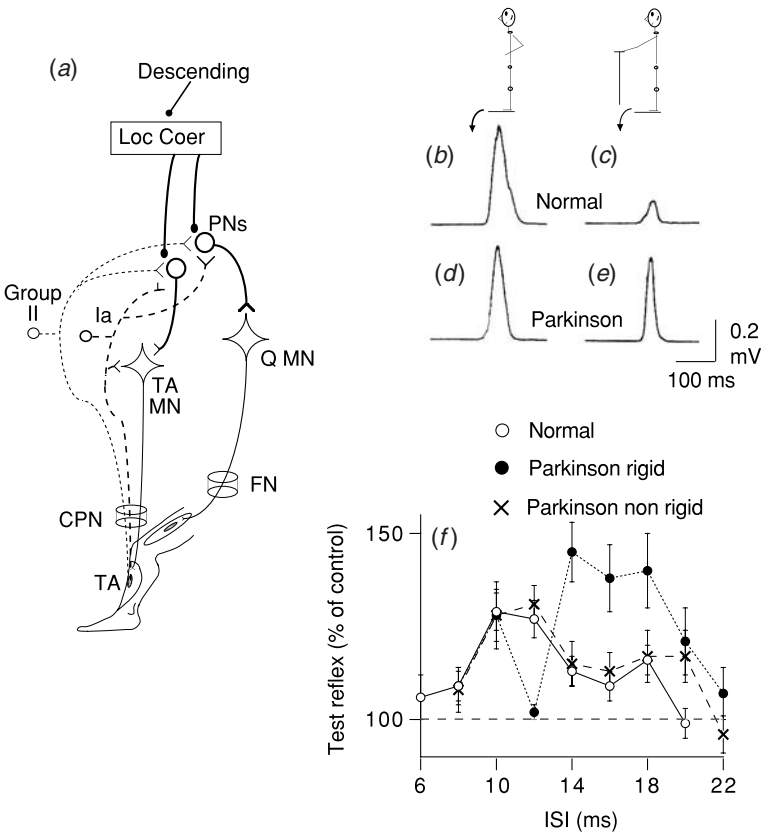


Fig. 7.15. Changes in group II excitation in patients with Parkinson's disease. (*a*) Sketch of the presumed pathways. Group Ia and group II afferents from tibialis anterior (TA) converge on propriospinal neurones (PN) projecting to quadriceps (Q) and TA motoneurones (MN). Transmission of group II excitation is gated by a monoaminergic tract from the locus coeruleus (Loc Coer). It is assumed that the locus coeruleus normally receives descending inhibition from higher centres. (*b*)–(*e*) Medium-latency responses in TA elicited by toe-down rotation of the platform during free stance ((*b*), (*d*)) and while holding a stable frame ((*c*), (*e*)) in a normal subject ((*b*), (*c*)) and in a parkinsonian patient ((*d*), (*e*)). The 'postural set' is sketched above the traces. (*f*) Changes in the Q H reflex after deep peroneal nerve (DPN) stimulation (2 × MT) at rest, plotted against the interstimulus interval (ISI) and expressed as a percentage of the control reflex value, in a normal subject (○), a rigid parkinsonian patient (●) and a non-rigid patient (×). DPN-induced group II excitation is increased in the rigid patient, not in the non-rigid patient. Each symbol is the mean of 20 measurements; vertical bars ±1 SEM. Modified from Schieppati & Nardone (1991) ((*b*)–(*e*)), and Simonetta-Moreau *et al.* (2002) (*f*), with permission.

pathways play a crucial role in the control of perturbations to upright stance; (ii) postural situations requiring co-contraction of leg and thigh muscles (e.g. of tibialis anterior and quadriceps when leaning backwards) are accompanied by facilitation of the transmission in the corresponding heteronymous group II pathways; (iii) during the stance phase of gait, the group II afferent discharge from ankle extensors contributes to the discharge of soleus motoneurones; (iv) peroneal group II facilitation of quadriceps motoneurones helps to stabilise the knee during the early stance phase of walking;

(v) stretch-induced group II responses in soleus during the early stance phase may also play a role in the stabilisation of the ankle of the supporting leg.

Changes in group II excitation and pathophysiology of movement disorders

Spasticity

In stroke patients, peroneal non-monosynaptic group I and group II excitations of quadriceps motoneurones are increased to a similar extent, presumably due to disinhibition of propriospinal neurones. In patients with spinal cord lesions, peroneal-induced group II excitation is more increased than the non-monosynaptic group I excitation, indicating that pathways mediating group II actions are disinhibited, probably due to damage to the descending monoaminergic pathways that gate group II actions. Monoaminergic agonists or precursors decrease the peroneal-induced group II excitation of quadriceps motoneurones and reduce spasticity. The contribution of increased group II excitation to spasticity may be accentuated by the projections of lumbar propriospinal neurones to γ motoneurones.

Parkinson's disease

The peroneal-induced group II excitation is selectively increased, and this increase is correlated with the degree of rigidity. This probably reflects a decrease in the monoaminergic gating of group II excitation from the locus coeruleus. A failure of this gating could also be responsible for the lack of attenuation of homonymous stretch-induced responses when standing and holding onto a stable frame.

Résumé

Background from animal experiments

Group II muscle afferents originate from muscle spindle secondary endings, which are sensitive to changes in muscle length, but relatively insensitive to the dynamic component of stretch. They have a smaller diameter and, accordingly, a higher electrical threshold and a slower conduction velocity than Ia afferents. Group II effects are mainly transmitted through interneurones which excite or inhibit motoneurones. Interneurones transmitting group II afferent effects to motoneurones are located in the intermediate zone, and are termed 'group II interneurones'. They are particularly concentrated in midlumbar segments, and are also referred to as 'lumbar propriospinal neurones' in the following. In anaesthetised low spinal cats, projections from group II interneurones to α motoneurones produce mainly flexor excitation and extensor inhibition. However, alternative pathways can be demonstrated in unanaesthetized animals. Group II interneurones also have strong excitatory projections to γ motoneurones. Besides their input from group II afferents, group II interneurones are also excited by group I afferents and descending tracts. There is a mutual post-synaptic inhibition between different subgroups of group II interneurones. Presynaptic inhibition with PAD of group II terminals is evoked mainly from group II afferents and from the reticular formation. However, the main systems gating group II actions are descending monoaminergic systems (in particular noradrenergic) originating from the locus coeruleus in the brainstem. Accordingly, the α_2 adrenergic receptor agonists, tizanidine and clonidine, are effective in producing selective blockade of transmission of group II excitation.

Methodology

Underlying principles

Group II afferents may be activated by stretching the receptor-bearing muscle or by electrical stimulation. Criteria for a group II response are: longer latency than Ia excitation due to a slower conduction velocity for the afferent pathway, electrical threshold about twice that of the Ia excitation, and suppression by monoaminergic agonists.

Stretch-induced homonymous group II excitation

In standing subjects, rotation of a supporting platform produces stretch responses in leg and foot muscles. In soleus and flexor digitorum brevis, toe-up rotation produces a short-latency response at latencies corresponding to those of monosynaptic Ia stretch reflexes, and a medium-latency response ~35 and 40 ms later, respectively. In the tibialis anterior, toe-down rotation of the platform elicits only the medium-latency response.

Electrically induced group II excitation

Group II excitation produced by electrical stimulation at 2–3 × MT of lower-limb nerves can be assessed in heteronymous motoneurones using the H reflex, the PSTH of single units, or the on-going EMG.

H reflex

Stimulation of the deep peroneal nerve produces biphasic facilitation of the quadriceps H reflex. There is an early low-threshold peak (~3 ms central delay; 0.6 × MT threshold), due to activation of lumbar propriospinal neurones by group I afferents, followed by a late high-threshold excitation (~5–6 ms later; 1.3 × MT threshold). The high-threshold late excitation is also observed in the quadriceps H reflex after stimulation of the tibial nerve, and in the semitendinosus H reflex after stimulation of the gastrocnemius medialis nerve.

PSTHs

The same conditioning stimuli evoke a similar high-threshold late excitation in the PSTHs of single motor units in quadriceps and semitendinosus.

On-going EMG

The high-threshold late excitation of quadriceps and peroneus brevis motoneurones to stimulation of the peroneal and tibial nerve, respectively, produces facilitation of the on-going EMG.

Evidence for muscle group II excitation

Cooling of the 'conditioning' nerve

Cooling produces an increase in latency that is greater for the late responses than for the early group I-mediated responses. This holds true for stretch-induced responses in the soleus and flexor digitorum brevis, and electrically induced late heteronymous excitation of quadriceps. Accordingly, the longer latency of the late peak is due to the activation of peripheral afferents of slower conduction velocity than Ia afferents, and not to a longer pathway in the central nervous system fed by Ia afferents.

Pharmacological validation

Short-latency group I responses are not affected, but late responses are suppressed by tizanidine. Here again, this holds true for both stretch-induced responses in the soleus and flexor digitorum brevis, and responses elicited in the peroneus brevis by electrical stimulation of the tibial nerve. This provides further support for a group II origin of the late responses elicited by stretch and by electrical stimulation.

Cutaneous and joint afferents

A significant contribution of cutaneous and joint afferents to the high-threshold late responses has been excluded.

Conclusions

There are several independent lines of evidence indicating that late responses evoked by stretch or by high-intensity electrical stimulation involve a spinal pathway fed by group II muscle afferents.

Critique of the tests used to reveal group II actions

Contamination by group I effects

Group II actions are necessarily contaminated by group I effects, which have a lower threshold and, because of the faster conduction velocity of group I afferents, are the first to reach the spinal cord. This complicates interpretations: overlap between group I effects and group II excitation makes precise assessment of the onset of group II excitation difficult; the post-spike AHP and recurrent inhibition following the firing of the tested motoneurone(s) by the group I discharge reduce their availability to the subsequent group II volley; because of the convergence of group I and group II afferents on the same interneurones (see below), activation of these neurones by group I volleys can be the source of different interactions between the two volleys: facilitation (if the group I effect is subliminal), occlusion (if the group I volley discharges the interneurones).

Stretch-induced responses during upright stance

These responses are only present during free stance and cannot be used to investigate transmission in group II pathways at rest or its changes during voluntary movement.

Common peroneal-induced facilitation of the quadriceps H reflex

This is suitable for investigating group II excitation in patients. However, during quadriceps contractions $\geq$10% of MVC, there may be reflex suppression due to convergence between the peroneal and femoral test volleys onto interneurones mediating autogenetic 'Ib inhibition'.

Organisation and pattern of connections

Peripheral pathway

The conduction velocities of Ia and group II afferents have been estimated at ~51 and 21.4 m s^{-1} for afferents mediating stretch-induced responses, and ~68 and 45 m s^{-1} for afferents mediating electrically induced heteronymous responses, respectively. The higher values found after electrical stimulation may be because electrical stimulation preferentially activates the fastest afferents, while this is not necessarily so with muscle stretch. In leg muscles, the conduction velocity of group II afferents is about 65% of that of Ia afferents, and the electrical threshold ~2.1 times that of Ia afferents. These ratios are similar to those found for group II/Ia afferents in the cat.

Central pathway: lumbar propriospinal neurones

The more caudal the motoneurone pool in the spinal cord, the longer the central delay. This suggests a pathway with neurones located rostral to motoneurones. There is indirect evidence that, in human subjects, group II and non-monosynaptic group I excitations are mediated through common lumbar propriospinal neurones.

Connections

Excitatory projections to motoneurones

Homonymous projections have only been explored in distal muscles, and are stronger in tibialis anterior and flexor digitorum brevis than in soleus. Heteronymous projections are widespread from distal muscles onto motoneurones of proximal muscles. They are particularly potent from gastrocnemius medialis to semitendinosus and from pretibial flexors to quadriceps. Projections between leg muscles are only disclosed by cortical stimulation. Bilateral projections to homologous muscles are observed after unilateral stretch.

Inhibition of excitatory effects

Inhibition of excitatory effects evoked by group I and group II afferent volleys can be produced by the same group I and group II volleys, but are generally detectable only in presence of cortical stimulation. There is evidence that the inhibition is exerted onto

propriospinal neurones through feedback inhibitory interneurones (and this constitutes a disfacilitation of motoneurones).

Lack of evidence for inhibition of motoneurones

The lack of evidence for group II inhibition exerted on motoneurone of human extensor muscles is the most striking difference from feline data.

Effects of corticospinal volleys

Corticospinal inputs facilitate lumbar propriospinal neurones co-activated by group I and group II afferents and inhibitory interneurones mediating feedback inhibition to these neurones. Overall, the dominant effect of corticospinal volleys on the propriospinal system is excitation of feedback inhibition, particularly in the pathway of propriospinal excitation to semitendinosus motoneurones.

Motor tasks and physiological implications

Voluntary contraction

There is a facilitation of the interneurones mediating group I and group II excitation to quadriceps motoneurones during voluntary contractions of quadriceps, but not (or hardly so) of those mediating group II excitation to semitendinosus motoneurones during contraction of semitendinosus.

Postural tasks

Homonymous stretch-induced medium-latency responses play a crucial role in the control of perturbations to upright stance, as indicated by the finding that they are considerably reduced when not required for equilibrium, e.g. when subjects have an external support. During postural co-contractions of tibialis anterior and quadriceps when leaning backwards, heteronymous group II excitation from tibialis anterior to quadriceps is facilitated with respect to voluntary co-contraction of the same muscles. Similarly heteronymous group II excitation from gastrocnemius medialis to semitendinosus is facilitated during the postural co-contraction of these two muscles when leaning forwards. Group II discharges from stretched leg muscles could help reinforce the co-contraction of leg and thigh muscles to maintain bipedal stance.

Gait

Homonymous group II afferents contribute to the activation of soleus motoneurones during the stance phase of walking. The evidence is based upon the finding that unexpected unloading of the ankle extensors suppresses the EMG of soleus, at the latency of a group II effect, and this suppression is modified little by ischaemic blockade of group I afferents. This finding implies that the group II afferent discharge from ankle extensors is used as an integral part of the motor command in the activation of the muscles. Peroneal-induced group II facilitation of the on-going quadriceps EMG is enhanced during the early stance phase of walking. At this time the weight of the body is shifted to the leg that is about to begin the stance phase, and the feedback support from group II afferents from ankle dorsiflexor muscles may help ensure the stabilising contraction of the quadriceps. Finally, stretch-induced group II responses in the soleus appear particularly in the early stance phase of walking, when they may play a role in the stabilisation of the supporting limb. In postural tasks and gait, group II excitation may be potentiated by group I activity converging on the relevant lumbar propriospinal neurones.

Studies in patients and clinical implications

Peripheral neuropathies

In patients with Charcot–Marie–Tooth type 1A disease, despite the loss of large-diameter nerve fibres, there are no balance problems, as long as the

medium-latency responses are present and not excessively delayed. In contrast, there is an increase in sway area in other types of neuropathy affecting fibres of all diameters (e.g. diabetic neuropathy).

Spasticity

In stroke patients, peroneal-induced facilitation of the quadriceps H reflex is increased on the affected side and not modified on the unaffected side. The greater peroneal-induced facilitation involves both the early non-monosynaptic group I and late group II peaks of excitation, and a common underlying mechanism is therefore probable. The findings can be explained satisfactorily by hyperexcitability of lumbar propriospinal neurones, due to the loss of corticospinal facilitation of inhibitory interneurones mediating feedback inhibition (i.e. a disinhibition). In patients with spinal cord injury, both peaks of peroneal excitation of the quadriceps H reflex are generally enhanced with respect to normal subjects, again suggesting disinhibition of lumbar propriospinal neurones. However, in most patients, the late group II excitation is increased more than the early group I excitation. Disruption by the spinal cord lesion of the monoaminergic gating of group II actions could account for this finding. Noradrenergic agonists (tizanidine in hemiplegic patients, intrathecal clonidine in paraplegic patients) reduce the peroneal group II facilitation of the quadriceps H reflex. They also reduce, though to a lesser extent, the early group I excitation. A possible explanation of this latter finding is that a tonic stretch-induced group II discharge from the pretibial flexors produces tonic depolarisation of propriospinal neurones, and this is suppressed by noradrenergic agonists. Assuming that part of the tendon jerk is mediated through propriospinal neurones, the depression of the quadriceps tendon jerk by L-dopa could reflect gating of tonic group II discharges contributing to the excitability of propriospinal neurones. Given that monoaminergic agonists selectively suppress transmission of group II excitation, the marked depression of spasticity by these drugs is consistent with a role for group II excitation in the exaggeration of the stretch reflex in spastic patients. The increase in peroneal excitation of quadriceps motoneurones is not correlated with the degree of spasticity, and this implies that facilitation of the transmission in lumbar propriospinal pathways to α motoneurones acts in concert with other mechanisms, such as the parallel actions of group II afferents on γ motoneurones.

Parkinson's disease

Peroneal group II facilitation of the quadriceps H reflex is increased, though only in rigid patients. This suggests decreased gating of transmission from group II afferents. The main abnormality in stretch-induced homonymous responses is the lack of attenuation of these responses, particularly in tibialis anterior, when standing and holding onto a stable frame. These abnormalities could result from cell loss in the locus coeruleus.

REFERENCES

Abbruzzese, G., Rubino, V. & Schieppati, M. (1996). Task-dependent effects evoked by foot muscle afferents on leg muscle activity in humans. *Electroencephalography and Clinical Neurophysiology*, **101**, 339–48.

Bajwa, S., Edgley, S. A. & Harrison, P. J. (1992). Crossed actions on group II-activated interneurones in the midlumbar segments of the cat spinal cord. *Journal of Physiology (London)*, **455**, 205–17.

Berger, W., Dietz, V. & Quintern, J. (1984). Corrective reactions to stumbling in man: neuronal coordination of bilateral leg muscle activity during gait. *Journal of Physiology (London)*, **405**, 1–37.

Bras, H., Jankowska, E., Noga, B. R. & Skoog, B. (1990). Comparison of effects of various types of NA and 5-HT agonists on transmission from group II muscle afferents in the cat. *European Journal of Neurosciences*, **2**, 1029–39.

Burke, D. & Lance, J. W. (1973). Studies of the reflex effects of primary and secondary spindle endings in spasticity. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 475–95. Basel: Karger.

Burke, D., Gillies, J. D. & Lance, J. W. (1970). The quadriceps stretch reflex in human spasticity. *Journal of Neurology, Neurosurgery and Psychiatry*, **33**, 216–23.

Burke, D., Gandevia, S. C. & McKeon, B. (1984). Monosynaptic and oligosynaptic contributions to human ankle jerk and H-reflex. *Journal of Neurophysiology*, **52**, 435–48.

Bussel, B. & Pierrot-Deseilligny, E. (1977). Inhibition of human motoneurones, probably of Renshaw origin, elicited by an orthodromic motor discharge. *Journal of Physiology (London)*, **269**, 319–39.

Cavallari, P. & Pettersson, L. G. (1991). Synaptic effects in lumbar α-motoneurones evoked from group II muscle afferents via two different interneuronal pathways in the cat. *Neuroscience Letters*, **129**, 225–8.

Chaix, Y., Marque, P., Meunier, S., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1997). Further evidence for non-monosynaptic group I excitation of motoneurones in the human lower limb. *Experimental Brain Research*, **115**, 35–46.

Christensen, L. O. D., Andersen, J. B., Sinkjær, T. & Nielsen, J. (2001). Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking. *Journal of Physiology (London)*, **531**, 545–57.

Corna, S., Grasso, M., Nardone, A. & Schieppati, M. (1995). Selective depression of medium-latency leg and foot muscle responses to stretch by an α2-agonist in humans. *Journal of Physiology (London)*, **484**, 803–9.

Corna, S., Galante, M., Grasso, M., Nardone, A. & Schieppati, M. (1996). Unilateral displacement of lower limbs evoked bilateral EMG responses in leg and foot muscles in standing humans. *Experimental Brain Research*, **109**, 83–91.

Davies, H. E. & Edgley, S. A. (1994). Inputs to group II-activated midlumbar interneurones from descending motor pathways in the cat. *Journal of Physiology (London)*, **479**, 463–73.

Davies, J., Johnstone, S. E., Hill, D. R. & Quillan, J. E. (1984). Tizanidine (Ds 103–282), a centrally acting muscle relaxant, selectively depresses excitation of feline dorsal horn neurons to noxious peripheral stimuli by an action at α2-adrenoreceptors. *Neuroscience Letters*, **48**, 197–202.

Delwaide, P. J. & Pennisi, G. (1994). Tizanidine and electrophysiologic analysis of spinal control mechanisms in humans with spasticity. *Neurology*, **44**, Suppl. 9, S21–7; discussion S27–8.

Diener, H. C., Dichgans, J., Guschlbauer, B. & Mau, H. (1984). The significance of proprioception on postural stabilization as assessed by ischaemia. *Brain Research*, **296**, 103–9.

Dietz, V., Quintern, J. B. & Sillem, M. (1987). Stumbling reactions in man: Significance of proprioceptive and preprogrammed mechanisms. *Journal of Physiology (London)*, **368**, 149–63.

Dyck, P. J., Chance, P., Lebo, R. & Carney, J. A. (1993). Hereditary motor and sensory neuropathies. In *Peripheral Neuropathies*, ed. P. J. Dyck, P. K. Thomas, J. W. Griffin, P. A. Low & J. F. Poduslo, pp. 1094–136. Philadelphia: W. B. Saunders.

Eccles, R. M. & Lundberg, A. (1959). Synaptic actions in motoneurones by afferents which may evoke the flexion reflex. *Archives Italiennes de Biologie*, **97**, 199–221.

Edgley, S. A. & Jankowska, E. (1987). An interneuronal relay for group I and II muscle afferents in the midlumbar segments of the cat spinal cord. *Journal of Physiology (London)*, **399**, 675–90.

Emre, M. (1993). New developments in the medical treatment of spasticity. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 372–84. Heidelberg: Springer Verlag.

Eriksson, J., Olausson, B. & Jankowska, E. (1996). Antispastic effects of L-Dopa. *Experimental Brain Research*, **111**, 296–304.

Fahn, S., Elton, R. L. & Members of the UPDRS Development Committee. (1987). Unified Parkinson's disease rating scale. In *Recent Developments in Parkinson's Disease*, ed. S. Fahn, C. D. Marsden, M. Goldstein & D. B. Calne, vol. 3, pp. 153–63. New Jersey: Macmillan.

Forget, R., Pantieri, R., Pierrot-Deseilligny, E., Shindo, M. & Tanaka, R. (1989). Facilitation of quadriceps motoneurones by group I afferents from pretibial flexors in man. 1. Possible interneuronal pathway. *Experimental Brain Research*, **78**, 10–20.

Fournier, E., Meunier, S., Pierrot-Deseilligny, E. & Shindo, M. (1986). Evidence for interneuronally mediated Ia excitatory effects to human quadriceps motoneurones. *Journal of Physiology (London)*, **377**, 143–69.

Franz, D. N. & Iggo, A. (1968). Conduction failure in myelinated and non-myelinated axons at low temperatures. *Journal of Physiology (London)*, **199**, 319–45.

Fukushima, Y. & Kato, M. (1975). Spinal interneurons responding to group II muscle afferent fibres in the cat. *Brain Research*, **90**, 307–12.

German, D. C., Manaye, K. F., White, C. L. *et al.* (1992). Disease-specific patterns of locus coeruleus cell loss. *Annals of Neurology*, **32**, 667–76.

Gladden, M. H., Jankowska, E. & Czarkowska-Bauch, J. (1998). New observations on coupling between group II muscle afferents and feline γ-motoneurones. *Journal of Physiology (London)*, **512**, 507–20.

Grey, M. J., Ladouceur, M., Andersen, J. B., Nielsen, J. B. & Sinkjær, T. (2001). Group II muscle afferents probably contribute to the medium latency soleus stretch reflex during

walking in humans. *Journal of Physiology (London)*, **534**, 925–33.

Hammar, I., Slawinska, U. & Jankowska, E. (2002). A comparison of postactivation depression of synaptic actions evoked by different afferents and at different locations in the feline spinal cord. *Experimental Brain Research*, **145**, 126–9.

Harrison, P. J. & Zytnicki, D. (1984). Crossed actions of group I muscle afferents in the cat. *Journal of Physiology (London)*, **356**, 263–73.

Holmqvist, B. & Lundberg, A. (1961). Differential supraspinal control of synaptic actions evoked by volleys in the flexion reflex afferents in alpha motoneurones. *Acta Physiologica Scandinavica*, **54**, suppl. 186, 1–51.

Hongo, T. & Pettersson, L. G. (1988). Comments on group II excitation in hindlimb motoneurones in high and low spinal cats. *Neuroscience Research*, **5**, 563–6.

Hunt, C. C. & Kuffler, S. W. (1951). Stretch receptor discharges during muscle contraction. *Journal of Physiology (London)*, **113**, 298–315.

Jankowska, E. (1992). Interneuronal relay in spinal pathways from proprioceptors. *Progress in Neurobiology* **38**, 335–378.

Jankowska, E. (1993). Monoaminergic inhibitory control of spinal interneurones. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 222–32. Heidelberg: Springer Verlag.

Jankowska, E. & Hammar, I. (2002). Spinal interneurones; how can studies in animals contribute to the understanding of spinal interneuronal systems in man? *Brain Research Reviews*, **40**, 19–28.

Jankowska, E. & Riddell, J. S. (1998). Neuronal systems involved in modulating synaptic transmission from group II muscle afferents. In *Presynaptic Inhibition and Neural Control*, ed. P. Rudomin, R. Romo & L. Mendell, pp. 315–28. New York: Oxford University Press.

Jankowska, E., Perfilieva, E. V. & Riddell, J. S. (1996). How effective is integration of information from muscle afferents in spinal pathways? *Neuroreport*, **7**, 2337–40.

Jankowska, E., Gladden, M. H. & Czarkowska-Bauch, J. (1998). Modulation of feline gamma-motoneurones by noradrenaline, tizanidine and clonidine. *Journal of Physiology (London)*, **512**, 521–31.

Jankowska, E., Hammar, I., Chojnicka, B. & Heden, C. H. (2000). Effects of monoamines on interneurons in four spinal reflex pathways from group I and/or group II muscle afferents. *European Journal of Neurosciences*, **12**, 701–14.

Jankowska, E., Slawinska, U. & Hammar, I. (2002). On organization of a neuronal network in pathways from group II muscle afferents in feline lumbar spinal segments. *Journal of Physiology (London)*, **542**, 301–14.

Kirkwood, P. A. & Sears, T. A. (1975). Monosynaptic excitation of motoneurones from muscle spindle secondary endings of intercostal and triceps surae muscles in the cat. *Journal of Physiology (London)*, **24**, 64P–6P.

Lamy, J. C., Wargon, I., Baret, M. *et al.* (2005). Post-activation depression in various spinal pathways in humans. *Experimental Brain Research*, in press.

Laporte, Y. & Bessou, P. (1959). Modifications in the excitability of homonymous motoneurons induced by the physiological activation of afferent fibers originating in group II muscles. *Journal de Physiologie (Paris)*, **51**, 897–908.

Laporte, Y. & Lloyd, D. P. C. (1952). Nature and significance of the reflex connections established by large afferent fibers of muscular origin. *American Journal of Physiology*, **169**, 609–21.

Lloyd, D. P. C. (1943). Neuron patterns controlling transmission of ipsilateral hind limb reflexes in cat. *Journal of Neurophysiology*, **6**, 293–315.

(1946). Integrative pattern of excitation and inhibition in two-neuron reflex arcs. *Journal of Neurophysiology*, **9**, 439–44.

Lourenço, G., Simonetta-Moreau, M., Pierrot-Deseilligny, E. & Marchand-Pauvert, V. (2005). Cortical control of spinal reflex pathways in the human lower limb. *Electroencephalography and Clinical Neurophysiology*, in preparation.

Lundberg, A., Malmgren, K. & Schomburg, E. D. (1977). Cutaneous facilitation of transmission in reflex pathways from Ib afferents to motoneurones. *Journal of Physiology (London)*, **265**, 763–80.

(1987a). Reflex pathways from group II muscle afferents. 1. Distribution and linkage of reflex actions to alpha-motoneurones. *Experimental Brain Research*, **65**, 271–81.

(1987b). Reflex pathways from group II muscle afferents. 2. Functional characteristics of reflex pathways to α-motoneurones. *Experimental Brain Research*, **65**, 282–93.

(1987c). Reflex pathways from group II muscle afferents. 3. Secondary spindle afferents and the FRA: a new hypothesis. *Experimental Brain Research*, **65**, 294–306.

Marchand-Pauvert, V. & Nielsen, J. B. (2002a). Modulation of non-monosynaptic excitation from ankle dorsiflexor afferents to quadriceps motoneurones during human gait. *Journal of Physiology (London)*, **538**, 647–57.

(2002b). Modulation of spinal reflexes during walking in healthy subjects and patients with spinal cord injuries. *Clinical Neurophysiology*, **113**, S72.

Marchand-Pauvert, V., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (1999). Cortical control of spinal pathways mediating group II excitation to thigh motoneurones. *Journal of Physiology (London)*, **517**, 301–13.

Marchand-Pauvert, V., Nicolas, G., Burke, D. & Pierrot-Deseilligny, E. (2002). Suppression of the H reflex by disynaptic autogenetic inhibitory pathways activated by the test volley. *Journal of Physiology (London)*, **542**, 963–76.

Marchand-Pauvert, V., Marque, P., Nicolas, G. & Pierrot-Deseilligny, E. (2005). Posture-related increase in group II excitation from ankle muscles to human thigh motoneurones. *Journal of Physiology (London)*, in press.

Marque, P., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1996). Evidence for excitation of the human lower limb motoneurones by group II muscle afferents. *Experimental Brain Research*, **109**, 357–60.

Marque, P., Nicolas, G., Marchand-Pauvert, V., Gautier, J., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (2001a). Group I projections from intrinsic foot muscles to motoneurones of leg and thigh muscles in humans. *Journal of Physiology (London)*, **536**, 313–27.

Marque, P., Simonetta-Moreau, M., Maupas, E. & Roques, C. F. (2001b). Facilitation of transmission in heteronymous group II pathways in spastic hemiplegic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 36–42.

Marque, P., Nicolas, G., Simonetta-Moreau, M., Pierrot-Deseilligny, E. & Marchand-Pauvert, V. (2005). Probable Group II excitations from plantar foot muscles to human leg and thigh motoneurones. *Experimental Brain Research*, **161**, 486–50.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and Their Central Action*, 630 pp. London: Arnold.

(1989). Long-latency stretch reflexes of two intrinsic muscles of the human hand analysed by cooling the arm. *Journal of Physiology (London)*, **419**, 519–38.

Maupas, E., Marque, P., Roques, C. F. & Simonetta-Moreau, M. (2004). Modulation of the transmission in group II heteronymous pathways by tizanidine in spastic hemiplegic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **75**, 130–5.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta, M. (1993). Pattern of monosynaptic heteronymous Ia connections in the human lower limb. *Experimental Brain Research*, **96**, 533–44.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1994). Pattern of heteronymous recurrent inhibition in the human lower limb. *Experimental Brain Research*, **102**, 149–59.

Nance, P. W., Shears, A. S. & Nance, D. M. (1985). Clonidine in spinal cord injury. *Canadian Medical Association Journal*, **G133**, 41–2.

Nardone, A. & Schieppati, M. (1998). Medium-latency response to muscle stretch in human lower limb: estimation of conduction velocity of group II fibres and central delay. *Neuroscience Letters*, **249**, 29–32.

(2004). Group II fibres and afferent control of stance. Clues for diabetic neuropathy. *Clinical Neurophysiology*, **115**, 779–89.

Nardone, A., Corrà, T. & Schieppati, M. (1990a). Different activations of the soleus and gastrocnemius muscles in response to various types of stance perturbation in man. *Experimental Brain Research*, **80**, 323–32.

Nardone, A., Giordano, A., Corrà, T. & Schieppati, M. (1990b). Responses of leg muscles in humans displaced while standing. Effects of types of perturbation and of postural set. *Brain*, **113**, 65–84.

Nardone, A., Grasso, M., Giordano, A. & Schieppati, M. (1996). Different effect of height on latency of leg and foot short- and medium-latency EMG responses to perturbation of stance in humans. *Neuroscience Letters*, **206**, 89–92.

Nardone, A., Tarantola, J., Miscio, G., Pisano, F., Schenone, A. & Schieppati, M. (2000). Loss of large-diameter spindle afferent fibres is not detrimental to the control of body sway during upright stance: evidence from neuropathy. *Experimental Brain Research*, **135**, 155–62.

Nardone, A., Corna, S. & Schieppati, M. (2001a). Group II afferent fibres in balance control: evidence from neurological disease. In *MCC 2001 From Basic Motor Control to Functional Recovery II*, ed. N. Gantchev, pp. 331–8. Sofia: Academic Publishing House.

Nardone, A., Galante, M., Lucas, B. & Schieppati, M. (2001b). Stance control is not affected by paresis and reflex hyperexcitability: the case of spastic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 635–43.

Nielsen, J. B. & Sinkjær, T. (2002). Afferent feedback in the control of human gait. *Journal of Electromyography and Kinesiology*, **12**, 213–17.

Noth, J., Schwarz, M., Podoll, K. & Motamedi, F. (1991). Evidence that low-threshold muscle afferents evoke long-latency reflexes in human hand muscles. *Journal of Neurophysiology*, **65**, 1089–97.

Paintal, A. S. (1965). Block of conduction in mammalian myelinated nerve fibres by low temperatures. *Journal of Physiology (London)*, **180**, 1–19.

Pierrot-Deseilligny, E. (1999). Heteronymous group II pathways in the human lower limb: spinal organization, cortical control and possible functional role. *Journal of Physiology (London)*, **518S**, 27P.

Pompeiano, O. (2001). Role of the locus coeruleus in the static and dynamic control of posture. *Archives Italiennes de Biologie*, **139**, 109–24.

Remy-Néris, O., Barbeau, H., Daniel, O., Boiteau, F. & Bussel, B. (1999). Effects of intrathecal clonidine on spinal reflexes and human locomotion in incomplete paraplegic subjects. *Experimental Brain Research*, **129**, 433–40.

Remy-Néris, O., Denys, P., Daniel, O., Barbeau, H. & Bussel, B. (2003). Effect of intrathecal clonidine on excitation transmitted by interneurones activated by groups I-II afferents in paraplegics. *Experimental Brain Research*, **148**, 509–14.

Riddell, J. S. & Hadian, M. (2000). Interneurones in pathways from group II muscle afferents in the lower-lumbar segments of the feline spinal cord. *Journal of Physiology (London)*, **522**, 109–23.

Rymer, W. Z., Houk, J. C. & Crago, P. E. (1979). Mechanisms of the clasp-knife reflex studied in an animal model. *Experimental Brain Research*, **37**, 93–113.

Schieppati, M. & Nardone, A. (1991). Free and supported stance in Parkinson's disease. The effect of posture and postural set on leg muscle responses to perturbation, and its relation to the severity of the disease. *Brain*, **4**, 749–55.

(1995). Time course of 'set'-related changes in muscle response to stance perturbation in humans. *Journal of Physiology (London)*, **487**, 787–96.

(1997). Medium-latency stretch reflexes of foot and leg muscles analysed by cooling the lower limb in standing humans. *Journal of Physiology (London)*, **503**, 691–8.

(1999). Group II spindle afferent fibers in humans: their possible role in the reflex control of stance. In *Progress in Brain Research*, vol. 123, ed. M. D. Binder, pp. 461–72. Amsterdam: Elsevier Science.

Schieppati, M., Nardone, A., Siliotto, R. & Grasso, M. (1995). Early and late stretch responses of human foot muscles induced by perturbation of stance. *Experimental Brain Research*, **105**, 411–22.

Schieppati, M., Nardone, A., Corna, S. & Bove, M. (2001). The complex role of spindle afferent input, as evidenced by the study of posture control in normal subjects and patients. *Neurological Sciences*, **22**, Suppl. 1, S15–20.

Schomburg, E. D. (1990). Spinal sensorimotor systems and their supraspinal control. *Neuroscience Research*, **7**, 265–340.

Simonetta-Moreau, M., Marque, P., Marchand-Pauvert, V. & Pierrot-Deseilligny, E. (1999). The pattern of excitation of human lower limb motoneurones by probable group II muscle afferents. *Journal of Physiology (London)*, **517**, 287–300.

Simonetta-Moreau, M., Meunier, S., Vidailhet, M., Pol, S., Galitzky, M. & Rascol, O. (2002). Transmission of group II heteronymous pathways is enhanced in rigid lower limb of de novo patients with Parkinson's disease. *Brain*, **125**, 2125–33.

Sinkjær, T., Andersen, J. B., Ladouceur, M., Christensen, L. O. D. & Nielsen, J. B. (2000). Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. *Journal of Physiology (London)*, **523**, 817–27.

Stauffer, E. K., Watt, D. G., Taylor, A., Reinking, R. M. & Stuart, D. G. (1976). Analysis of muscle receptor connections by spike-triggered averaging. 2. Spindle group II afferents. *Journal of Neurophysiology*, **39**, 1393–402.

Steward, E. K., Barbeau, H. & Gautier, S. (1991). Modulation of locomotor patterns and spasticity with clonidine in spinal cord injured patients. *Canadian Journal of the Neurological Sciences*, **18**, 321–32.

Wilson, V. J. & Kato, M. (1965). Excitation of extensor motoneurons by group II afferent fibers in ipsilateral muscle nerves. *Journal of Neurophysiology*, **28**, 545–54.

8

Presynaptic inhibition of Ia terminals

The synaptic efficacy of the afferent volleys entering the spinal cord can be modulated by presynaptic inhibition. As a result, the information flowing through sensory terminals can be modified before it reaches the target neurones through a process that can be controlled selectively by supraspinal centres to optimise motor performance and sensory discrimination. All afferents are subject to presynaptic inhibition controlled by descending tracts (cf. Rudomin & Schmidt 1999) but, so far, methods have been developed for human subjects to estimate only presynaptic inhibition of Ia terminals. This is because it is easy to stimulate Ia afferents selectively, and they are the only afferents to have significant monosynaptic projections onto motoneurones.

Background from animal experiments

Initial findings

In the cat, Frank and Fuortes (1957) described a depression of monosynaptic Ia EPSPs in motoneurones occurring without a detectable change in motoneurone membrane potential or conductance. This presynaptic inhibition was extensively investigated by Eccles and colleagues. They described its main features and showed that the inhibition is associated with primary afferent depolarisation (PAD), both phenomena most probably mediated by the same interneurones acting on Ia terminals through axo-axonic synapses (see Eccles, 1964). These interneurones are referred to as PAD interneurones in the following, even though there is so far no record of PAD in human subjects.

General features

Location

Although PAD interneurones have not yet been specifically labelled, there are strong indications that last-order PAD interneurones mediating presynaptic inhibition of Ia terminals are located within the intermediate zone.

Mechanisms

The mechanisms underlying presynaptic inhibition involve, at least in part, local modulation of transmitter release at the Ia-motoneurone synapse by means of $GABA_A$ receptors. Activation of $GABA_A$ receptors in Ia terminals increases the efflux of Cl^- ions and produces depolarisation of the afferent terminals. As a result, the amplitude of the propagated action potential in the intraspinal afferent terminals is reduced, and that blocks or reduces Ca^{2+} influx and thereby transmitter release (see Rudomin & Schmidt, 1999).

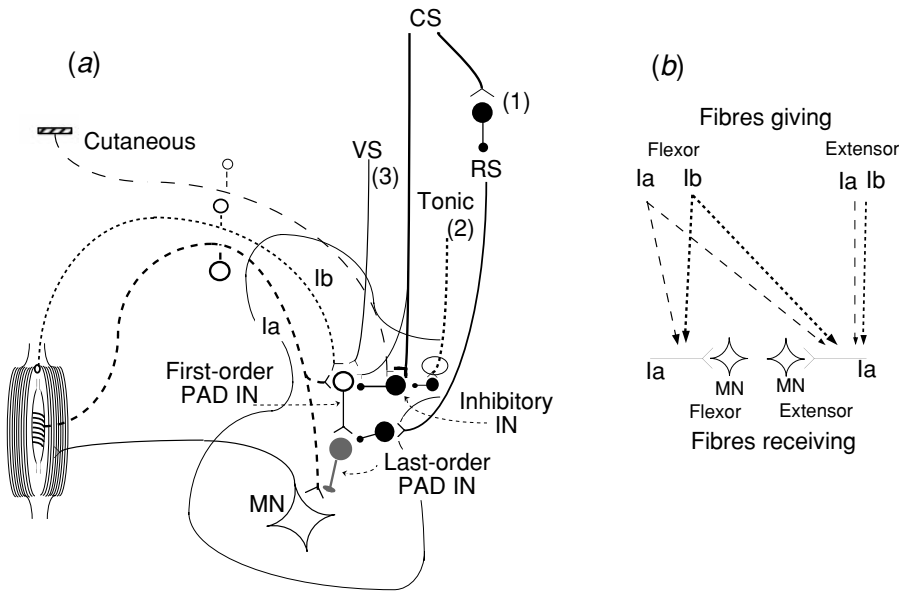


Fig. 8.1. Wiring diagram of pathways of presynaptic inhibition with primary afferent depolarisation (PAD) of Ia terminals in the cat. (*a*) In this and subsequent figures, excitatory synapses are represented by Y-shape bars and inhibitory synapses by small filled circles, first-order excitatory PAD interneurones (IN) by open circles, last-order GABA-ergic PAD INs by filled grey circles and inhibitory INs by large filled circles. First-order PAD INs receive excitation from Ia and Ib afferents and the vestibulospinal (VS [3]) tract. They receive inhibition through the same inhibitory INs from cutaneous afferents and the corticospinal (CS) tract (though there is an alternative corticospinal pathway facilitating first-order PAD INs, indicated by the thin continuous line). Inhibitory INs inhibiting first-order PAD INs receive descending tonic inhibition (dotted line [2]). Last-order PAD INs receive inhibition from reticulospinal (RS) pathways, themselves inhibited from higher centres ([1]). From data in Rudomin & Schmidt (1999). Three mechanisms (referred to as [1], [2], [3] in the sketch of Fig. 8.1 (*a*)) could contribute to the tonic level of presynaptic inhibition observed at rest in human subjects: (i) tonic inhibition from higher centres of the brainstem structures through which RS pathways maintain tonic inhibition on last-order PAD INs (i.e. control of RS suppression: pathway [1]); (ii) tonic inhibitory control of the inhibitory INs transmitting cutaneous inhibition of first-order PAD INs (i.e. control of afferent suppression: pathway [2]); (iii) tonic VS excitation of first-order PAD INs (i.e. descending excitation: pathway [3]). (*b*) Relative strength of presynaptic inhibition (indicated approximately by width of arrows) elicited by Ia (dashed lines) and Ib (dotted lines) afferents from flexors and extensors on Ia terminals projecting to flexor and extensor motoneurones (MN).

Organisation

The shortest pathway mediating segmental presynaptic inhibition of Ia terminals has two interposed interneurones, the last order (in grey in Fig. 8.1(*a*)) being GABA-ergic. Single last-order interneurones have connections with a restricted number of collaterals of individual Ia afferents, and single collaterals receive connections from more than one interneurone. This may be considered the basic circuitry required for independent control of information flow in selected collaterals of individual afferents (cf. Rudomin & Schmidt, 1999).

Electrophysiology

An electrophysiological feature which differentiates presynaptic inhibition of Ia terminals from postsynaptic inhibition is its very long duration (several hundred of milliseconds). This was attributed to sustained activity of PAD interneurones (by Eccles,

Kostyuk & Schmidt, 1962b), but subsequent studies have indicated that, instead, this may be due to the slow dynamics of GABA release and/or uptake (see Rudomin, Jimenez & Quevedo, 1998). Presynaptic inhibition from peripheral inputs is also characterised by a long central latency ($\sim$ 5 ms, see Eccles, 1964).

Inputs to PAD interneurones

Peripheral effects

Group I afferents

Volleys in Ib and (to a lesser extent) Ia afferents, mainly from flexor muscles, activate first-order PAD interneurones, and produce presynaptic inhibition distributed to Ia terminals of all ipsilateral muscles in the hindlimb of the spinal cat (Eccles, Magni & Willis, 1962a; Fig. 8.1(*b*)). PAD interneurones can be activated by short trains of volleys in the nerves of the ipsilateral flexors (see Eccles, 1964), by group I discharges elicited by muscle stretch or contraction (Devanandan, Eccles & Yokota, 1965; Devanandan, Eccles & Stenhouse, 1966), or by pure Ia discharges, from flexors and extensors, induced by vibration (Gillies *et al.*, 1969; Barnes & Pompeiano, 1970a, b).

Cutaneous and articular afferents

These afferents depress transmission in PAD pathways at the level of the first-order PAD interneurones (see Lund, Lundberg & Vyklický, 1965; Rudomin *et al.*, 1983).

Descending effects

Descending suppression

The main descending control on PAD interneurones mediating presynaptic inhibition of Ia terminals is depressive (see Fig. 8.1(*a*)), i.e. it decreases PAD and switches off presynaptic inhibition. Corticospinal fibres and cutaneous afferents converge onto inhibitory interneurones which depress the first-order PAD interneurones (see Lundberg & Vycklický, 1963; Rudomin *et al.*, 1983; Fig. 8.1(*a*)). Last-order PAD interneurones are tonically inhibited from different reticulospinal pathways (see Rudomin & Schmidt, 1999). Suppression of this strong tonic depressive control is responsible for the dramatically increased excitability of PAD interneurones after spinalisation in decerebrate animals. Brainstem structures responsible for the tonic depression of presynaptic inhibition of Ia terminals receive a descending inhibition from higher centres. Accordingly, presynaptic inhibition is suppressed in the decerebrate animal.

Descending facilitatory projections exist

(i) A cortical facilitatory effect on PAD interneurones probably also exists, but is generally weaker than the cortical depression (as discussed by Hongo, Jankowska & Lundberg, 1972); and (ii) first-order PAD interneurones receive excitation from vestibular nuclei (Carpenter, Endberg & Lundberg, 1966). In addition, the inhibition exerted by cutaneous (and articular) afferents on first-order PAD interneurones is subjected to a tonic descending inhibition, which disappears after spinalisation (see Rudomin & Schmidt, 1999). This tonic suppressive effect on the cutaneous inhibition of PAD interneurones contributes to the maintenance of a tonic level of presynaptic inhibition.

Selectivity of the control of presynaptic inhibition

As will be shown on p. 348, selectivity of control was first established in human experiments during selective voluntary contractions (Hultborn *et al.*, 1987b). Animal experiments subsequently confirmed that presynaptic inhibition exerted on collaterals of the same Ia afferent may be differentially depressed by cortical and cutaneous inputs (Eguibar *et al.*, 1994). The diffuse pattern of presynaptic inhibition of Ia terminals observed in the acute spinal cat (Eccles, Magni & Willis, 1962a) is probably due to the convergence onto last order PAD interneurones of subsets of first-order PAD interneurones

which differ in their input (at least from the brain, Lundberg, 1998).

Conclusions

Presynaptic inhibition of Ia afferents functions as a gate on the monosynaptic Ia input to motoneurones. It can be distinguished from post-synaptic inhibition by its long central latency and long duration. The gating can be very potent: a short train to flexor group I afferents can completely suppress the monosynaptic reflex in extensor muscles (Eccles, Schmidt & Willis, 1962c). Despite its potency, the role of this gating has long been neglected in discussions on the control of the Ia inflow during movement. This is probably because it was difficult to make functional sense of the diffuse pattern of distribution of presynaptic inhibition on Ia terminals of all muscles in the ipsilateral limb, as originally described for the acute spinal cat. Presynaptic inhibition of Ia terminals functions also as a gate on the Ia input to interneurones (cf. Enriquez-Denton *et al.*, 2000; Chapter 5, pp. 200–1).

Methodology

Different methods have been developed to assess changes in presynaptic inhibition of Ia terminals in human subjects. They rely on different principles and have different advantages and disadvantages.

Discrepancy between the variations in the on-going EMG and those in the H reflex

Underlying principle

Changes in presynaptic inhibition of Ia terminals in human subjects were first inferred from discrepancies between changes in the H reflex amplitude and in the on-going EMG recorded in the same muscle during various motor activities: voluntary contraction and flexor reflex in the tibialis anterior (Pierrot-Deseilligny & Bussel, 1973); walking and standing in the soleus (Morin *et al.*, 1982; Capaday & Stein, 1987). It was reasoned that, if H reflex amplitude only depended on α motoneurone excitability, the variations in reflex amplitude and in the on-going EMG should parallel one another. In contrast, changes in presynaptic inhibition of Ia terminals should affect the H reflex via the Ia afferents in the test volley more than the on-going EMG which could be affected only by influencing background Ia activity and any fusimotor-driven enhancement during voluntary contractions.

Critique

As appealing as this method is because of its simplicity (recordings of the H reflex and the on-going EMG), the results cannot be attributed unequivocally to differences in the level of presynaptic inhibition of Ia terminals.

(i) Descending and/or peripheral inputs related to the different motor tasks tested may have an uneven distribution to early and late recruited motoneurones and thereby change the recruitment gain of the reflex (cf. Chapter 1, pp. 18–20). As a result, an equivalent level of EMG discharge does not guarantee equivalent excitability of the α motoneurones that are not involved in the contraction and thus an equal amplitude of the reflex response to a constant Ia volley.

(ii) Presynaptic inhibition of Ia terminals is not the only mechanism able to gate the afferent volley of the test reflex. For example, disynaptic Ib inhibitory pathways help determine the size of the H reflex, and a difference in the control of these pathways could contribute to changes in the size of the test H reflex (cf. Marchand-Pauvert *et al.*, 2002; Chapter 1, pp. 14–16 and 27).

Activating PAD INs by a conditioning volley to assess their excitability

Underlying principle

Presynaptic inhibition of Ia terminals mediating the afferent volley of the test H reflex is experimentally

induced using vibration or electrical stimulation to produce a conditioning afferent volley. The resulting reflex depression depends on the excitability of PAD interneurones: the larger this excitability, the greater the presynaptic inhibition of the test afferent volley and the greater the reflex depression. Different methods relying on this principle have been proposed.

Prolonged vibration of the homonymous tendon is not a valid technique

Vibration paradox

Studies of presynaptic inhibition in human subjects started with the phenomenon that has become known as the 'vibration paradox' (see Desmedt & Godaux, 1978). Application of vibration to a muscle or its tendon results in a strong discharge in homonymous Ia fibres (Burke *et al.*, 1976) and depresses the tendon jerk and H reflex of that muscle (De Gail, Lance & Neilson, 1966; Delwaide, 1973). Since the vibration-induced depression is seen along with a motor discharge (the tonic vibration reflex, TVR; see De Gail, Lance & Neilson, 1966; Hagbarth & Eklund, 1966), there was presumably an increase in excitability at motoneurone level, and the reflex depression therefore must have resulted from a presynaptic mechanism. In experiments in the cat, vibration produced PAD that paralleled the reflex depression (Gillies *et al.*, 1969; Barnes & Pompeiano, 1970a, b). The presynaptic mechanism operating in human experiments was therefore, not unreasonably at the time, attributed to presynaptic inhibition of Ia terminals with PAD (Delwaide, 1973).

Post-activation depression

However, conditioning vibration applied to the homonymous tendon activates another presynaptic mechanism, homosynaptic or post-activation depression, due to repetitive activation of the Ia-motoneurone synapse, and this also contributes to the vibratory-induced depression of the reflex (Katz *et al.*, 1977; Crone & Nielsen, 1989b; Hultborn *et al.*, 1996; Wood, Gregory & Proske, 1996). This post-activation depression is probably related to reduced probability of transmitter release (Lev-Tov & Pinco, 1992), and is quite potent (see Chapter 2, pp. 96–9). It differs from presynaptic inhibition with PAD in several aspects: (i) its very long duration (up to 10–15 s vs. 400 ms at most for presynaptic inhibition with PAD); (ii) its limitation to afferents previously activated by the vibration; (iii) its insensitivity to $GABA_A$-antagonists (see Nielsen & Hultborn, 1993). It is arguable which mechanism, post-activation depression or presynaptic inhibition with PAD, is the more potent under physiological conditions. Either way, when both conditioning and test volleys are mediated through the same synaptic pathway, the vibration-induced depression is caused, at least in part, by post-activation depression and the extent of the depression cannot be used to estimate presynaptic inhibition of Ia terminals with PAD (Hultborn *et al.*, 1987a, 1996).

Activity-dependent hyperpolarisation of Ia afferents

There is a further problem with prolonged vibration: conducting an impulse train raises the threshold of the activated axon, even when the trains are naturally induced (see Coppin, Jack & McLennan, 1970; Fetz *et al.*, 1979; Vagg *et al.*, 1998). Accordingly, long-lasting vibration of the 'conditioning' tendon can be used as a method to raise preferentially the electrical threshold of Ia afferents (Cavallari & Katz, 1989; Chapter 2, p. 76). As a result, the same stimulus will evoke a smaller Ia afferent volley during and after vibration than it did before vibration, and it may be possible to stimulate Ib afferents electrically without activating many Ia afferents.

Presynaptic inhibition elicited by a heteronymous group I volley

Short vibration of a heteronymous tendon

To eliminate the drawbacks related to prolonged vibration of the homonymous tendon, another method has been developed: brief vibration (train

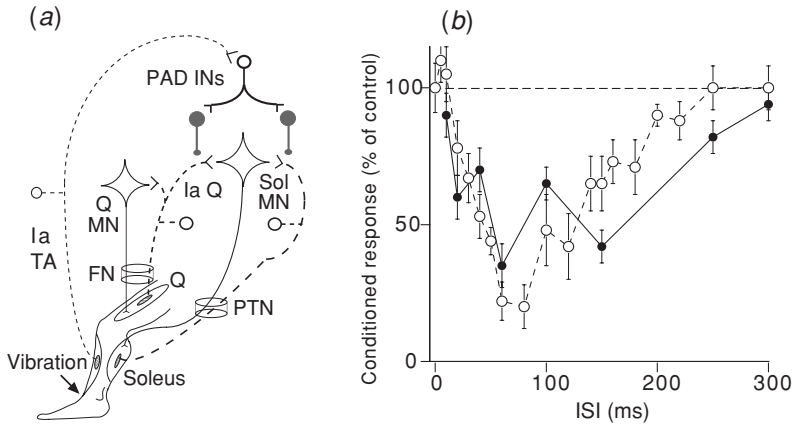


Fig. 8.2. Presynaptic inhibition elicited by brief vibration. (*a*) Sketch of the presumed pathways: a Ia volley from the tibialis anterior (TA), induced by brief vibration of the TA tendon, activates interneurones (PAD INs) mediating presynaptic inhibition of quadriceps (Q) and soleus (Sol) Ia terminals projecting on Sol motoneurones (MN). (*b*) Time course of the changes induced by brief vibration (three cycles, 200 Hz) applied to the TA tendon in both the Sol H reflex and its facilitation by femoral nerve (FN) stimulation (1 × MT, −6.2 ms ISI). The size of the reflex (❍) and the amount of FN-induced facilitation (●), conditioned by TA vibration and expressed as a percentage of their control values, are plotted against the inter-stimulus interval (ISI). The H reflex suppression is preceded by a brief weak facilitation due to the spread of the vibration to the test muscle (see Chapter 2, p. 86). Each point represents the means of 20 measurements (data from a single subject). Vertical bars ±1 SEM. Modified from Morin, Pierrot-Deseilligny & Hultborn (1984) (❍), and from Hultborn *et al.* (1987a) (●), with permission.

of three shocks at 200 Hz or a single tap) applied to the tendon of a *heteronymous* muscle (tibialis anterior or biceps femoris in the lower limb, ECR in the upper limb) at an intensity below the threshold of the tendon jerk (Morin, Pierrot-Deseilligny & Hultborn, 1984; Hultborn *et al.*, 1987a; Nielsen & Petersen, 1994; Nakashima *et al.*, 1989). The resulting Ia volley is designed to activate PAD interneurones (see the sketch of Fig. 8.2(*a*)) and evoke presynaptic inhibition of Ia afferents mediating the afferent volley of the test reflex. Such a conditioning volley produces clear inhibition of the soleus (and quadriceps) H reflexes lasting 200–300 ms (Fig. 8.2(*b*)), much as has been described for presynaptic inhibition of Ia afferents in the cat hindlimb (see Eccles, 1964). Figure 8.2(*b*) shows that the same conditioning volley also reduces, to a similar extent and for a similar duration, the purely monosynaptic facilitation of the reflex evoked by a heteronymous femoral Ia volley. The suppression faithfully reflects the amount of on-going presynaptic inhibition of heteronymous Ia terminals on soleus motoneurones (cf. pp. 345–6; Hultborn *et al.*, 1987a). Accordingly, the parallel long-lasting inhibition of the H reflex may be attributed to presynaptic inhibition with PAD of homonymous Ia terminals (Hultborn *et al.*, 1987a). Further evidence for the presynaptic origin of the inhibition elicited by a heteronymous tendon tap was provided by Nielsen and Petersen (1994). They showed that a biceps femoris tendon tap elicited a similar long-lasting depression of both the H reflex of tibialis anterior and the peak of homonymous monosynaptic Ia excitation in the PSTHs of single units, but did not modify the peak evoked by cortical stimulation. This indicates that the depression was not due to post-synaptic inhibition (which should have suppressed the two responses to the same extent). Neither could it have been due to a change in the recruitment gain in the motoneurone pool because the suppression was also observed in single motor units (cf. Chapter 1, p. 20). The observations also provide evidence that monosynaptic cortico-motoneuronal terminals

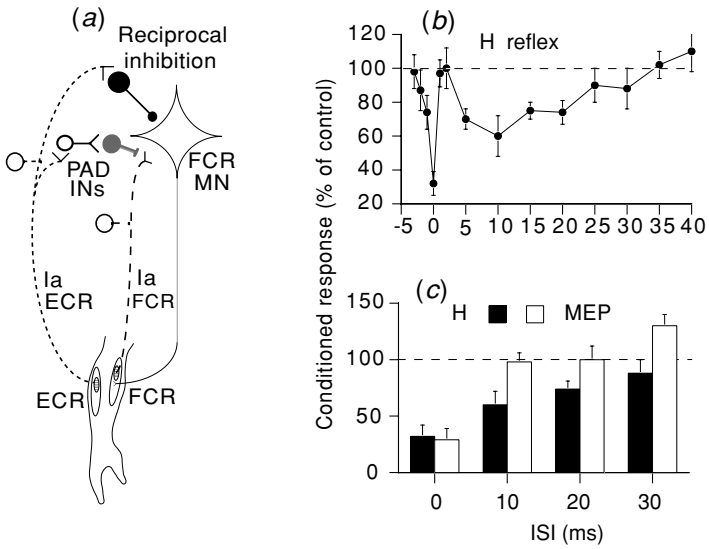


Fig. 8.3. 'D1' inhibition of the flexor carpi radialis (FCR) H reflex. (*a*) Sketch of the presumed pathways: extensor carpi radialis (ECR) Ia afferents activate interneurones (IN) mediating disynaptic non-reciprocal group I inhibition of flexor carpi radialis (FCR) motoneurones (MN) and PAD INs mediating presynaptic inhibition of FCR Ia terminals. (*b*) The size of the FCR H reflex (expressed as a percentage of its unconditioned value), conditioned by a radial stimulation at 1 × MT, is plotted against the interstimulus interval (ISI): the early disynaptic non-reciprocal group I inhibition is followed by a late inhibition. Each symbol represents the mean of 20 measurements. Vertical bars ±1 SEM (data from one subject). (*c*) The size of the H reflex (■) and of the MEP (□), are compared at various ISIs after radial nerve stimulation during voluntary FCR contraction (data from six subjects, vertical bars 1 SEM). Because the recruitment sequence in a voluntarily activated motoneurone pool is the same for Ia and corticospinal inputs (see Morita *et al.*, 2000a), the differential effect of the radial group I volley on the reflex and the MEP at the 10–20 ms ISIs may be attributed to presynaptic inhibition of Ia terminals mediating the afferent volley of the FCR H reflex. The alternative possibility that the radial input facilitates that part of the corticospinal volley which is mediated through propriospinal neurones may be ruled out, because a propriospinally mediated facilitation is over at 7–8 ms (see Chapter 10, Fig. 10.2(*g*)). The relatively short duration of the late depression is due to a superimposed post-synaptic facilitation (see p. 344). Modified from Meunier & Pierrot-Deseilligny (1998) (*b*), and Berardelli *et al.* (1987) (*c*), with permission.

are not subjected to presynaptic inhibition from Ia afferents.

Electrically induced 'D1' and 'D2' inhibitions

Presynaptic inhibition of Ia terminals may also be evoked by an electrical volley to group I afferents in the nerve supplying muscles antagonistic to the test motoneurone pool. As a result, the so-called 'D1/D2' inhibition of the H reflex appears (Mizuno, Tanaka & Yanagisawa, 1971).

In the upper limb, a conditioning volley to the radial nerve (single shock, 0.9 × MT) produces in the FCR H reflex an initial period of inhibition, peaking around the 0 ms ISI, due to disynaptic post-synaptic inhibition (see Chapter 5, p. 205), followed by a second depression occurring when the ISI is 5–30 ms (Fig. 8.3(*b*)). The initial phase was originally attributed to reciprocal Ia inhibition, but it is now believed to be non-reciprocal group I inhibition (Chapter 5, pp. 211–14). Evidence that the second phase of inhibition reflects presynaptic inhibition of Ia afferents mediating the afferent volley of the test reflex came from comparison of the effects of the conditioning radial volley on the H reflex and the MEP elicited by cortical stimulation on the FCR

during voluntary contractions (Fig. 8.3(*c*); Berardelli *et al.*, 1987). At the 0 ms ISI, the post-synaptic 'reciprocal' group I inhibition suppressed the two responses to the same extent; in contrast, at the 10–20 ms ISIs, the same conditioning volley suppressed the H reflex but not the MEP. The most parsimonious explanation for this differential effect is that the radial group I volley evokes presynaptic inhibition of Ia terminals mediating the afferent volley of the FCR H reflex. Similarly, stimulation of the median nerve elicits early reciprocal inhibition in the ECR H reflex, followed by a late long-lasting suppression. Again the late suppression is likely to be due to presynaptic inhibition of Ia terminals mediating the afferent volley of the test reflex because it is not paralleled by suppression of the MEP (Burke *et al.*, 1994). In both cases, the second phase of inhibition appears to be a discrete event that ends at 30 ms. It was thought to be only the first 30 ms of a longer inhibition with a duration typical of presynaptic inhibition, separated from the rest of the phase (the late inhibition) by a superimposed facilitation (Berardelli *et al.*, 1987). However, recent experiments suggest that the second and late inhibitions are distinct processes with different underlying mechanisms (Huang *et al.*, 2004; p. 372).

In the lower limb, conditioning stimulation to the common peroneal nerve with a train of 3–5 shocks at 1–1.4 × MT suppresses the H reflex of soleus. The inhibition is long lasting and has two phases, termed 'D1' at 5–30 ms, and 'D2' at 70–200 ms (Mizuno, Tanaka & Yanagisawa, 1971; El-Tohamy & Sedgwick, 1983). Here again, these two phases of inhibition may be attributed to presynaptic inhibition of Ia terminals mediating the afferent volley of the test reflex because the same conditioning volley does not modify the MEP in the soleus at conditioning-test intervals corresponding to D1 (Faist, Dietz & Pierrot-Deseilligny, 1996) or D2 (Capaday, Lavoie & Cormeau, 1995). Here, there is no evidence that the division of the long-lasting inhibition into two phases implies two separate inhibitory processes. There may be only a single long-lasting process interrupted by a facilitation, that may be of cutaneous origin and is probably transmitted over a transcortical pathway.

Critique

Care must be taken to avoid spread of the vibration (or the tap) to the tested muscle because this could result in activation of homonymous Ia afferents by the conditioning stimulus, and thereby post-activation depression. This can be done by reducing the amplitude of the vibration so that there is no significant early facilitation of the test reflex to indicate monosynaptic Ia excitation. If this is done, the dominant effect of the conditioning stimulation is activation of PAD interneurones mediating presynaptic inhibition of the afferent volley of the H reflex. However, there are still some limitations.

Long-latency post-synaptic facilitation

Long-latency post-synaptic facilitation due to activation of cutaneous afferents by the conditioning stimulus can contaminate and partly suppress (see above) the reflex depression (Hultborn *et al.*, 1987a). Similarly, the amplitude of the FCR or the ECR H reflex during the time course of 'D1' is the net result of different effects including a post-synaptic facilitation (particularly at conditioning-test intervals >20 ms, Burke *et al.*, 1994). Because of the overlapping facilitation there are errors when the amount of heteronymous vibratory or D1/D2 inhibition is used to make a *quantitative* assessment of changes in presynaptic inhibition during various motor tasks.

Use of the compound H reflex

Because all of the above methods use the compound H reflex, a change in the reflex depression in a given situation could reflect a change in the recruitment gain in the motoneurone pool or a change in the efficacy of autogenetic inhibition from afferents in the test volley (see Chapter 1, pp. 14–20).

Occlusion

A more serious drawback, particular to this method, is that decreased vibratory or D1/D2 inhibition may reflect decreased excitability of PAD interneurones

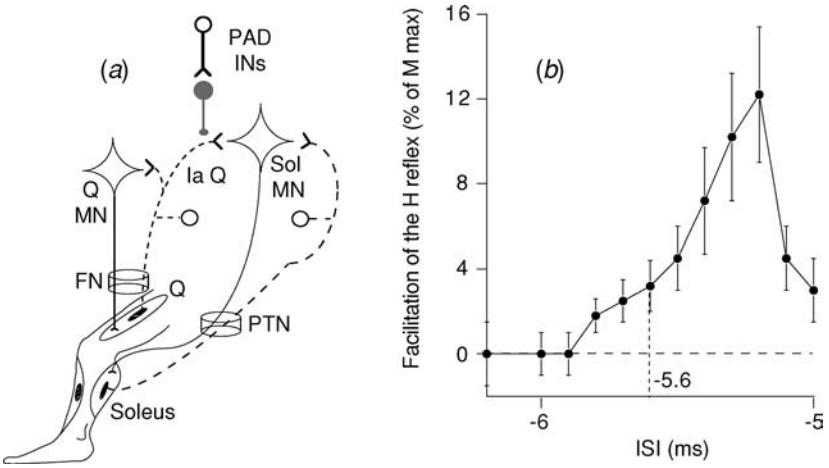


Fig. 8.4. Heteronymous facilitation of the soleus H reflex. (*a*) Sketch of the presumed pathways: the soleus (Sol) H reflex, elicited by stimulation of the posterior tibial nerve (PTN), is facilitated by a heteronymous monosynaptic Ia volley from quadriceps (Ia Q) evoked by stimulation applied to the femoral nerve (FN). Q Ia afferents have monosynaptic projections to Sol motoneurones (MN), which are subjected to tonic presynaptic inhibition mediated through PAD interneurones (INs). (*b*) The soleus H reflex was conditioned by FN stimulation at 4 × MT in order to activate all Ia afferents in the FN (cf. Gracies, Pierrot-Deseilligny & Robain, 1994). The amount of reflex facilitation (expressed as a percentage of M_{max}) is plotted against the inter-stimulus interval (ISI) (the test shock has to be delivered before the conditioning stimulus due to the more proximal position of the conditioning electrode, and the ISI is then negative). Facilitation started at the −5.8 ms ISI. The −5.6 ms ISI (dashed vertical line) was chosen to assess the amount of reflex facilitation because the later facilitation, after −5.2 ms, may be contaminated by oligosynaptic effects. Each point represents the mean of 20 measurements. Vertical bars ±1 SEM. Data from 1 subject. Modified from Meunier & Pierrot-Deseilligny (1998), with permission.

but, paradoxically, it can also occur when their excitability is increased because they receive central and/or peripheral input that is too strong for the particular test conditions. The presynaptic network may then become saturated and unresponsive to the conditioning volley evoking vibratory or D1/D2 inhibition. This probably occurs during active standing and gait (see pp. 363–6). As a result, the method is not reliable when used by itself.

Background presynaptic inhibition inferred from Ia facilitation of the H reflex

Underlying principle

A further method relies on the measurement of the background presynaptic inhibition exerted on Ia terminals mediating a monosynaptic conditioning volley, be it heteronymous or homonymous (Hultborn *et al.*, 1987a; Meunier & Pierrot-Deseilligny, 1989). Within the first 0.6 ms, the monosynaptic Ia excitation is not contaminated by disynaptic inputs (Hultborn *et al.*, 1987a; Fig. 8.4(*b*)), and the amount of reflex facilitation depends only on the size of the conditioning Ia EPSP. A constant conditioning stimulus should elicit an EPSP of constant size in motoneurones, and thereby a constant reflex facilitation, unless the degree of presynaptic inhibition of Ia afferents mediating the conditioning volley changes. The amount of facilitation can therefore be used to assess the background presynaptic inhibition on these Ia fibres: the larger the reflex facilitation, the smaller the presynaptic inhibition.

The method requires that the conditioning heteronymous volley produces a reasonably large monosynaptic Ia facilitation of the test reflex

This is the case for the projections from quadriceps to soleus and tibialis anterior motoneurones, from soleus to quadriceps motoneurones (Meunier, Pierrot-Deseilligny & Simonetta, 1993) and from intrinsic hand muscles to FCR motoneurones (Marchand-Pauvert, Nicolas & Pierrot-Deseilligny, 2000). A similar method has been developed to assess on-going presynaptic inhibition of homonymous soleus Ia terminals using conditioning stimulation applied to the inferior soleus nerve (see Meunier & Pierrot-Deseilligny, 1989; Chapter 2, p. 69). The earliest ISI at which it is possible to record the monosynaptic facilitation of the test reflex must first be established, using 0.1–0.2 ms steps. If the ISI then chosen is only 0.2–0.6 ms longer (see Fig. 8.4(*b*)), there is little risk of contamination by non-monosynaptic Ia or Ib effects (Pierrot-Deseilligny *et al.*, 1981; Hultborn *et al.*, 1987a; Chapter 2, p. 67).

Validation of the method

(i) The validity of the method was established in animal experiments in which presynaptic inhibition of Ia afferents and post-synaptic events in motoneurones could be assessed by direct measurement, including intracellular recordings from motoneurones and assessment of the excitability of Ia afferents. It was shown that the amount of heteronymous facilitation of the reflex faithfully reflects the level of presynaptic inhibition of Ia terminals projecting to the tested motor nucleus and is not affected by post-synaptic inhibition of motoneurones (Hultborn *et al.*, 1987a).

(ii) The specificity of the method in measuring presynaptic inhibition of Ia afferents was also ensured by showing that EPSPs produced by a descending monosynaptic input (not subject to presynaptic inhibition) to the same motoneurone were not affected by conditioning stimuli that depressed monosynaptic Ia EPSPs through presynaptic inhibition of Ia terminals. This has been shown in the cat with stimulation of the ventromedial fasciculus while recording EPSPs in motoneurones (Rudomin, Jimenez & Enriquez, 1991) and in man with stimulation of the motor cortex while recording PSTHs for single motor units in tibialis anterior (Nielsen & Petersen, 1994).

Critique: advantages, limitations, conclusions

(i) What is tested here is the background presynaptic inhibition exerted on the Ia fibres mediating the conditioning volley, and there is therefore no risk of occlusion at the level of PAD interneurones between this volley and other task-specific inputs.

(ii) However, if a change in the on-going presynaptic inhibition of Ia afferents mediating the conditioning volley will produce a change in the H reflex facilitation, changes in the recruitment gain in the motoneurone pool might also alter the amount of reflex facilitation elicited by a constant conditioning stimulus (Chapter 1, pp. 18–20). The ways to ensure that changes in reflex facilitation do not result from such a 'pool problem' are discussed below.

Techniques using single motor units

Recordings from single motor units can be used to avoid 'pool problems'. (i) Stimulation of homonymous or heteronymous Ia afferents evokes in the PSTHs of voluntarily activated single motor units a peak of early excitation due to the compound group I EPSP (cf. Chapter 2, pp. 69–73). The first 0.6 ms of this peak, measured using a bin width of 0.1 or 0.2 ms, contains the only unequivocally monosynaptic component of the increased probability of discharge (Chapter 1, p. 34). Changes in this early peak faithfully reflect a change in presynaptic inhibition of the corresponding Ia terminals,

provided that the firing rate of the motor unit is stable, such that the peak of Ia excitation occurs at the same moment on the AHP following the previous motoneurone discharge (Katz, Meunier & Pierrot-Deseilligny, 1988). The reliability of the method is excellent but it requires the subject to maintain a single motor unit firing at a stable rate. This is possible during tonic contractions but not during phasic contractions. (ii) With the method of the unitary H reflex, it is possible to measure the response of a single motoneurone to a homonymous Ia volley (see Chapter 1, pp. 37–9). The compound and the unitary H reflexes are similarly sensitive to monosynaptic heteronymous Ia facilitation (Shindo *et al.*, 1994). The amount of heteronymous facilitation of the unitary H reflex can therefore be used to assess presynaptic inhibition of Ia afferents projecting to a single motoneurone.

Conclusions

Investigation of single units

The only accepted way to eliminate the possibility of a change in the recruitment gain in the motoneurone pool with certainty is to confirm results obtained with the compound H reflex in single motor units using either PSTHs of a voluntarily activated motor unit or the H reflex of a single motor unit.

Comparison of results obtained with Ia facilitation and heteronymous inhibition

When using the compound H reflex, the problem of a change in the recruitment gain as the cause of the results may be avoided by comparing the changes in monosynaptic facilitation of the reflex and those in D1/D2 or vibratory inhibition under the same conditions (Pierrot-Deseilligny, 1997). A change in the recruitment gain producing an increase (or decrease) in the slope of the input–output relationship in the motoneurone pool (Fig. 1.9) should similarly enhance (or reduce) the amount of heteronymous facilitation of the reflex and that of the D1/D2 or vibratory suppression of the reflex, whereas a decrease in presynaptic inhibition of Ia terminals should enhance the monosynaptic facilitation but decrease the D1/D2 or vibratory suppression (and vice versa for an increase in presynaptic inhibition of Ia terminals). Thus, the results cannot be explained by a change in the recruitment gain of the reflex when the amount of monosynaptic facilitation and that of vibratory (or D1/D2) inhibition of the reflex vary in the opposite direction. This illustrates the necessity of obtaining congruent results with different methods relying on independent principles, when using the indirect methods available in human subjects.

Changes in presynaptic inhibition of Ia terminals at the onset of movement

Changes in vibration-induced inhibition and femoral-induced facilitation of the soleus H reflex have been used to compare the amount of presynaptic inhibition of Ia terminals to soleus motoneurones at rest and at the onset of a voluntary contraction of soleus (cf. Hultborn *et al.*, 1987b; pp. 355–8). This has been criticised by Stein (1995), because the excitability of the soleus motoneurones tested was different at rest and during contraction when they would have been depolarised. It is therefore important that there was a similar difference in presynaptic inhibition when the amount of presynaptic inhibition of Ia terminals to soleus motoneurones was compared at the onset of contraction and during a tonic contraction, at equivalent levels of EMG activity and presumably similar levels of depolarisation (see Pierrot-Deseilligny, 1997; p. 355; Fig. 8.9(*c*)–(*e*)).

Organisation and pattern of connections

Projections on Ia terminals directed to different motoneurone types

In the cat, presynaptic inhibition of Ia terminals is stronger on terminals on motoneurones supplying

slow motor units than on terminals on motoneurones of fast units (Zengel *et al.*, 1983). A similar effect has been found in human subjects (Aimonetti *et al.*, 2000a). The monosynaptic Ia peak elicited by homonymous radial nerve stimulation in the PSTHs of single slow and fast ECR motor units has been assessed in the absence and in the presence of presynaptic inhibition, as measured using median-induced D1 inhibition. Under control conditions, the smaller the level of force at which a single unit was recruited the larger the Ia peak (cf. Chapter 2, pp. 79–80), but the size of the homonymous monosynaptic Ia peak was reversed by presynaptic inhibition in favour of fast units (Fig. 8.5(*a*), (*b*)). This reversal was due to the fact that the lower the unit's threshold for recruitment, the more marked was the reduction of the monosynaptic Ia peak produced by presynaptic inhibition (cf. Fig. 8.5(*c*)–(*f*)). This result was not due to the fact that fast units are recruited at a stronger level of force, requiring a stronger descending excitatory drive. Indeed, it was also obtained in simultaneous recordings from pairs of units (one low-threshold, the other high-threshold), when there is, of necessity, the same descending excitatory drive and peripheral input to the motoneurones (Fig. 8.5(*c*)–(*f*)). The reversal by presynaptic inhibition of the effects of the Ia excitatory input in favour of fast motor units could be functionally important in rapid movements.

Organisation in subsets with regard to the target motoneurones of Ia afferents

Ia terminals from a given muscle to homonymous and heteronymous motoneurones

At the onset of a selective voluntary contraction of quadriceps, presynaptic inhibition of Ia terminals to quadriceps motoneurones is decreased, whereas presynaptic inhibition of Ia terminals (both homonymous and heteronymous) to soleus motoneurones is increased, and vice versa at the onset of a voluntary contraction of the soleus (cf. pp. 359–60). Such a control during movement implies that presynaptic inhibition of Ia terminals from one muscle to homonymous and heteronymous motoneurones is mediated by separate subsets of PAD interneurones, which are differentially controlled.

Ia terminals on the target muscle

Presynaptic inhibition of homonymous and heteronymous Ia terminals to a given motoneurone pool is modulated in parallel, with the same magnitude and time course, during voluntary contractions of various muscles (the muscle itself, a synergist, an antagonist), gait or active standing (see pp. 355–67). This indicates that the control of presynaptic inhibition of Ia terminals during various motor tasks is related to the target motoneurones, and suggests that presynaptic inhibition of homonymous and heteronymous Ia terminals to a motoneurone pool is mediated through common PAD interneurones (at least the first order ones, as sketched in Figs. 8.9(*a*), 8.10(*a*), (*b*)). Thus, the increase in presynaptic inhibition of the homonymous Ia feedback from the inactive soleus during a selective quadriceps contraction (for which there is no obvious functional significance) could be a simple correlate of the required task-dependent increase in presynaptic inhibition of heteronymous Ia afferents from quadriceps to soleus motoneurones (see pp. 359–60). The same applies for the increase in presynaptic inhibition of heteronymous quadriceps Ia afferents to soleus motoneurones at the onset of tibialis anterior contraction (pp. 360–1), for which there is again no obvious functional significance.

Peripheral projections to PAD interneurones

Excitation from group I afferents

There is some evidence that, in human subjects, PAD interneurones are facilitated by volleys in group Ia and possibly Ib afferents, as in the cat (cf. p. 339).

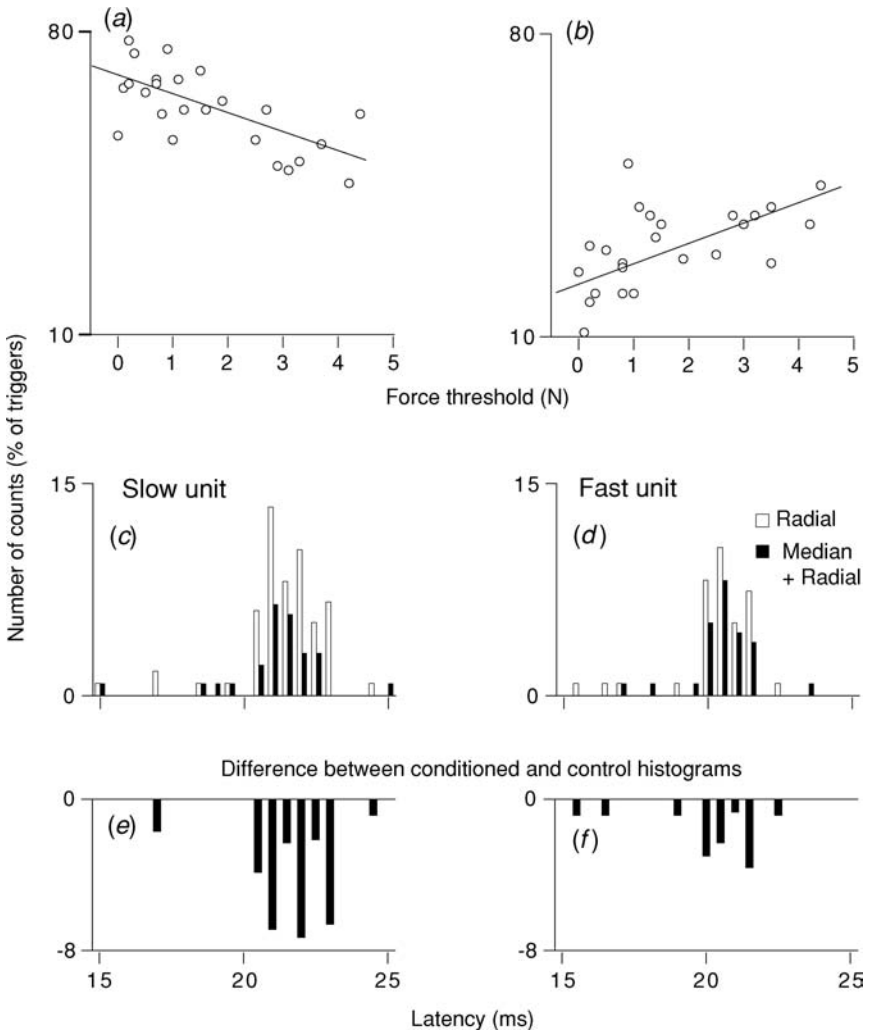


Fig. 8.5. When presynaptic inhibition of Ia terminals is active, the size of the monosynaptic Ia peak may become greater in fast than in slow units. (*a*), (*b*) The size of the homonymous monosynaptic Ia peak evoked in the PSTHs (0.25 ms bin width) of single ECR units by radial stimulation (assessed as the sum of the consecutive bins with increased firing probability contributing to the peak, and expressed as a percentage of the number of triggers) is plotted against the force at recruitment in the absence ((*a*) control situation) and the presence (*b*) of presynaptic 'D1' inhibition elicited by a median nerve group I volley (single shock, 0.8 × MT, 20 ms ISI, cf. p. 344). (*c*), (*d*) The monosynaptic peak recorded in the absence (□) and in the presence (■) of a preceding median nerve volley is compared in a slow-twitch motor unit ((*c*), recruited at force 0.61 N) and in a fast-twitch motor unit ((*d*), recruited at 3.82 N), recorded simultaneously, i.e. when there is, of necessity, the same descending excitatory drive and peripheral input to the motoneurones. (*e*), (*f*) Difference between conditioned and control histograms showing that the monosynaptic peak was more reduced in presence of presynaptic inhibition in the slow unit (*e*) than in the fast unit (*f*). Note that there is greater reduction in the peak of the slow unit when only the first 0.5 ms of the peak is considered. Modified from Aimonetti *et al.* (2000a), with permission.

Ia afferents

Ia discharges from flexor muscles (tibialis anterior and biceps femoris) evoked by brief vibration or by a weak tap produce long-lasting inhibition of the H reflexes of soleus and quadriceps due to presynaptic inhibition of Ia terminals with PAD (pp. 341–2; Fig. 8.2). The pattern of activation of presynaptic inhibition of Ia terminals evoked by lower limb Ia volleys may be inferred from the effects of prolonged vibration applied to heteronymous tendons: (i) there are powerful effects from flexor to extensor Ia afferents; (ii) actions from flexor to flexor and from extensor to extensor are weaker; (iii) actions from extensor to flexor are very weak; and (iv) the strength of presynaptic inhibition from one muscle to another decreases as the muscles become more anatomically distant (Iles & Roberts, 1987).

Ib afferents

There is no direct evidence that Ib afferents activate PAD interneurones in human subjects. However, the finding that the threshold of the peroneal-induced D1 inhibition of the soleus (0.9-1 × MT; Mizuno, Tanaka & Yanagisawa, 1971; Iles, 1996) is higher than that of the reciprocal Ia inhibition (0.6–0.7 × MT, cf. Chapter 5, p. 204) is compatible with a contribution from Ib afferents.

Depression of presynaptic inhibition by cutaneous afferents

Cutaneous volleys can reduce presynaptic inhibition with PAD, as in the cat (p. 339). D2 inhibition of the soleus H reflex is reduced by stimulation of low-threshold cutaneous afferents and there is a local sign for this suppression of presynaptic inhibition (Iles, 1996): it is seen after light brushing of both distal dorsal and plantar surfaces of the ipsilateral foot, but not after brushing of the proximal dorsal part of the foot. Weak stimulation of cutaneous afferents from the hand reduces the radial-induced D1 inhibition of the FCR H reflex, without evidence for a local sign. Removal of the cutaneous input by intravenous lignocaine increases presynaptic inhibition, suggesting that cutaneous afferents exert a tonic depressive influence on the excitability of PAD interneurones (Nakashima *et al.*, 1990). Similarly, brushing of the palmar side of the hand reduces presynaptic inhibition of ECR Ia terminals (Aimonetti *et al.*, 2000b).

Corticospinal projections

Presynaptic inhibition of Ia terminals is powerfully controlled from the motor cortex, but the dominant effect is different in the upper and lower limbs. There is corticospinal inhibition of PAD interneurones in the lumbar enlargement and corticospinal facilitation in the cervical enlargement. This has been established in studies on motoneurone pools and single motor units (Meunier & Pierrot-Deseilligny, 1998).

Lower limb

Depression of vibratory or D1 inhibition

Motor cortex stimulation reduces homonymous vibration-induced inhibition (Valls-Solé, Alvarez & Tolosa, 1994), D2 inhibition (Iles, 1996) and D1 inhibition (Meunier & Pierrot-Deseilligny, 1998) of the soleus H reflex. These findings suggest corticospinal depression of PAD interneurones mediating presynaptic inhibition of soleus Ia terminals. This has been confirmed in experiments using other experimental paradigms (see below). The time course of the depression of D1 inhibition was, however, complex with two waves of depression separated by a return to control values. This occurred when the cortical and peroneal volleys arrived simultaneously at the S1 spinal level.

Facilitation of heteronymous excitation

The facilitation of the soleus H reflex on combined stimulation of the motor cortex and the femoral nerve is greater than the sum of the effects of separate stimuli (Fig. 8.6(*b*)–(*e*)). The existence of such an extra facilitation, observed in parallel with the

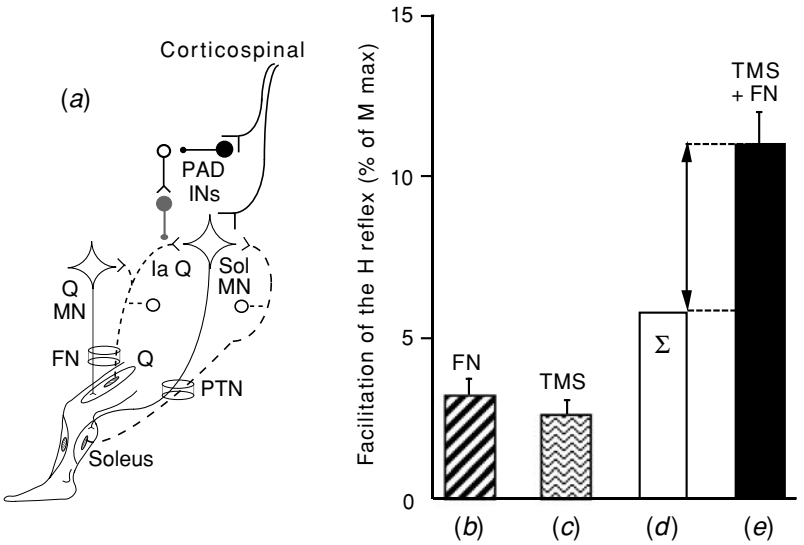


Fig. 8.6. Corticospinal depression of presynaptic inhibition of soleus Ia terminals. (*a*) Sketch of the presumed pathways: it is assumed that the same cortical site activates motoneurones (MN) of a given pool (here soleus [Sol]) and depresses PAD interneurones (INs) mediating presynaptic inhibition of Ia terminals projecting to this pool. (*b*)–(*e*) The amount of soleus H reflex facilitation (expressed as a percentage of M_{max}) is compared after separate stimulation of the femoral nerve (FN, (*b*), 1.1 × MT, ISI 0.4 ms after the onset of the facilitation), separate TMS ((*c*), 42% of the maximal stimulator output), and combined stimulation ((*e*) TMS preceding femoral stimulation by 15 ms). The difference between the effect on combined stimulation and the sum (Σ) of effects of separate stimuli (*d*) is indicated by the double-headed arrow and represents the extra facilitation on combined stimulation, i.e. the supplementary Ia excitation due to decreased presynaptic inhibition of Ia terminals. Each column represents the mean of 20 values. Vertical bars 1 SEM. Data from a single subject. Modified from Meunier & Pierrot-Deseilligny (1998), with permission.

decrease in D1 inhibition, implies a depression of PAD interneurones mediating presynaptic inhibition of Ia terminals projecting to soleus motoneurones (cf. p. 347).

Focused corticospinal drive

A similar method, i.e. the heteronymous facilitation of the H reflex evoked in target motoneurones combined with TMS, has been used to investigate the corticospinal changes in on-going presynaptic inhibition of quadriceps Ia terminals on tibialis anterior motoneurones and of soleus Ia terminals on quadriceps motoneurones. Cortical stimulation decreased presynaptic inhibition when, and only when, the corticospinal volley was focused on the motoneurone pool receiving the conditioning Ia volley under test, e.g. posterior tibial-induced facilitation of the quadriceps H reflex was only increased when cortical stimulation was focused on quadriceps motoneurones. This suggests that the same cortical site activates motoneurones of a given pool and depresses PAD interneurones mediating presynaptic inhibition of Ia terminals projecting to that pool (as sketched in the wiring diagram in Fig. 8.6(*a*)).

Data for single units

These data have provided further evidence for corticospinal depression of PAD interneurones. Fig. 8.7(*a*)–(*g*) shows that corticospinal stimulation at 0.8 × threshold for the MEP facilitated the peak of homonymous monosynaptic Ia excitation evoked by posterior tibial nerve stimulation in a soleus unit. The facilitation included the first 0.6 ms of the peak,

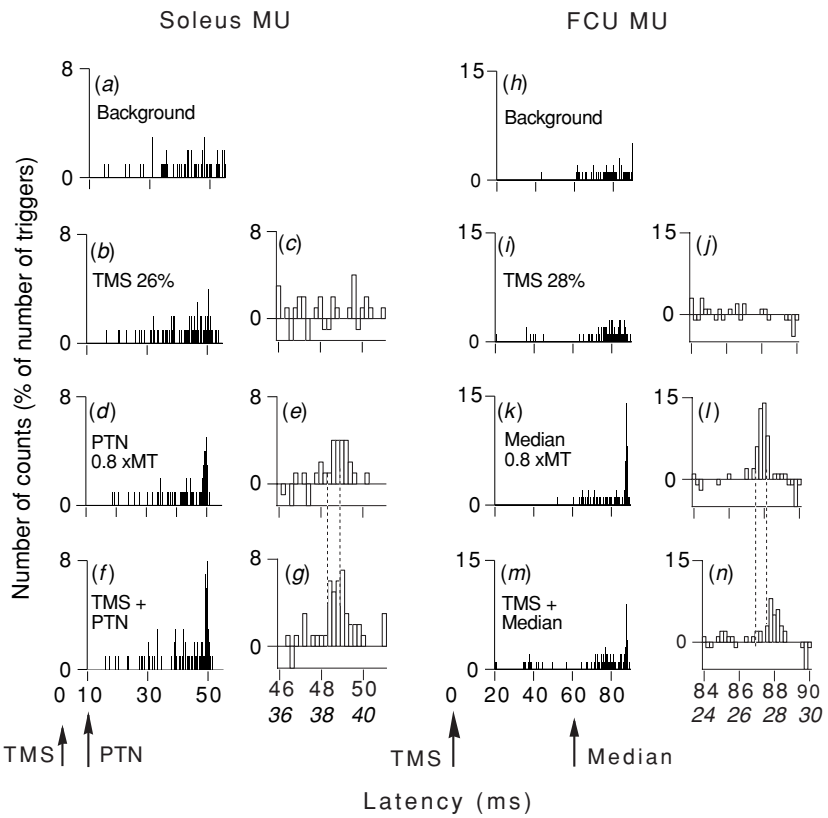


Fig. 8.7. Effects of corticospinal stimulation on the peak of monosynaptic Ia excitation in the PSTHs of single units. Bin width: 0.2 ms. Background firing probability in (*a*) and (*h*), effects of TMS by itself in (*b*), (*c*) (26%) and (*i*), (*j*) (28%), effects of separate stimulation of the posterior tibial nerve (PTN, 0.8 × MT, (*d*), (*e*)), of the median nerve (0.8 × MT, (*k*), (*l*)) and of combined stimulation ((*f*), (*g*), 10 ms ISI and (*m*), (*n*) 60 ms ISI). In the raw histograms ((*a*), (*b*), (*d*), (*f*), (*h*), (*i*), (*k*), (*m*)), zero on the abscissa corresponds to the timing of TMS. In the subtraction histograms (□, conditioned – background, in (*c*), (*e*), (*g*), (*j*), (*l*), (*n*)) the scale of the abscissa is expanded and there is a double abscissa (the upper related to TMS; the lower, in italics, related to peripheral nerve stimulation). Vertical dotted lines show the first three bins of the peak of monosynaptic Ia excitation. Arrows at the bottom indicate the time of the stimuli. *Soleus unit* ((*a*)–(*g*)): the weak TMS failed to increase the firing probability at the latency of the MEP ((*b*), (*c*)). Stimulation of the PTN ((*d*), (*e*)) evoked a peak of monosynaptic Ia excitation at 48.4 ms (i.e. 38.4 ms after the PTN stimulus). On combined stimulation ((*f*) and (*g*)), the homonymous Ia peak was significantly facilitated. The facilitation included the first 0.6 ms of the peak (48.4–48.8 ms after the PTN stimulus, between vertical dotted lines). *FCU unit* ((*h*)–(*n*)): AHP prevented the unit from firing during the first 50 ms of the window of analysis ((*h*), (*i*), (*k*), (*m*)). The low intensity of TMS and its delivery early in the AHP (5 ms after the previous spike) explain why TMS by itself failed to evoke an increase in firing probability at the latency of the MEP (25 ms). At latencies above 60 ms there was no TMS-evoked silent period (*i*). Stimulation of the median nerve by itself evoked a peak of heteronymous monosynaptic Ia excitation 27.6 ms after the stimulus ((*k*) and (*l*)). On combined stimulation ((*m*) and (*n*)), this peak was markedly reduced. The depression included the first 0.6 ms of the peak at 87.6–88 ms (i.e. equivalent to 27.6–28 ms after the median stimulus, between vertical dotted lines). Modified from Meunier & Pierrot-Deseilligny (1998) ((*h*)–(*n*)) and unpublished ((*a*)–(*g*)), with permission.

i.e. its purely monosynaptic part, and therefore presumably results from a decrease in presynaptic inhibition of homonymous Ia terminals. The decrease implies that there was a tonic level of presynaptic inhibition under the control conditions (see below).

Upper limb

The D1 inhibition of the FCR H reflex, whether elicited by electrical stimulation to the radial nerve or by a weak ECR tendon tap, was increased by a corticospinal volley focused on FCR motoneurones. Additional experiments in single motor units confirmed this finding. Thus Fig. 8.7(*h*)–(*n*) shows that the peak of heteronymous monosynaptic excitation evoked in the PSTH of a FCU motor unit was suppressed by cortical stimulation that was insufficient by itself to affect the motor unit discharge. The suppression included the first 0.6 ms of the peak, and presumably therefore resulted from an increase in presynaptic inhibition of median Ia terminals. The monosynaptic peak produced by stimulation of homonymous Ia afferents was similarly reduced by TMS in motor units of other forearm muscles (FCR, ECR, FDS), confirming that the dominant corticospinal effect on PAD interneurones mediating presynaptic inhibition of Ia terminals is facilitatory in the upper limb.

Conclusions

In the cat hindlimb, stimulation of the motor cortex has different effects on presynaptic inhibition of Ia terminals: (i) a dominant depressive effect on the first-order PAD interneurones through inhibitory interneurones onto which cutaneous afferents converge; and (ii) a probable opposite facilitatory effect (cf. p. 339; Fig. 8.1(*a*)). Results in human subjects are consistent with these animal findings.

Lower limb

In the lower limb, the dominant corticospinal effect is depression of presynaptic inhibition of Ia terminals, and there is evidence for convergence of cutaneous and corticospinal inputs onto interneurones inhibiting PAD interneurones (Iles, 1996). However, when the corticospinal and peroneal volleys arrive simultaneously at spinal level, they can evoke EPSPs summating in first-order PAD neurones. This may allow the opposite facilitatory effect to appear, and this would explain why the depression of the D1 inhibition is then interrupted (see above).

Upper limb

In the upper limb, the dominant effect is corticospinal facilitation of PAD interneurones. This could be functionally relevant because: (i) presynaptic inhibition favours the recruitment of fast units by the Ia input (see pp. 347–8), and this could be of importance in rapid upper limb movements; (ii) the gating of the Ia input would bias the motoneurone in favour of the descending excitation over the peripheral excitatory feedback. This could be advantageous for some skilled movements, provided that the peripheral feedback could still modulate the motor output. In this respect, cutaneous stimuli can reverse corticospinal facilitation to suppression when it is necessary to increase the gain in the Ia loop (S. Meunier, unpublished observations).

Vestibulospinal projections

The effects of galvanic stimulation of the vestibular apparatus on presynaptic inhibition of soleus Ia terminals have been investigated (Iles & Pisini, 1992). The results suggest a convergence of the peripheral Ia and vestibulospinal volleys onto PAD interneurones, much as has been described in the cat (cf. p. 339).

Tonic level of presynaptic inhibition of Ia terminals

The decrease in presynaptic inhibition of Ia terminals at the onset of voluntary contractions (see below) of necessity implies a tonic level of presynaptic inhibition under control conditions at rest. Such a tonic level has been described in the cat with acute spinal transection and after administration of DOPA (Andén *et al.*, 1966). Three mechanisms

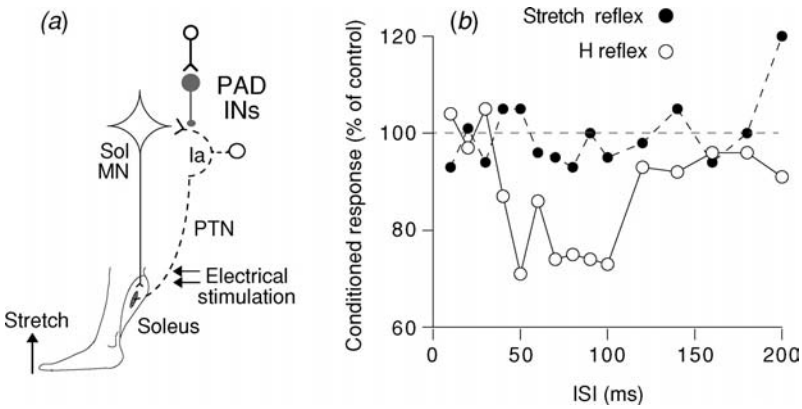


Fig. 8.8. Different sensitivity of H and stretch reflexes to presynaptic inhibition. (*a*) Sketch of the presumed pathways. Monosynaptic Ia excitation of soleus (Sol) motoneurones (MN) is evoked by electrical stimulation of Ia afferents in the posterior tibial nerve (PTN) or brisk passive dorsiflexion (vertical arrow). PAD interneurones (INs) control the efficacy of the Ia volley in firing Sol MNs. (*b*) The H reflex (○) and the spinal stretch reflex (●) of the soleus are conditioned by a biceps femoris tendon tap (1 mm amplitude, 2 ms duration). The size of the conditioned responses (expressed as a percentage of their control values) is plotted against the interstimulus interval (ISI). The two reflexes were adjusted to have the same size (2–3% of M_{max} in the control situation). Data for the stretch reflex are advanced by 12 ms in relation to the H reflex to take its longer latency into account. Data from a single subject. Modified from Morita *et al.* (1998), with permission.

could contribute to the tonic level of presynaptic inhibition at rest (as sketched in the wiring diagram in Fig. 8.1(*a*)): (i) the most-likely mechanism is probably tonic inhibition from higher centres of the brainstem structures through which reticulospinal pathways maintain tonic inhibition of last-order PAD interneurones (i.e. control of reticulospinal suppression); (ii) tonic inhibitory control of the inhibitory interneurones transmitting cutaneous inhibition of first-order PAD interneurones (i.e. control of afferent suppression); (iii) a possible tonic vestibulospinal excitation of first-order PAD interneurones (i.e. descending excitation).

Weak sensitivity of stretch-evoked Ia volleys to presynaptic inhibition

Evidence for differential sensitivity

Presynaptic inhibition of soleus Ia terminals, whether induced by a biceps femoris tendon tap or an electrical volley to the common peroneal nerve (D1), reduces the H reflex much more than the tendon jerk or the reflex response to abrupt stretch of soleus (Fig. 8.8(*b*); Morita *et al.*, 1998). Accordingly, under physiological situations, such as voluntary co-contractions of the antagonists or the stance phase of gait, in which presynaptic inhibition of Ia terminals is increased (see pp. 360–1 and pp. 365–7), the stretch reflex is less suppressed than the H reflex (Nielsen *et al.*, 1994; Sinkjaer, Andersen & Larsen, 1996). This indicates that extrapolation of the results obtained with the H reflex to the stretch reflex during movement should be made with caution.

Possible mechanisms and functional significance

The different sensitivity to presynaptic inhibition of electrically and mechanically evoked reflexes may be explained by the repetitive discharge of Ia afferents in the stretch-induced volley and the differences in dispersion of the afferent volleys. Presynaptic inhibition may be compensated for by the increased probability of transmitter release when the Ia motoneurone synapse is activated repetitively at short intervals, as occurs with abrupt muscle stretch, but it may exert its inhibitory action fully

on the highly synchronised electrically induced volley. Thus, the depressive effect of presynaptic inhibition on Ia excitation could depend on the rate with which Ia afferents activate motoneurones: it has been speculated that 'presynaptic inhibition is more efficient when the Ia afferents are discharging either only once (H reflex) or at relatively low rate (20 Hz) as in the case for the normal background of Ia afferents during movement, but not when they are discharging at a higher rate (200 Hz) as during stretch reflexes' (Nielsen, 1998; Nielsen & Sinkjær, 2002). As a result, presynaptic inhibition might effectively modulate 'natural' physiological feedback signals, without interfering with the full regulatory role of the reflex responses to abrupt perturbations (cf. Chapter 11, p. 548). While this issue needs to be kept in mind, only with abrupt stretch will the spindle discharge reach rates of 200 Hz, and this they will do only transiently. Hence, the caveat is likely to be important for the reflex responses to abrupt external disturbances rather than the reflex support to most natural motor activities.

Motor tasks and physiological implications

The Ia spinal stretch reflex has been shown to contribute to many natural motor tasks (cf. Chapter 2, pp. 87–90). Because presynaptic inhibition of Ia terminals allows the central nervous system to control the gain of the Ia feedback, changes in presynaptic inhibition of Ia terminals have been systematically sought during various motor tasks.

Ia terminals on lower limb motoneurones involved in voluntary contractions

Evidence for decreased presynaptic inhibition

Heteronymous facilitation of the H reflex

The amount of femoral-induced facilitation of the soleus H reflex is virtually the same at rest and during tonic soleus contractions, but is greatly increased at the onset of a selective voluntary contraction of the soleus (Fig. 8.9(*c*)–(*e*); Hultborn *et al.*, 1987b; Meunier & Pierrot-Deseilligny, 1989). There were comparable levels of EMG activity during the tonic contraction and at the onset of the contraction, and it is likely that the net excitability (and depolarisation) of the motoneurone pool was similar in the two tasks (Pierrot-Deseilligny, 1997). The huge increase in reflex facilitation (Δ, Fig. 8.9(*e*)) observed at the onset of contraction presumably reflects a decrease in presynaptic inhibition of quadriceps Ia terminals projecting to soleus motoneurones.

Vibratory inhibition

The contraction-related decrease in presynaptic inhibition of Ia terminals on soleus motoneurones has been confirmed by the finding that the depression of the soleus H reflex produced at rest by a short train of vibration to the tibialis anterior tendon disappears completely at the onset of a soleus voluntary contraction (Fig. 8.10(*e*); Hultborn *et al.*, 1987b). The decrease in the vibratory inhibition, in parallel with the increased heteronymous facilitation of the reflex, implies depression of PAD interneurones mediating presynaptic inhibition of Ia terminals projecting to soleus motoneurones (cf. p. 347).

Presynaptic inhibition of quadriceps Ia afferents

The vibratory inhibition of the quadriceps H reflex similarly disappears almost completely at the onset of a selective voluntary quadriceps contraction (Fig. 8.10(*c*); Hultborn *et al.*, 1987b).

Changes in presynaptic inhibition during various contractions

The supplementary femoral-induced facilitation of the soleus H reflex at the onset of a contraction compared with that at rest (Δ in Fig. 8.9(*e*)) presumably results from a decrease in presynaptic inhibition of quadriceps Ia terminals on soleus motoneurones. The time course of this supplementary facilitation has been investigated during voluntary

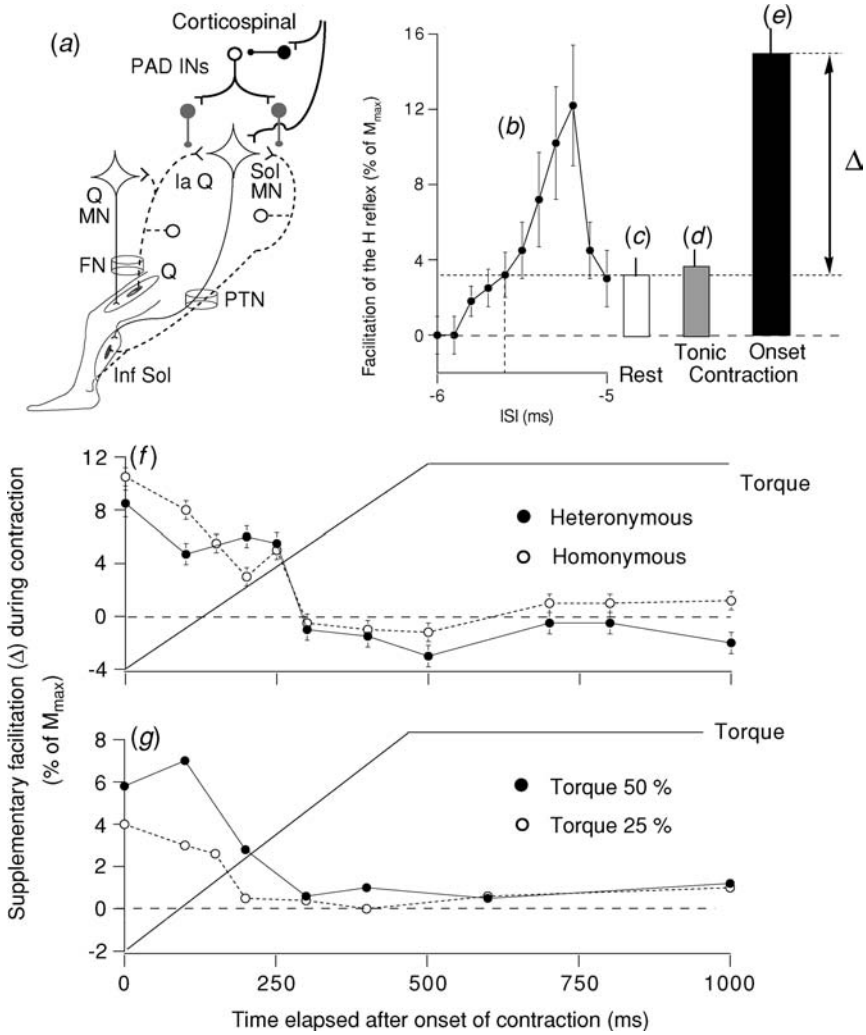


Fig. 8.9. Decrease in presynaptic inhibition of soleus Ia terminals at the onset of soleus voluntary contraction. (*a*) Sketch of the presumed pathways. Presynaptic inhibition of homonymous (in the inferior soleus [Inf Sol] nerve) and heteronymous (from quadriceps [Q] in the femoral nerve [FN]) Ia afferents to soleus (Sol) motoneurones (MN) is mediated through a subset of common first-order PAD interneurones (INs). (*b*) The amount of facilitation of the Sol H reflex elicited by FN stimulation at 4 × MT (expressed as a percentage of M_{max}) is plotted against the ISI, and the −5.6 ms ISI (dashed vertical line) was chosen to assess the amount of reflex facilitation. (*c*)–(*e*) The amount of reflex facilitation at rest ((*c*) and horizontal dotted line), during a soleus tonic contraction ((*d*) 20% MVC) and at the onset of a selective voluntary contraction of soleus (*e*). The supplementary facilitation of the reflex at the onset of contraction, i.e. the difference (Δ = (*e*) − (*c*)) is due to decreased presynaptic inhibition of Ia terminals, and is indicated by the double-headed arrow. (*f*)–(*g*) Time course of the changes in facilitation of the Sol H reflex during a selective ramp-and-hold contraction of Sol (profile of the torque: continuous thin line; both the ramp and the holding phases lasted 500 ms). The supplementary facilitation during contraction (i.e. the difference Δ in (*e*)) is plotted against time elapsed after onset of contraction. (*f*) Comparison of the changes in homonymous (○, Inf Sol, 1.1 × MT, 2.5 ms ISI) and heteronymous (●, FN as in (*b*)) facilitation. (*g*) Changes in heteronymous facilitation (FN 4 × MT, ISI 0.4 ms after the onset of facilitation) during ramp contractions to 50% (●) and 25% (○) of MVC. Each point and column represents the mean of 20 measurements. Vertical bars in (*b*), (*f*), (*g*) ±1 SEM, in (*c*)–(*e*) 1 SEM. (*b*)–(*f*) and (*g*) are from two different subjects. Modified from Pierrot-Deseilligny (1997) ((*b*)–(*e*)), and Meunier & Pierrot-Deseilligny (1989) ((*f*), (*g*)), with permission.

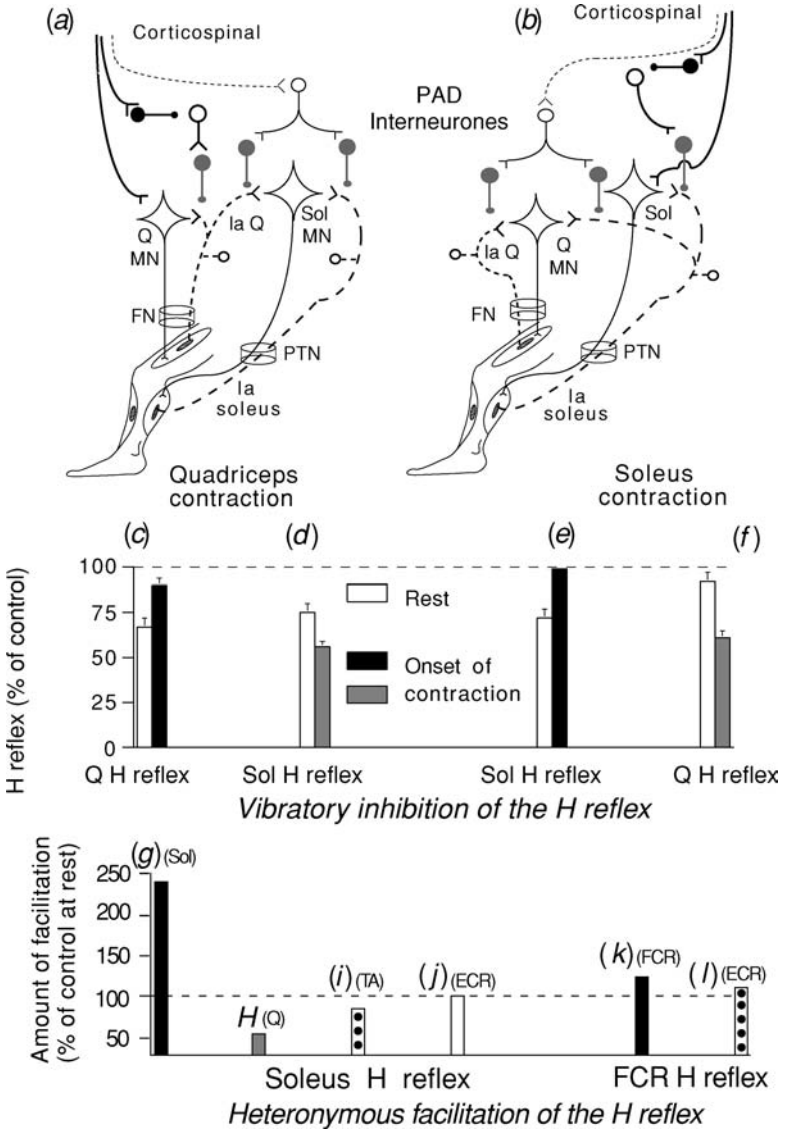


Fig. 8.10. Changes in presynaptic inhibition at the onset of voluntary contraction of various muscles. (*a*), (*b*) Sketch of the presumed PAD pathways involved at the onset of quadriceps (Q) (*a*) and soleus (Sol) (*b*) contractions. Presynaptic inhibition of homonymous and heteronymous Ia terminals to a given motoneurone (MN) pool (Sol or Q) is mediated through common first-order PAD INs. In addition, there is corticospinal depression (thick continuous line) of PAD INs mediating presynaptic inhibition of Ia terminals on MNs involved in the contraction, and facilitation (thin dotted line) of those acting on Ia terminals on MNs not involved in the contraction. (*c*)–(*f*) *Vibratory suppression of the H reflex*, elicited by a train of three taps (200 Hz) applied to the TA tendon, at rest (open columns) and at the onset of selective voluntary contractions of the homonymous (black columns) or heteronymous (grey columns) muscle. The H reflex (as a percentage of its unconditioned value, dashed horizontal line) of Q at the onset of Q (*c*) and Sol (*f*) contractions and of Sol at the onset of Q (*d*) and Sol (*e*) contractions. Each column represents the mean of 100 measurements in a single subject. Vertical bars 1 SEM. (*g*)–(*l*) *Heteronymous facilitation of the H reflex* (expressed as a percentage of the amount of facilitation at rest, dashed horizontal line) is compared at the onset of a selective contraction of the homonymous muscle (black columns), a synergist (grey column), an antagonist (columns with dots), or a remote muscle (open column). (*g*)–(*j*) Femoral-induced (FN 4 × MT, ISI 0.4 ms after the onset of facilitation) facilitation of the soleus H reflex at the onset of Sol (*g*), Q (*h*), TA (*i*) and ECR (*j*) contraction. (*k*), (*l*) Facilitation of the FCR H reflex elicited by a Ia volley from intrinsic hand muscles (median nerve at the wrist, 1 × MT, 6 ms ISI) at the onset of FCR (*k*) and ECR (*l*) contraction. Each column represents the mean of results obtained in six subjects. Modified from Hultborn *et al.* (1987b) ((*c*)–(*h*)), Meunier & Morin (1989) ((*i*), (*j*)), and Aymard *et al.* (2001) ((*k*), (*l*)), with permission.

ramp-and-hold contractions of triceps surae for various durations and at different forces (Meunier & Pierrot-Deseilligny, 1989).

Time course of changes in presynaptic inhibition

At the onset of the contraction, presynaptic inhibition of quadriceps Ia terminals to soleus motoneurones decreases markedly. During the first half of the ramp, it remains much less than at rest but, in the middle of the ramp, it returns to its rest level (Fig. 8.9(*f*)). Figure 8.9(*f*) also shows that the changes in presynaptic inhibition of homonymous Ia terminals in the inferior soleus nerve and of heteronymous quadriceps Ia terminals are of much the same magnitude and time course. A similar time course, i.e. decrease in resting presynaptic inhibition of Ia terminals to soleus motoneurones during the first half of the ramp with a return to rest values in the middle of the ramp, was observed with ramps of different duration (250, 500 or 1000 ms). This indicates that the duration of the decrease in presynaptic inhibition of Ia terminals projecting to motoneurones of the contracting muscle depends on the ramp duration and not on the time elapsed from the onset of the contraction. The return to the rest level in the middle of the ramp always occurred when the force was increasing more slowly, because of deceleration during the second half of the ramp as the target level was approached.

Relationship to force

The stronger the target contraction the greater was the decrease in presynaptic inhibition at the onset of the ramp contraction (Fig. 8.9(*g*)). However, the time courses of the decreases were similar in the two cases.

Tonic contraction

Heteronymous facilitation of the soleus H reflex was not significantly increased during relatively strong tonic contractions of soleus at 20% of MVC (Meunier & Pierrot-Deseilligny, 1989; Fig. 8.9(*d*)), although a weak increase may be observed for small levels of tonic plantar flexion (Nielsen & Kagamihara, 1993). This may be due to a balance between descending inhibition of PAD interneurones and their peripheral excitation by the natural feedback from the contracting muscle.

Origin and functional implications

Origin

The decrease in presynaptic inhibition of Ia afferents to the contracting muscle occurs ~50 ms before the contraction (Nielsen & Kagamihara, 1993), indicating its descending origin. Given (i) the selectivity of this control (cf. below), (ii) the dominant depressive effect of corticospinal drives on lower limb PAD interneurones (cf. pp. 350–2), and (iii) the focusing of this drive (cf. p. 351), it is tempting to speculate that the selective decrease in presynaptic inhibition of Ia terminals directed to the contracting motoneurone pool at the onset of contraction is due to focused corticospinal drive. Indeed, the same cortical site both activates motoneurones of a given pool and depresses PAD interneurones mediating presynaptic inhibition of Ia terminals projecting to that pool (as sketched in the wiring diagrams in Figs. 8.6(*a*), 8.9(*a*)). The Ia/Ib discharge from a contracting muscle produces presynaptic inhibition of Ia terminals in the cat spinal cord (see p. 339). An increased group I afferent discharge from a contracting muscle could thus activate PAD interneurones and contribute to the re-appearance of presynaptic inhibition in the middle of a ramp contraction (Fig. 8.9(*f*), (*g*)). However, the same time course was observed during ischaemic blockade of group I afferents (Meunier & Pierrot-Deseilligny, 1989), and the re-appearance always occurred in the middle of the ramp, whatever the ramp duration. These findings suggest that the re-appearance of presynaptic inhibition after its initial decrease is centrally preprogrammed, much as is the suppression of presynaptic inhibition and the degree of suppression. In

other words, all of the changes in presynaptic inhibition at the onset of and during a ramp contraction of a lower-limb muscle can be attributed to descending drives, not peripheral inputs.

Functional implications

The decreased gating of homonymous Ia terminals on the contracting muscle assures that the excitation from primary spindle endings becomes available to motoneurones activated in the movement. At the beginning of a movement, when the exact load is not yet known, this would allow the monosynaptic Ia excitation to compensate rapidly and automatically for minor errors in the programmed movement. Later, in the middle of the ramp, the decrease in presynaptic inhibition disappears and the gain of the monosynaptic loop returns to its control value. However, by that time, other mechanisms in the central nervous system would be available to maintain the desired trajectory and, in addition, the decrease in gain is required to prevent oscillations from developing (see Matthews, 1972). This control of presynaptic inhibition, with an initial decrease in presynaptic inhibition followed by a return to rest values is presumably achieved through corticospinal control of PAD interneurones, and is pre-programmed at the onset of the movement according to the intended strength and duration of the contraction.

Ia terminals directed to motoneurones of inactive synergistic muscles

Increased presynaptic inhibition of Ia terminals on synergistic motoneurones

Soleus and quadriceps are linked by bidirectional heteronymous monosynaptic Ia connections (Meunier, Pierrot-Deseilligny & Simonetta, 1993; Table 2.1). The large *decrease* in presynaptic inhibition of Ia terminals on motoneurones involved in a selective voluntary contraction was accompanied by a prominent *increase* in presynaptic inhibition of Ia terminals on motoneurones of synergistic muscles not involved in the contraction. Thus, at the onset of a selective voluntary contraction of quadriceps, presynaptic inhibition of homonymous Ia terminals to quadriceps motoneurones is reduced (Fig. 8.10(*c*)), but presynaptic inhibition of heteronymous Ia terminals from quadriceps to soleus motoneurones is enhanced, as shown by the decreased femoral-induced facilitation of the soleus H reflex (Fig. 8.10(*h*)).

Origin

Given the time between the onset of contraction and the contraction-induced Ib discharge (Binder *et al.*, 1977) or the Ia discharge due to the contraction-associated increase in γ drive (see Chapter 3, p. 133), it is unlikely that peripheral afferents contribute to the increased presynaptic inhibition of heteronymous Ia terminals from quadriceps to soleus motoneurones at the onset of quadriceps contractions. Descending facilitation of PAD interneurones could be due to: (i) a facilitatory effect of corticospinal drives, normally hidden by an opposite and dominant depressive effect (see p. 339 and p. 353); (ii) increased descending inhibition of inhibitory interneurones transmitting cutaneous (and corticospinal) inhibition of first-order PAD interneurones (pathway [2] in the sketch in Fig. 8.1(*a*)).

Functional implications

Monosynaptic Ia connections from quadriceps to soleus motoneurones are particularly well developed in human subjects, where they probably play a role in the reflex control of motor tasks, such as running and hopping, in which co-contraction of the two muscles is required (see Chapter 2, pp. 93–4). However, during a selective contraction of quadriceps, there will be an enhanced Ia discharge from the contracting quadriceps, due to increased fusimotor drive (see Chapter 3, pp. 133–5), and this would excite motoneurones of the relaxed soleus. The

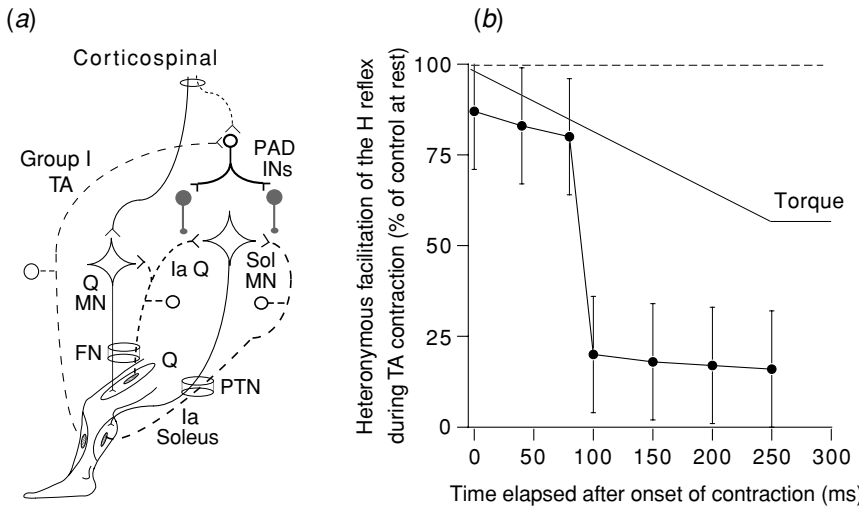


Fig. 8.11. Changes in presynaptic inhibition of Ia afferents to soleus motoneurones during voluntary contraction of the antagonistic muscle. (*a*) Sketch of the presumed pathways: (i) presynaptic inhibition of homonymous and heteronymous (from quadriceps, Q) Ia terminals on soleus (Sol) motoneurones (MN) is mediated through common first-order PAD interneurones (INs), and (ii) the corticospinal excitation to tibialis anterior (TA) MNs is accompanied by descending facilitation (thin dotted line) of PAD INs mediating presynaptic inhibition of Ia terminals on Sol MNs. (*b*) During a ramp-and-hold voluntary contraction of TA to 20% of MVC (250 ms ramp phase; torque profile illustrated by the continuous thin line), the amount of facilitation of the soleus H reflex (expressed as a percentage of its value at rest) produced by femoral nerve stimulation (4 × MT, ISI 0.4 ms after the onset of facilitation) is plotted against time elapsed after the onset of TA contraction. Each point represents the mean of 20 measurements. Vertical bars ±1 SEM. Data from a single subject. Modified from Meunier & Morin (1989), with permission.

great enhancement of presynaptic inhibition of quadriceps Ia terminals to soleus motoneurones at the onset of a selective voluntary contraction of quadriceps would help prevent soleus motoneurones from being activated. The corticospinal control of presynaptic inhibition, selectively 'opening' Ia transmission to voluntarily activated motoneurones while 'closing' transmission to motoneurones of relaxed muscle(s), would increase motor contrast and contribute to the selective activation of muscles in discrete movements (see Chapter 11, p. 517). The increased presynaptic inhibition on the homonymous Ia feedback from the inactive soleus (Fig. 8.10(*d*)) could then simply result from the mediation through common PAD pathways of presynaptic inhibition of homonymous and heteronymous Ia terminals directed to soleus motoneurones, as discussed on p. 348 and sketched in Fig. 8.10(*a*).

Presynaptic inhibition of Ia terminals during contraction of antagonistic muscles

Selective contraction of the antagonistic muscle

At the onset of tibialis anterior contractions, presynaptic inhibition of heteronymous quadriceps Ia terminals to soleus motoneurones is not increased or is only marginally so, unless the contraction is strong and brisk (Figs. 8.10 (*i*); Meunier & Morin, 1989), in which case the increase appears ~50 ms before the contraction (Nielsen & Kagamihara, 1993), indicating that it is descending in origin (see the wiring diagram in Fig. 8.11(*a*)). This presynaptic inhibition increases little during the first 80 ms of a tibialis anterior ramp contraction, but is then

abruptly enhanced, perhaps reinforced from peripheral sources (Fig. 8.11(*b*); Meunier & Morin, 1989). Finally, during tonic dorsiflexion, presynaptic inhibition of heteronymous Ia terminals from quadriceps to soleus tends to increase with the strength of the contraction, but the maximal inhibition is reached in rather weak contractions (Crone & Nielsen, 1989a). The increased inhibition is at least partly supraspinal in origin, because it is not changed by a nerve block using ischaemia or lidocaine (cf. Chapter 5, p. 220). This indicates that, during blockade of the afferent feedback, descending facilitation of PAD interneurones can compensate for the loss of excitation due to the afferent input. In any event, whether descending or peripheral in origin, presynaptic inhibition of Ia terminals on motoneurones of the antagonist of the active muscle remains modest.

Co-contractions of antagonists

During tonic co-contraction of soleus and tibialis anterior, the femoral-induced facilitation is smaller than during voluntary plantar flexion at matched levels of background activity in the soleus muscle (Nielsen & Kagamihara, 1993). This result was observed in the motoneurone pool with the H reflex (Fig. 8.12(*b*)–(*e*)) and in PSTHs from single motor units (Fig. 8.12(*f*)), and indicates that presynaptic inhibition of the quadriceps Ia projections to soleus motoneurones is greater during co-contraction of the antagonists than during voluntary plantar flexion. The peak of homonymous monosynaptic Ia excitation elicited by stimulation of the posterior tibial nerve in soleus units was also decreased during co-contraction, indicating once again a parallel control of presynaptic inhibition of homonymous and heteronymous Ia terminals on the same target motoneurones. The increase in presynaptic inhibition is of descending origin, since it appears ~50 ms before the co-contraction and persists during ischaemic blockade of group I afferents. Thus, at equivalent levels of soleus EMG activity, there is a differential descending control of presynaptic inhibition of the same Ia terminals to soleus during plantar flexion and co-contraction (cf. Chapter 11, p. 533).

Functional implications

The increase in presynaptic inhibition of Ia terminals directed to motoneurones of active antagonistic muscles was initially interpreted as a mechanism to prevent the ankle extensor stretch reflex from obstructing voluntary dorsiflexion (Meunier & Morin, 1989; Crone & Nielsen, 1989a), or oscillations from developing during co-contraction (Nielsen & Kagamihara, 1993). However, this interpretation is less likely if the sensitivity of the stretch reflex to presynaptic inhibition of Ia terminals is weak (see Morita *et al.*, 1998 and pp. 354–5). In addition, the stretch reflex elicited in ankle extensors is not depressed during strong co-contraction (Nielsen *et al.*, 1994), despite the increase in presynaptic inhibition. In the cat, presynaptic inhibition of Ia afferents reduces the Ia input to interneurones mediating reciprocal Ia inhibition (cf. Chapter 5, pp. 200–1). If these data can be transposed to man, the main role of the increased presynaptic inhibition of Ia afferents during contraction of antagonistic muscles could be to depress reciprocal Ia inhibition: (i) during voluntary ankle dorsiflexion, increased presynaptic inhibition would help prevent the Ia discharge produced by soleus stretch from firing soleus-coupled Ia interneurones and thus inhibiting tibialis anterior motoneurones (cf. Chapter 11, p. 520); (ii) during co-contraction, transmission in the Ia inhibitory pathway must be depressed to allow the parallel activation of the two antagonistic muscles (Chapter 11, p. 532).

Presynaptic inhibition of Ia terminals during contraction of remote muscles

In order to elucidate the extent to which the changes in presynaptic inhibition accompanying a voluntary contraction are specific, changes in femoral-induced facilitation of the soleus H reflex were investigated at the onset of a voluntary contraction of an upper

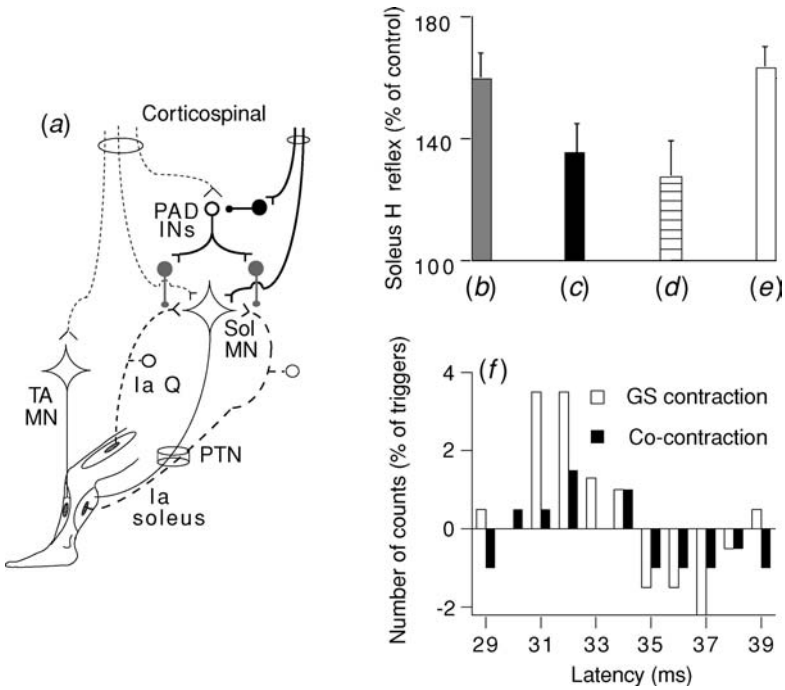


Fig. 8.12. Changes in presynaptic inhibition during a voluntary co-contraction of antagonistic muscles. (*a*) Sketch of the presumed pathways. During voluntary ankle plantar-flexion and co-contraction of ankle extensors and flexors: (i) the corticospinal command to soleus (Sol) motoneurones (MN) is conveyed through different pathways; and (ii) PAD interneurones (INs) transmitting presynaptic inhibition of homonymous and heteronymous Ia afferents (from quadriceps [Q]) to Sol motoneurones (MN) receive a suppressive corticospinal input during voluntary ankle plantar-flexion (thick continuous line), whereas they receive a facilitatory corticospinal drive during co-contraction of ankle extensors and flexors (thin dotted line). (*b*)–(*e*) The soleus H reflex (as a percentage of unconditioned reflex size) is facilitated by femoral nerve stimulation (1.2 × MT, 0.5 ms after the onset of facilitation) at rest (*b*), during tonic co-contraction of the soleus and TA (*c*), during a tonic contraction only of TA (*d*), and during a tonic contraction of only soleus (*e*), at the same EMG levels. Data from a single subject.(*f*) PSTHs (after subtraction of the background firing, 1 ms bin width) elicited in the same soleus unit by FN stimulation at 1.1 × MT during a contraction of gastrocnemius-soleus (GS, □) and during co-contraction of ankle extensors and flexors (■), using equivalent levels of GS EMG activity. The number of counts (as a percentage of the number of triggers) is plotted against the latency after stimulation. Note that the decrease in the peak during co-contraction affects the first bin. Modified from Nielsen & Kagamihara (1993), with permission.

limb muscle (ECR or FCR; Meunier & Morin, 1989). When the contraction was moderate (20% of MVC), no significant change was observed (Fig. 8.10(*j*)), but a slight increase in presynaptic inhibition of heteronymous Ia terminals from quadriceps to soleus was observed when the ECR contraction was brisk and maximal. This suggests that the reflex reinforcement produced by the Jendrassik manoeuvre is not due to decreased presynaptic inhibition, as has been suggested (Zehr & Stein, 1999; Chapter 3, p. 133).

Changes in presynaptic inhibition of Ia terminals on upper limb motoneurones

Changes in presynaptic inhibition of Ia terminals to FCR motoneurones may be explored on homonymous Ia terminals using the radial-induced D1 inhibition of the FCR H reflex, and on heteronymous Ia monosynaptic projections from intrinsic hand muscles using the facilitation of the H reflex. With the two methods a decrease in presynaptic inhibition of

Ia terminals on FCR motoneurones was observed at the onset of voluntary contractions of FCR (Aymard *et al.*, 2001). This decrease in presynaptic inhibition differs from that observed in the lower limb.

(i) It is quantitatively less: at the onset of FCR contraction, D1 inhibition for FCR is only moderately reduced, whereas vibratory inhibition is completely suppressed for the contracting muscle at the onset of a lower-limb contraction. Similarly, the moderate amount of increased heteronymous facilitation of the FCR H reflex (Fig. 8.10(*k*)) contrasts with the huge increase in heteronymous facilitation observed at the onset of soleus contraction (Fig. 8.10(*g*)).

(ii) There is a decrease in presynaptic inhibition during tonic FCR contraction of much the same magnitude as that observed at the onset of contraction. However, with soleus, the large decrease in presynaptic inhibition at the onset of contraction is transient (Fig. 8.9(*f*)), and there is no significant change in presynaptic inhibition during tonic voluntary contractions (Fig. 8.9(*d*)).

(iii) The most striking difference is the finding that there are similar decreases in presynaptic inhibition of Ia terminals on FCR motoneurones at the onset of a voluntary wrist extension (Fig. 8.10(*l*)). With soleus, there is, if anything, an increase in presynaptic inhibition of Ia terminals on soleus motoneurones at the onset of a voluntary contraction of the antagonistic tibialis anterior (Fig. 8.10(*i*)).

The slight depression of PAD interneurones mediating presynaptic inhibition of Ia terminals on FCR motoneurones at the onset of various forearm voluntary contractions is unlikely to be of corticospinal origin, given the dominant facilitatory control existing from the motor cortex onto PAD interneurones in the human cervical enlargement (p. 353). Instead the non-specificity of this depression is consistent with reticulospinal depression acting on the last-order PAD interneurones in the cat (cf. p. 339).

Changes in presynaptic inhibition during upright stance

Presynaptic inhibition of Ia terminals on various lower limb motor nuclei has been compared when standing with and without back support (Katz, Meunier & Pierrot-Deseilligny, 1988).

Investigations using single units

Alterations in presynaptic inhibition of Ia terminals on quadriceps, soleus and tibialis anterior motoneurones have been inferred from changes in the peak of homonymous or heteronymous monosynaptic Ia excitation (in particular, its initial part) elicited in the PSTHs of voluntarily activated single motor units. Compared with the control situation, the peak of femoral Ia excitation was increased in quadriceps units (Fig. 8.13(*b*)), indicating a decrease in presynaptic inhibition of homonymous quadriceps Ia terminals, and suppressed in soleus units (Fig. 8.13(*c*)), indicating increased presynaptic inhibition of the heteronymous Ia projection from quadriceps to soleus motoneurones. The peak of homonymous excitation in soleus produced by stimulation of the posterior tibial nerve was similarly suppressed, indicating, once again, that the presynaptic inhibitions of homonymous and heteronymous Ia terminals on soleus motoneurones are modulated in a parallel fashion. No change was observed in the presynaptic inhibition of homonymous tibialis anterior Ia terminals.

Investigations using the soleus H reflex

These investigations provide an example of non-congruent results with the different methods used to assess presynaptic inhibition of Ia terminals.

(i) The femoral-induced facilitation of the soleus H reflex was decreased during standing without support, and this seemed to confirm the increased presynaptic inhibition of quadriceps Ia terminals on soleus motoneurones (Katz, Meunier & Pierrot-Deseilligny, 1988).

(ii) However, whereas increased excitability of PAD interneurones would increase D1 inhibition, peroneal-induced D1 inhibition of the soleus H reflex is decreased during active standing (Faist, Dietz & Pierrot-Deseilligny, 1996). Changes in the heteronymous facilitation and in the D1 inhibition of the soleus H reflex in the same direction raise the

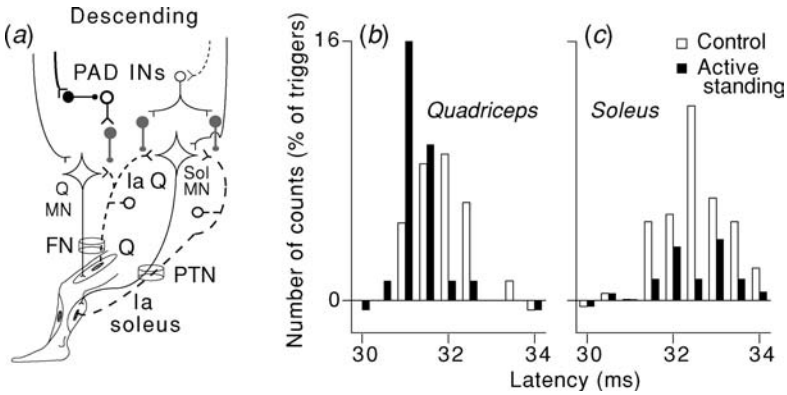


Fig. 8.13. Changes in presynaptic inhibition during standing without support. (*a*) Sketch of the presumed pathways: in standing without support PAD interneurones (INs) mediating presynaptic inhibition of homonymous and heteronymous Ia afferents from quadriceps (Q) projecting to soleus (Sol) motoneurones (MN) receive descending facilitation (thin dotted line) whereas those mediating presynaptic inhibition of Ia terminals projecting to Q motoneurones receive descending suppression (thick continuous line). (*b*), (*c*) PSTHs (after subtraction of the background firing, 0.5 ms bin width) with the number of counts (as a percentage of the number of triggers) plotted against the latency after stimulation. The peak of monosynaptic excitation elicited by stimulation of the femoral nerve (FN) in a Q motor unit ((*b*), FN at 1 × MT) and in a soleus unit ((*c*) FN at 4 × MT) is shown when standing with back support (□, control) and when standing without support (■). Because the firing rate of the motor unit tested and its variability were similar in the two situations, a change in the size of the peak, and in particular of its initial 0.5 ms, may be attributed to a change in the underlying monosynaptic EPSP, i.e. to a change of presynaptic inhibition of Ia terminals. Modified from Katz, Meunier & Pierrot-Deseilligny (1988), with permission.

possibility of a change in the gain of the motoneurone pool (cf. p. 347). However, a similar reduction in the heteronymous and homonymous Ia monosynaptic peaks was observed in single soleus motor units, and this eliminates such a possibility. The absence of an increase in D1 inhibition may have a number explanations (which are not mutually exclusive, see Capaday, Lavoie & Cormeau, 1995): (i) the conditioning group I volley in the common peroneal nerve may be gated by the 'natural' group I discharge related to active standing; (ii) occlusion at the level of PAD interneurones may occur between this group I 'natural' discharge and the conditioning volley, but there is no clear enhancement of the background Ia traffic in the peroneal nerve when subjects are standing without support (Aniss *et al.*, 1990), and occlusion would need to come from increased descending (e.g. vestibulospinal) excitation of PAD interneurones; and (iii) a change in the superimposed facilitation that creates two separate phases of inhibition from a single inhibitory process (cf. p. 344). Either way, this highlights that D1 inhibition may not always be a reliable method to assess an increase in presynaptic inhibition.

Functional implications

The decreased presynaptic inhibition of homonymous quadriceps Ia terminals ensures that the full excitatory Ia feedback is available to provide a safety factor for the quadriceps contraction, which supports the body weight (when the knees are not locked in extension). Increased presynaptic inhibition of soleus Ia terminals could play a role in depressing the stretch reflex during balancing tasks so that the balance of the subject is not endangered by a sudden perturbation (Llewellyn, Yang & Prochazka, 1990; Chapter 11, pp. 540–1). In addition, the increased presynaptic inhibition of soleus Ia terminals could contribute to the depression of

reciprocal Ia inhibition, through presynaptic inhibition of the Ia input to interneurones mediating reciprocal Ia inhibition, much as is likely during co-contraction of antagonistic muscles. When standing without support, posture is potentially unstable, and contractions may be required in either of the antagonistic muscles operating at the ankle. This creates a situation where a decrease in reciprocal Ia inhibition may be helpful in controlling body sway.

Changes in presynaptic inhibition during gait

Presynaptic inhibition of homonymous quadriceps Ia terminals during walking

At heel strike, the quadriceps H reflex is greater than during a voluntary contraction at an equivalent level of quadriceps EMG, and this suggests a decrease in presynaptic inhibition (Dietz, Faist & Pierrot-Deseilligny, 1990). This view is further supported by the differential effect on the on-going EMG activities of the quadriceps and triceps surae of Ia excitation produced by tendon vibration (Verschueren *et al.*, 2003). Vibration applied to the patellar tendon enhances the quadriceps EMG in early stance, while vibration to the Achilles tendon does not modify that of the triceps surae during gait. This differential effect of vibration-induced Ia excitation is consistent with a differential control of presynaptic inhibition on Ia terminals on the motoneurones of the two muscles: increased for triceps surae motoneurones (see below), but decreased for quadriceps motoneurones. At this time the weight of the body is shifted to the leg that is about to begin the stance phase, and a strong quadriceps contraction would be required to extend the knee joint to support the body. Decreased presynaptic inhibition of Ia terminals provides a safety factor for the quadriceps contraction, and this might be important in compensating for the unevenness of the ground. Later during early stance, presynaptic inhibition of homonymous quadriceps Ia terminals progressively increases, a change that could be necessary to allow for the yield of the knee and hence the smoothness of the gait (cf. Chapter 11, pp. 545, 547).

Presynaptic inhibition of Ia terminals on soleus motoneurones during walking

Differences in the size of the H reflex at equivalent levels of EMG activity

The possibility of an increase in presynaptic inhibition of soleus Ia terminals during gait first emerged from comparisons of the soleus H reflex during walking and standing at the same level of on-going EMG activity. Thus, Morin *et al.* (1982) showed that ~50 ms after the onset of soleus EMG activity during the stance phase of gait, the soleus H reflex was significantly smaller than at the same moment after the onset of an equivalent voluntary contraction when standing. This difference could reflect stronger presynaptic inhibition of soleus Ia terminals during walking. The same observation by Capaday & Stein (1987) was also interpreted as increased presynaptic inhibition. The existence of a presynaptic gating of group I afferents has also been invoked to explain the reduction of cortical somatosensory potentials evoked by posterior tibial nerve stimulation during gait (Dietz, Quintern & Berger, 1985). Because the amplitude of the H reflex was even lower during difficult beam walking, it was argued that the presumed increase in presynaptic inhibition of soleus Ia terminals was then stronger (Llewellyn, Yang & Prochazka, 1990). However, because differences in the modulations of the EMG and H reflex may have other causes (cf. p. 340), more specific methods have been used to investigate possible changes in presynaptic inhibition of Ia terminals during gait.

Changes in D1 and D2 inhibition

During the stance phase of gait, D2 and D1 inhibitions are decreased with respect to values obtained during voluntary contractions when sitting (Capaday, Lavoie & Cormeau, 1995; Faist, Dietz & Pierrot-Deseilligny, 1996). Since presynaptic inhibition of soleus Ia terminals appears likely to be increased

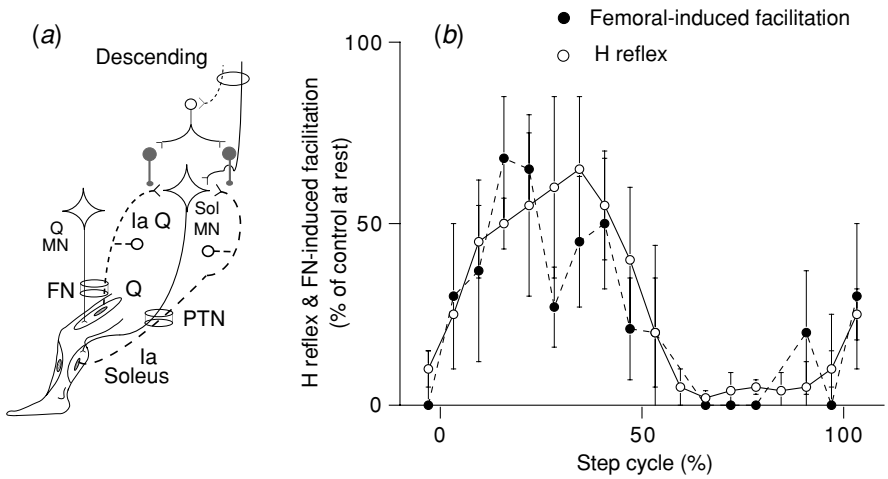


Fig. 8.14. Changes in presynaptic inhibition of soleus Ia terminals throughout the step cycle. (*a*) Sketch of the presumed pathways. During gait, soleus (Sol) motoneurones (MN) receive descending excitation, and PAD interneurones (INs) mediating presynaptic inhibition of homonymous and heteronymous Ia afferents projecting to Sol MNs receive descending facilitation. (*b*) The Sol H reflex (○) and the facilitation elicited by femoral stimulation (4 × MT, ●, ISI 0.4 ms after the onset of facilitation), expressed as a percentage of the values measured during relaxed sitting are plotted throughout the step cycle. Group data from 7 subjects. Vertical bars ±1 SEM. Abscissa, step cycle normalised as a percentage of the duration of one stride from heel strike (0%) to the next heel strike (100%). Modified from Faist, Dietz & Pierrot-Deseilligny (1996), with permission.

during gait (cf. below), this finding can probably be attributed to the same mechanisms as during active standing (i.e. gating of the conditioning peroneal volley and/or occlusion at the level of PAD interneurones, cf. above).

Heteronymous facilitation of the H reflex

Changes in femoral-induced facilitation of the soleus H reflex have been compared to the modulation of the H reflex during a complete step cycle. As had previously been found (Capaday & Stein, 1986), the amplitude of the soleus H reflex was strongly inhibited throughout the step cycle: it increased progressively during stance, reaching a maximum at ∼30% of the step cycle, where it was still only 80% of its control value. It then decreased abruptly at the end of the stance phase to disappear more or less completely during the swing phase. The heteronymous facilitation had a similar time course, probably reflecting modulation of the presynaptic inhibition of heteronymous Ia afferents from quadriceps to soleus motoneurones (Figure 8.14(*b*); Faist, Dietz & Pierrot-Deseilligny, 1996). The parallel modulation (time course and magnitude) of the soleus H reflex and of its femoral-induced facilitation throughout the stance phase suggests, once again, that presynaptic inhibition of homonymous and heteronymous Ia terminals on soleus motoneurone are modulated through common PAD interneurones.

Functional implications

During the stance phase of gait, contraction of triceps surae resists the passive ankle dorsiflexion produced by extrinsic forces (kinetic force and gravity) and thereby slows the movement. Nevertheless triceps surae tension must be overcome by extrinsic forces if the body is to be brought forward. During most of the stance phase, triceps surae undergoes a lengthening contraction, known to evoke strong Ia discharges. Increased presynaptic inhibition of the

homonymous Ia excitatory feedback, together with other mechanisms (cf. Chapter 11, pp. 546–7), could be necessary to prevent excessive activation of ankle extensor motoneurones and a stiff gait.

Running

Increased presynaptic inhibition of soleus Ia terminals

During the stance phase of running the H reflex has been reported to be smaller than during walking (Capaday & Stein, 1987), or of the same amplitude when the H reflex amplitude is expressed as a percentage of M_{max}, which varies throughout the gait cycle (Simonsen & Dyhre-Poulsen, 1999). Either way, given the much higher level of EMG activity during running, there is evidence for an increase in presynaptic inhibition of soleus Ia terminals for running compared to walking.

Functional significance

Capaday & Stein (1987) suggested that the increased presynaptic inhibition would reduce the gain of the stretch reflex to minimise the potential for instability of the motoneurone pool (tremor) caused by saturation of the pool. This view was challenged by Simonsen & Dyhre-Poulsen (1999), who maintained that there is little danger of saturation of the motoneurone pool by the stretch reflex during running. In any case, presynaptic inhibition may have only weak depressive effects on the reflex responses to abrupt stretch (see pp. 354–5; Morita *et al.*, 1998). Accordingly, during running, the spinal stretch reflex has been shown to contribute significantly to the triceps surae contraction during the pushing off of the foot and to provide automatic load compensation for an unexpected disturbance (see Chapter 2, p. 87). Thus, as stated by Ferris *et al.* (2001), the 'physiological advantages for the increased' presynaptic inhibition of soleus Ia terminals during running are still unclear. A somewhat paradoxical explanation could be that increased presynaptic inhibition of Ia afferents contributes to securing the triceps surae stretch reflex. This could occur because presynaptic inhibition of Ia terminals produces Ib disinhibition through a reduction of the Ia input to interneurones mediating non-reciprocal group I inhibition (see Chapter 6, pp. 260–1). In this respect (i) presynaptic inhibition of gastrocnemius-soleus Ia afferents has been shown to produce a large decrease in gastrocnemius medialis-induced non-reciprocal group I inhibition of soleus motoneurones (Rossi, Decchi & Ginanneschi, 1999), and (ii) Ia excitation can be opposed by non-reciprocal group I inhibition, especially during strong contractions (Marchand-Pauvert *et al.*, 2002). It is therefore conceivable, though counter-intuitive, that depression of the Ia input to interneurones mediating non-reciprocal group I inhibition is required to maintain the contribution of the soleus stretch reflex to the pushing off of the foot.

Studies in patients and clinical implications

Methodology

The different techniques reviewed on pp. 340–6 can be used to assess presynaptic inhibition in patients with various central nervous system (CNS) lesions.

Clinical studies

In clinical studies on patients, simple methods are preferable. A decrease in D1 inhibition may be difficult to interpret in situations, such as contraction or gait, in which there is a 'natural' peripheral input to PAD interneurones (because this could result in paradoxical findings due to occlusion, see pp. 344–5). Nevertheless D1 inhibition is the easiest and most convenient method to investigate presynaptic inhibition with PAD at rest. In the lower limb, the soleus H reflex is conditioned by a peroneal volley (train of three shocks, 300 Hz, 1.2 × MT, 21 ms ISI between the first shock of the train and the test stimulation). In the upper limb, the FCR H reflex is conditioned by a single shock to the radial nerve (0.95 × MT,

13 ms ISI). Suppression of the H reflex by brief vibration or a tap to the tendon of a heteronymous flexor muscle delivered 60 ms before the test stimulus eliciting the test volley is also a simple and convenient method.

Changes with ageing

There is a progressive decrease in both the amount of heteronymous vibratory inhibition (Butchart *et al.*, 1993) and the extent of femoral-induced facilitation (Morita *et al.*, 1995) of the soleus H reflex with ageing. Because these changes are in the same direction, they cannot be due to a change in presynaptic inhibition of Ia terminals (cf. p. 347). They may reflect a decrease in the number of Ia afferents and/or in their conduction velocities. Whatever their origin, these changes must be taken into account when using these methods to assess presynaptic inhibition in patients.

Spasticity

Over-interpretation of decreased presynaptic inhibition

In the 1970s–1990s, it was popularly held that a decrease in presynaptic inhibition of Ia terminals was one of the spinal mechanisms, perhaps even the main mechanism, underlying the stretch reflex exaggeration characterising spasticity. Intellectually satisfying at the time, this view was based on what is now known to be a flawed technique: the depression of the soleus H reflex by prolonged homonymous vibration on the Achilles tendon. It was postulated and for long accepted that the mechanism underlying this reflex suppression is presynaptic inhibition mediated by PAD interneurones. Because this reflex suppression is decreased in most spastic patients, it became generally accepted that there was a decrease in presynaptic inhibition of Ia terminals with PAD in these patients (Delwaide, 1973, 1993; Delwaide & Pennisi, 1994; Burke & Ashby, 1972; Ashby, Verrier & Carleton, 1980; Taylor, Ashby & Verrier, 1984; Iles & Roberts, 1986; Koelman *et al.*, 1993; Calancie *et al.*, 1993; Childers *et al.*, 1999; see also the review by Stein, 1995). As emphasised on p. 341, when both conditioning and test volleys are mediated through the same synaptic pathway, two other processes could operate to depress the H reflex, and the vibration-induced depression cannot be used to estimate presynaptic inhibition of Ia terminals with PAD. These two factors are activity-dependent hyperpolarisation of Ia afferents and post-activation (homosynaptic) depression of transmission at the Ia-motoneurone synapse (see p. 341). The problem is accentuated by the fact that post-activation depression is decreased in spastic patients (see Chapter 2, pp. 99–100). In addition, the finding that presynaptic inhibition of Ia terminals with PAD has only a small effect on the reflex responses to abrupt stretch (cf. pp. 354–5) makes it unlikely that a decrease could contribute significantly to the clinically exaggerated stretch reflex. However, decreased presynaptic inhibition of Ia afferents with PAD does exist in some spastic patients and contributes to their stiff gait, and it may be clinically useful to evaluate its extent because there are drugs which act mainly on this mechanism.

Changes in presynaptic inhibition in patients with hemiplegia after stroke

Lower limb

In contrast to the many investigations which relied on homonymous vibratory inhibition of the soleus H reflex (an inappropriate technique, see above), the results obtained with two independent and reliable methods show that there is no change in presynaptic inhibition of Ia terminals in the lower limb of patients with hemiplegic spasticity. Thus, the amount of femoral-induced heteronymous facilitation of the soleus H reflex is similar on the affected side of hemiplegic patients and in age-matched normal subjects (Fig. 8.15(*a*), (*c*); Faist *et al.*, 1994). Similarly, presynaptic inhibition of homonymous soleus Ia terminals, as assessed with D1 inhibition of the soleus H reflex, was found to be symmetrical on the

affected and unaffected sides of hemiplegic patients after stroke, and of much the same magnitude as in normal subjects (Aymard *et al.*, 2000).

Upper limb

In contrast, in the upper limb, D1 inhibition of the FCR H reflex is significantly decreased on the affected side of patients with hemiparesis after stroke compared with normal subjects (Nakashima *et al.*, 1989; Artieda, Queseda & Obeso, 1991; Aymard *et al.*, 2000). No correlation has been found between the severity of spasticity and the reduction in D1 inhibition. The reduction in the D1 inhibition of the FCR H reflex suggests that presynaptic inhibition of FCR Ia terminals is depressed on the affected side in patients with hemiplegia. D1 inhibition was also reduced, although to a lesser extent, on the unaffected side of stroke patients (Aymard *et al.*, 2000; Chapter 12, p. 579).

Changes in presynaptic inhibition of Ia terminals in patients with spinal cord lesions

In contrast with results obtained in the lower limb of hemiplegic patients, presynaptic inhibition is consistently depressed in the lower limb of patients with spinal cord lesions, whatever the nature of the lesion.

(i) In multiple sclerosis patients, the inhibition of the soleus H reflex elicited by a tap to the tendon of biceps femoris (60 ms ISI) is reduced, and the heteronymous facilitation of the soleus H reflex is larger than in healthy subjects (Nielsen, Petersen & Crone, 1995).

(ii) In patients with amyotrophic lateral sclerosis, heteronymous vibratory inhibition of the soleus H reflex elicited by a short train of 3 taps on the tibialis anterior tendon (300 Hz, 40 ms ISI) is significantly less than in normal subjects (Pierrot-Deseilligny, 1990).

(iii) In patients with localised lesions of the spinal cord, mainly traumatic, heteronymous Ia facilitation of the soleus H reflex is significantly greater than in normal subjects (Fig. 8.15(*b*); Faist *et al.*, 1994).

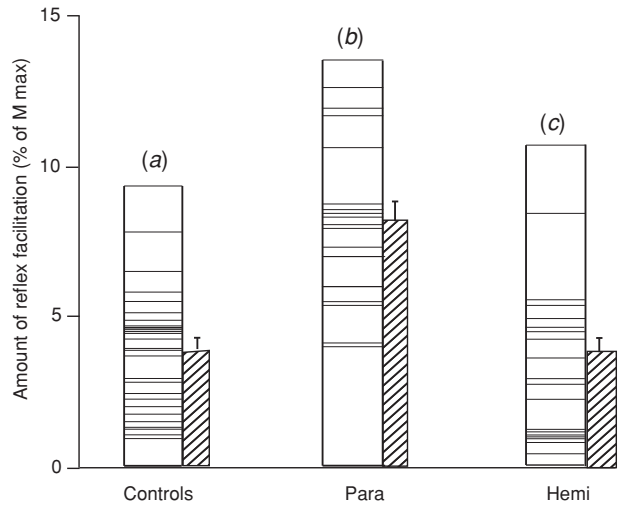


Fig. 8.15. Changes in presynaptic inhibition of femoral Ia terminals to soleus in spastic patients. The amount of heteronymous facilitation of the H reflex, produced by femoral stimulation at 4 × MT (ISI 0.4 ms after the onset of facilitation), and expressed as a percentage of M_{max}, for 28 healthy control subjects, (*a*) 17 paraplegic patients, ((*b*) 'Para', essentially traumatic) and 18 hemiplegic patients ((*c*) 'Hemi', affected side). Each horizontal bar represents one subject and the hatched columns show the mean and 1 SEM in the three populations. Modified from Faist *et al.* (1994), with permission.

(iv) Complete disappearance of D1 inhibition of the FCR H reflex was observed in two patients with tetraplegia due to a spinal cord lesion at C5–C6 (Aymard *et al.*, 2000).

Whatever the nature of the lesion, no correlation has been found between the amount of reflex facilitation and the severity of spasticity.

Mechanisms underlying changes in presynaptic inhibition in spastics

Cerebral lesions

The different effects on presynaptic inhibition of Ia afferents of the lower and upper limbs after unilateral corticospinal lesion in patients with hemiplegia are in keeping with the normal pattern of corticospinal control on PAD interneurones in the lumbar and cervical enlargements: depression of lumbar and

facilitation of cervical PAD interneurones (pp. 350–3). If the corticospinal control was normally exerted tonically, corticospinal lesions would be expected to produce a decrease in presynaptic inhibition of Ia terminals on FCR and an increase in presynaptic inhibition of Ia terminals on soleus. The former has been found consistently, but the latter has not been observed. This might reflect a normal tonic corticospinal control of PAD interneurones in the cervical spinal cord, but not the lumbar cord. This would imply that the organisation of the cortical control of presynaptic inhibition in the upper and lower limbs might be different not only in its sign (dominant facilitation versus depression) but also in its character (tonic or not). However, this view is not supported by evidence from parkinsonian patients (p. 371).

Spinal cord lesions

Whatever the lesion in the spinal cord, presynaptic inhibition is decreased on Ia terminals of the lower limb. This cannot be due to the interruption of the corticospinal tract (which, if anything, would produce increased presynaptic inhibition of Ia terminals in the lumbar enlargement, see above). It therefore probably results from interruption of other descending pathways which help maintain a tonic level of presynaptic inhibition of Ia terminals in normal subjects under resting conditions (e.g. pathway [2] in Fig. 8.1(*a*) mediating descending suppression of inhibitory interneurones transmitting cutaneous inhibition of first-order PAD interneurones).

Changes in presynaptic inhibition and pathophysiology of spasticity

Several findings suggest that the changes in presynaptic inhibition of Ia terminals observed in spastic patients may play little pathophysiological role in the motor disability or spasticity as assessed under resting conditions (cf. Aymard *et al.*, 2000).

(i) There is no correlation between the extent to which presynaptic inhibition is decreased and the severity of spasticity or motor impairment in the corresponding muscle(s).

(ii) Although the Achilles tendon jerk was clearly exaggerated on the affected side of most hemiplegic patients, there was no evidence for decreased presynaptic inhibition of Ia terminals on soleus, even in patients with a lesion in the territory of the anterior cerebral artery.

(iii) Presynaptic inhibition of FCR Ia afferents is also reduced, although to a lesser extent, on the 'unaffected' non-spastic upper limb of patients with hemiplegia in the absence of any other evidence to suggest spasticity or motor impairment.

Changes in presynaptic inhibition during motor tasks in spastic patients

A decrease in presynaptic inhibition of Ia terminals may not be responsible for the stretch reflex exaggeration which characterises spasticity measured at rest, but the lack of control of PAD interneurones during motor tasks could still contribute to the motor disability of these patients. This has been examined during both voluntary movement and gait.

Changes in presynaptic inhibition during voluntary contraction

In spastic multiple sclerosis patients, presynaptic inhibition of homonymous soleus Ia terminals was decreased at rest and not reinforced at the onset of voluntary ankle dorsiflexion (Morita *et al.*, 2001). Nevertheless, given the low sensitivity of the stretch reflex to presynaptic inhibition of Ia terminals (cf. pp. 354–5), it is probable that the absence of increase in presynaptic inhibition of antagonistic Ia terminals is not the main mechanism responsible for the occurrence of a stretch reflex in the antagonistic muscle during voluntary movement (see Chapter 12, pp. 574–5).

Changes in presynaptic inhibition during gait

The absence of the normal modulation of the presynaptic inhibition of Ia terminals could contribute to the stiff spastic gait of patients with spinal cord lesions. Modulation of the soleus H reflex of patients

with spinal cord injuries has been examined during treadmill walking (Yang, Stein & James, 1991). The most common pattern observed was a lack of H reflex modulation throughout the stance phase and slight depression of the reflex in the swing phase, considerably less modulation than in normal subjects under comparable walking conditions (see Fig. 8.14). The responsible abnormality is probably lack of modulation of presynaptic inhibition of soleus Ia terminals. In normal subjects, there is a profound modulation of the quadriceps tendon jerk throughout the step cycle, with the reflex peaking in early stance and then decreasing progressively until almost abolished during the swing phase. Reflex modulation throughout the step cycle is reduced on the affected side of hemiplegic patients, and almost completely abolished in patients with spinal lesions (Faist *et al.*, 1999). The authors argued that these differences reflect differences in the modulation of presynaptic inhibition of Ia terminals on quadriceps motoneurones.

Changes in presynaptic inhibition in Parkinson's disease

The depression of the soleus H reflex by prolonged homonymous vibration on the Achilles tendon is not modified with respect to normal subjects (Delwaide, Pepin & Maertens de Noordhout, 1993), but homonymous vibration produces complex effects which are difficult to interpret (see Chapter 12, p. 587). Others studies indicate that presynaptic inhibition is decreased in Parkinson's disease.

Upper limb

Radial-induced D1 inhibition of the FCR H reflex is decreased in patients with Parkinson's disease (Lelli, Panizza & Hallett, 1991). The finding of similar results for both sides in asymmetrical patients indicates that the abnormality does not correlate with the degree of rigidity. However, inconsistent results have been reported. Only the late inhibition at ISIs of 70–100 ms was found to be reduced in the patients explored by Tsai, Chen & Lu (1997), and Nakashima *et al.* (1994) also found no reduction of the radial-induced D1 inhibition of the FCR H reflex at ISIs around 20 ms.

Lower limb

(i) Inhibition of the soleus H reflex by a heteronymous tendon tap is reduced in parkinsonian patients, all of whom were taking dopaminergic medication (Roberts *et al.*, 1994). No significant relationship has been found between the amount of presynaptic inhibition so assessed and various clinical variables: rigidity in limb studied, Webster rating, duration of disease, duration of dopaminergic treatment.

(ii) The soleus H reflex facilitation induced by femoral stimulation is significantly increased in patients with Parkinson's disease (Morita *et al.*, 2000b). There was no correlation between the decrease in presynaptic inhibition and grade of rigidity or disease severity on the Hoehn and Yahr scale, but the decrease in presynaptic inhibition was significantly correlated with the degree of bradykinesia and the time required to walk 10 m. Of particular interest was the finding that, in those patients who were responsive to L-dopa and were examined on and off the medication, the amount of presynaptic inhibition increased with L-dopa along with improvement in both bradykinesia and walking speed. This suggests that a descending pathway controls tonic presynaptic inhibition of Ia terminals through a dopa-responsive mechanism (though it does not imply that the descending pathway itself is dopaminergic).

Changes in presynaptic inhibition of Ia terminals in patients with dystonia

Changes in radial-induced D1 inhibition of the FCR H reflex

Decreased presynaptic inhibition of FCR Ia terminals

The co-contraction of agonists and antagonists typical of dystonia suggests a breakdown of the normal

pattern of reciprocal innervation between opposing muscles. Radial-induced inhibition of the FCR H reflex has been investigated in patients with different types of dystonia: simple occupational cramp (i.e. a task-specific focal action dystonia), dystonic occupational cramp (the focal action dystonia was also evident in other manual acts than writing), blepharospasm, spasmodic torticollis, generalised dystonia and symptomatic hemidystonia related to lesions of the contralateral basal ganglia (Panizza, Hallett & Cohen, 1987; Panizza *et al.*, 1990; Nakashima *et al.*, 1989). The consistent finding is that the second phase of the radial-induced D1 inhibition of the FCR H reflex was decreased in all types of dystonia. The more severe the dystonia the more marked was the decrease in presynaptic inhibition. An interesting finding of these studies is that disynaptic non-reciprocal group I inhibition was not depressed in the patients studied by the Queen Square group (Nakashima *et al.*, 1989; Huang *et al.*, 2004). This suggests that the CNS dysfunction underlying dystonia causes a specific change in the descending control of PAD interneurones. It is also interesting that a similar decrease in radial-induced D1 inhibition of the FCR H reflex was also observed in the unaffected 'normal' arm of patients with writer's cramp (Chen, Tsai & Lu, 1995). This is in keeping with the finding that abnormalities of the hand representation in sensory cortex are more obvious in the hemisphere driving the non-dystonic limb, even though they are correlated to the severity of the dystonic limb motor impairment (Meunier *et al.*, 2001).

Differential effect of repetitive TMS (rTMS) on the second and late phases of radial-induced depression of the FCR H reflex

The second phase and the late phase of the radial-induced inhibition of the FCR H reflex (cf. p. 344) are decreased in patients with generalised dystonia associated with the DYT1 gene mutation. After 20 minutes of 1 Hz rTMS over the premotor area, a significant increase in the late inhibition occurred whereas the second phase was not modified. This result supports the hypothesis that, while the second phase is due to presynaptic inhibition of Ia terminals, the late phase may involve long-loop inhibitory connections to the brainstem (spino-bulbo-spinal) or even the cerebral cortex (Huang *et al.*, 2004).

Possible decrease in group III-induced presynaptic inhibition of ECR Ia afferents

In normal subjects, electrical stimulation over the ECR tendon elicits a transient inhibition of the ongoing ECR EMG activity. It has been argued that this suppression is due to slowly conducting afferents from the tendon (possibly group III) activating presynaptic inhibition of Ia terminals (Priori *et al.*, 1998). This suppression is not modified in patients with *simple* occupational dystonia, but is decreased in patients with generalised dystonia (Lorenzano *et al.*, 2000). The latter finding could reflect decreased presynaptic inhibition of Ia terminals, but this conclusion needs to be confirmed by techniques assessing presynaptic inhibition more specifically.

Conclusions

Role of changes in presynaptic inhibition of Ia terminals in normal motor control

Changes in presynaptic inhibition of Ia terminals may have little effect on the reflex response to abrupt stretch. Instead, the role of changes in the presynaptic gating during motor tasks probably lies in the modulation of physiological feedback from primary endings, i.e. in modulation of natural background Ia inputs and changes in discharge of relatively low rate. So far, the changes in the gating of the Ia inflow during movement appear to be significant only in the lower limb.

During flexion-extension movements, the focused corticospinal drive produces a decrease in presynaptic inhibition of Ia terminals to motoneurones

responsible for the movement. This ensures that the full feedback excitatory support from primary muscle spindle endings is available to active motoneurones. In parallel, presynaptic inhibition is enhanced on heteronymous Ia terminals on inactive motoneurone pools. The corticospinal control of presynaptic inhibition selectively 'opening' Ia transmission to motoneurones voluntarily activated, while 'closing' transmission to motoneurones of relaxed muscle(s), increases motor contrast and contributes to the selective activation of muscles in discrete movements.

During voluntary co-contraction of ankle flexors and extensors and during active standing, presynaptic inhibition of Ia terminals of ankle muscles is increased. This probably contributes to the depression of reciprocal Ia inhibition required for co-contractions involving antagonistic muscles.

The decrease in presynaptic inhibition of quadriceps Ia terminals during active standing and in the early part of the stance phase of gait ensures that excitatory Ia feedback is available to provide a safety factor to the quadriceps contraction, when it must support much of the body weight. At the end of the stance phase of gait, presynaptic inhibition of soleus Ia terminals is markedly increased, to help limit the activation of ankle extensor motoneurones and allow the body to move forward.

Changes in presynaptic inhibition and pathophysiology of movement disorders

Spasticity

Contrary to what has long been claimed, presynaptic inhibition of Ia terminals is not modified in the lower limb of hemiplegic patients at rest. There is a decrease in presynaptic inhibition of Ia terminals in patients with spinal cord lesions, but there is no correlation between the extent to which presynaptic inhibition is decreased and the severity of spasticity or motor impairment in the corresponding muscle(s). However, the absence of modulation of presynaptic inhibition of Ia terminals to soleus and quadriceps motoneurones probably contributes to the stiff gait of these patients.

Parkinson's disease

Presynaptic inhibition of Ia terminals is decreased in patients with Parkinson's disease, and this decrease is related to the severity of gait disturbance.

Dystonia

The CNS dysfunction underlying dystonia causes a decrease in presynaptic inhibition of forearm Ia terminals.

Résumé

Background from animal experiments

Presynaptic inhibition of Ia terminals is accompanied by primary afferent depolarisation (PAD) and reduces the size of monosynaptic Ia EPSPs in motoneurones without change in the motoneurone membrane or its conductance (i.e. without an IPSP in motoneurones). Presynaptic inhibition is a potent mechanism since, in the acute spinal cat, it can completely suppress the monosynaptic reflex. It has a long central delay (∼5 ms) and a long duration (300–400 ms). The shortest pathway mediating presynaptic inhibition of Ia terminals has two interposed interneurones (referred to as PAD interneurones), the last-order being $GABA_A$-ergic. First-order PAD interneurones are excited by Ib and (to a lesser extent) Ia afferents mainly from flexor muscles, and also by projections from vestibular nuclei. They are inhibited through inhibitory interneurones onto which cutaneous and corticospinal inputs converge. The dominant effect of corticospinal volleys on PAD interneurones is depression, and this normally

masks an opposite facilitatory effect. Last-order PAD interneurones are powerfully inhibited from different reticulospinal pathways.

Methodology

Discrepancy between the variations in the on-going EMG and those in the H reflex

It was reasoned that changes in presynaptic inhibition of Ia terminals should affect the H reflex more than the on-going EMG. However, discrepancies between the H reflex and the on-going EMG may also result from other factors.

Activating PAD interneurones by a conditioning volley to assess their excitability

Underlying principle

PAD interneurones mediating presynaptic inhibition of Ia afferents responsible for the afferent volley of the test H reflex are activated by a conditioning volley. The resulting reflex depression depends on the excitability of PAD interneurones, and the greater their excitability, the greater the reflex depression.

Prolonged vibration of the homonymous tendon is a flawed technique

Application of vibration to the Achilles tendon produces marked depression of the soleus H reflex, which reflects a presynaptic mechanism. It was long accepted that this mechanism was presynaptic inhibition with PAD. However, when the conditioning vibration is applied on the homonymous tendon, other mechanisms contribute to the reflex depression: post-activation depression, evoked by repetitive activation of the Ia fibre-motoneurone synapse (see Chapter 2, pp. 96–9); and elevated threshold of the Ia afferents responsible for the H reflex, such that a greater current is required to produce the same afferent volley. Accordingly, the H reflex suppression will be caused by a number of factors, and it cannot be used to estimate presynaptic inhibition of Ia terminals with PAD.

Presynaptic inhibition evoked by a heteronymous group I volley

To eliminate the problems associated with prolonged vibration of the homonymous tendon, brief vibration (train of three shocks or single tap) is applied to the tendon of a heteronymous muscle. The resulting Ia volley activates PAD interneurones and evokes a long-lasting (200–300 ms) depression of the H reflex due to presynaptic inhibition of Ia afferents. A different technique measures the 'D1' inhibition of the H reflex elicited by an electrical volley to group I afferents in the nerve supplying muscles antagonistic to the motoneurone pool tested. A radial volley depresses the FCR H reflex at ISIs of 5–20 ms due to presynaptic inhibition of FCR Ia terminals. Similarly a stimulus to the common peroneal nerve elicits a long lasting inhibition of the H reflex of soleus with two phases, 'D1' (5–30 ms) and 'D2' (70–200 ms), due to presynaptic inhibition of soleus Ia terminals.

Limitations

The amplitude of the test reflex is the net result of presynaptic inhibition and of a late post-synaptic facilitation; a change in the reflex depression in a given situation could reflect a change in the recruitment gain in the motoneurone pool; a more serious drawback is that decreased vibratory or D1/D2 inhibition may reflect decreased excitability of PAD interneurones, but could also result from increased excitability, if there is occlusion between the conditioning volley and 'natural' excitatory inputs.

Routine studies

Vibration (3 shocks at 200 Hz) or single tap is applied to the tendon of the tibialis anterior or the biceps femoris 40–60 ms before the test stimulus eliciting the soleus H reflex. D1 inhibition of the soleus H

reflex is evoked by a train of 3 shocks (at 300 Hz, 1.2 × MT) to the common peroneal nerve with the first shock 21 ms before the stimulus eliciting the H reflex. D1 inhibition of the FCR H reflex is elicited by a radial volley (single shock, ≤1 × MT) 10–20 ms before the stimulus evoking the FCR H reflex.

Assessing monosynaptic Ia facilitation of the H reflex

This technique measures the on-going presynaptic inhibition exerted on Ia terminals of the *conditioning* volley. Thus, the test reflex is facilitated by a monosynaptic Ia volley, generally heteronymous. During its first 0.6 ms the reflex facilitation depends only on the size of the conditioning Ia EPSP. A constant conditioning stimulus should elicit a constant degree of reflex facilitation, unless there is a change in presynaptic inhibition of Ia afferents mediating the conditioning volley. The larger the reflex facilitation, the smaller the presynaptic inhibition. However, changes in the amount of reflex facilitation can also be due to a change in the recruitment gain of the motoneurone pool (see pp. 18–20). The method requires that the conditioning heteronymous volley elicits a sizeable facilitation of the test reflex. In practice this is usually the case for the femoral-induced facilitation of the soleus H reflex and for the facilitation of the FCR H reflex elicited by stimulation of Ia afferents from the intrinsic hand muscles. The earliest conditioning-test interval (I_0) at which it is possible to elicit heteronymous Ia facilitation of the test reflex is first established using 0.1–0.2 ms steps, and the ISI is then set to be 0.4–0.6 ms later than I_0.

How to eliminate changes in the recruitment gain in the motoneurone pool

(i) The only way to exclude with certainty a change in the recruitment gain in the motoneurone pool is to confirm results obtained with the compound H reflex in *single motor units*. The first 0.6 ms of the peak of homonymous or heteronymous monosynaptic Ia excitation in the PSTHs of single units contains the only unequivocally monosynaptic component of the increased probability of firing. Changes in the size of this initial part of the peak faithfully reflect changes in presynaptic inhibition of the corresponding Ia terminals, provided that the firing rate of the motor unit is stable. The method cannot be used during phasic contractions, in which case the H reflex of a single motor unit might be used (see Chapter 1, pp. 37–9).

(ii) When using the compound H reflex, the problem of a change in recruitment gain can be tested by comparing the changes in monosynaptic facilitation of the reflex and those in D1 or vibratory inhibition. A change in the recruitment gain that produced an increase in the slope of the input-output relationship of the motoneurone pool should enhance both the amount of heteronymous reflex facilitation and the amount of the D1 or vibratory suppression, whereas a decrease in presynaptic inhibition of Ia terminals should enhance the monosynaptic facilitation and decrease the D1 or vibratory suppression.

Organisation and pattern of connections

(i) Presynaptic inhibition is stronger on Ia terminals on motoneurones supplying slow-twitch units than on those innervating fast-twitch units. As a result, when presynaptic inhibition of Ia afferents is active, the probability of discharge to the monosynaptic Ia input may be reversed in favour of fast-twitch units, i.e. the opposite of the usual order of recruitment.

(ii) The pathways mediating presynaptic inhibition of Ia terminals are organised in subsets with regard to the target motoneurones to which Ia afferents project. Thus, presynaptic inhibition of homonymous and heteronymous Ia projections from one muscle to different motoneurone pools is mediated through different subsets of PAD interneurones with a different control of first-order PAD interneurones. Conversely, presynaptic inhibition of homonymous and heteronymous Ia terminals projecting to a given motoneurone pool is in all likelihood mediated through the same subset of first-order PAD interneurones.

(iii) PAD interneurones are excited from Ia afferents and probably from Ib afferents, and are inhibited by cutaneous afferents.

(iv) Cortical stimulation can produce inhibition and facilitation of PAD interneurones, and the dominant effect is different in the upper and lower limbs: corticospinal facilitation of PAD interneurones in the cervical enlargement and corticospinal inhibition in the lumbar enlargement. The focused corticospinal drive to PAD interneurones in the lumbar enlargement suggests that the same cortical site both activates motoneurones of a given pool and depresses PAD interneurones mediating presynaptic inhibition of Ia terminals projecting to that pool.

(v) Vestibulospinal and group I inputs converge onto common interneurones facilitating presynaptic inhibition of Ia terminals in the lower limb.

(vi) A stimulus that produces significant presynaptic inhibition of the afferent volley of the H reflex barely suppresses the spinal reflex response to abrupt stretch. This suggests that presynaptic inhibition might effectively modulate physiological feedback signals, without interfering with compensation for abrupt transients.

Motor tasks and physiological implications

Ia terminals on lower-limb motoneurones involved in voluntary contraction

At the onset of a selective voluntary contraction of one muscle, presynaptic inhibition of Ia terminals on motoneurones of the contracting muscle is decreased below its level at rest or during a tonic contraction with an equivalent level of voluntary EMG activity. This effect is highly selective and of similar magnitude on both homonymous and heteronymous Ia terminals projecting to the motoneurones responsible for the contraction (see below). The decrease in presynaptic inhibition appears 50 ms before the onset of the movement, persists unchanged during the first half of the ramp phase of a ramp-and-hold contraction whatever the ramp duration (250–1000 ms), and then abruptly returns to its control value. The stronger the force at the end of the ramp the greater the decrease in presynaptic inhibition at the onset of the ramp. This control of presynaptic inhibition is achieved through descending control of PAD interneurones, pre-programmed before movement onset according to the likely strength and duration of the contraction at the end of the ramp. The focused corticospinal drive seen in experiments using cortical stimulation is a good candidate for this descending control. The resulting increase in the gain in the monosynaptic Ia loop assures that full feedback support from primary spindle endings is available to motoneurones activated in the movement. At the beginning of a movement, before the load is known, a high gain might allow the reflex pathway to compensate rapidly for errors in estimation of the load. Later, the decrease in presynaptic inhibition disappears and the gain of the monosynaptic loop returns to its control value but, by that time, other mechanisms are available to maintain the desired trajectory and, in addition, the decrease in the gain is required to prevent oscillations from developing. Similarly, during tonic voluntary contractions, presynaptic inhibition of Ia terminals on motoneurones of the contracting muscle is not decreased or is hardly so.

Ia terminals on motoneurones of inactive synergistic muscles of the lower limb

The decreased presynaptic inhibition of homonymous Ia afferents seen at the onset of a selective voluntary contraction of a muscle is accompanied by increased presynaptic inhibition of the collaterals of these Ia afferents to inactive heteronymous muscles. This increase is descending in origin. Transjoint monosynaptic Ia connections are well developed in human subjects, probably to provide the more elaborate reflex assistance required for bipedal stance and gait. However, during isolated contractions of one muscle, the Ia discharge from the contracting muscle will tend to excite motoneurones linked by Ia connections. Enhanced presynaptic inhibition of

heteronymous Ia terminals to other motoneurone pools prevents these pools from being activated.

Ia afferents to antagonists

Presynaptic inhibition is increased on Ia afferents projecting to motoneurones antagonistic to the voluntarily activated motoneurone pool. This increase becomes significant only when PAD interneurones are activated by the peripheral feedback. During co-contraction of antagonistic muscles, the increase in presynaptic inhibition is significantly greater, and probably contributes to the depression of reciprocal Ia inhibition, through presynaptic suppression of the peripheral input to Ia interneurones.

Presynaptic inhibition in the upper limb

In the upper limb, there is a slight decrease in presynaptic inhibition of Ia terminals to motoneurones of the contracting muscle at the onset of a voluntary contraction, but this decrease differs from that observed in the lower limb in several respects: (i) the decrease is quantitatively less prominent; (ii) there is a similar decrease during tonic contractions; and (iii) there is a decrease of similar magnitude during voluntary contractions of antagonistic muscles. The lack of specificity in this slight depression suggests reticulospinal depression.

Stance and gait

(i) *Presynaptic inhibition of quadriceps* Ia terminals is decreased during standing without support and in the early part of the stance phase of gait. In the early stance phase of walking, as in standing, the quadriceps contraction may need to support much of the body weight. The decreased presynaptic inhibition of homonymous quadriceps Ia terminals then observed assures that the excitatory Ia feedback is available to reinforce the quadriceps contraction.

(ii) *Presynaptic inhibition of soleus* Ia terminals is increased throughout the step cycle, particularly at the end of the stance phase and during the swing phase. During the stance phase, the triceps surae contraction resists the passive ankle dorsiflexion, and the triceps surae tension must be overcome to allow the body to move forward. The increased presynaptic inhibition of the homonymous Ia excitatory feedback contributes to this. During standing without support, the increased presynaptic inhibition of soleus Ia terminals could contribute to the depression of reciprocal Ia inhibition, through presynaptic inhibition of the Ia input to interneurones of reciprocal Ia inhibition.

Studies in patients and clinical implications

Methodology

Studying changes in the inhibition of a test H reflex elicited by a heteronymous tap or an electrical stimulus (D1) is the simplest and most convenient method for clinical use. There is a progressive decrease in the amount of femoral-induced facilitation and in heteronymous inhibition of the soleus H reflex with ageing, and this must be taken into account when investigating patients.

Spasticity

Over-interpretation of findings using prolonged vibration of the homonymous tendon

A decrease in presynaptic inhibition of Ia terminals has long been considered one of the spinal mechanisms underlying the stretch reflex exaggeration characteristic of spasticity. This conclusion is, however, flawed: the method used to investigate presynaptic inhibition was vibratory inhibition of the homonymous tendon, and the vibration-induced depression of the H reflex is then also caused by post-activation depression and by activity-dependent hyperpolarisation of Ia afferents. The former is decreased in spastic patients (see Chapter 2, pp. 99–100).

Stroke patients

There is no change in presynaptic inhibition of Ia terminals in the lower limb of spastic patients with

hemiplegia. In the upper limb, presynaptic inhibition of FCR Ia terminals is consistently reduced on the affected side of hemiplegic patients.

Patients with spinal cord lesions

Whatever the lesion in the spinal cord (traumatic, multiple sclerosis, amyotrophic lateral sclerosis), presynaptic inhibition of Ia terminals is decreased in the lower limb. This reflects the interruption of descending pathways which help maintain a tonic level of presynaptic inhibition of Ia terminals in normal subjects under resting conditions.

Conclusions

There is a decrease in presynaptic inhibition of Ia terminals in patients with spinal cord lesions and in the upper limb of stroke patients. This abnormality does not seem to be responsible for the undue stretch reflex exaggeration observed at rest or for the occurrence of a stretch reflex during voluntary contraction of the antagonistic muscle. However, the absence of modulation of presynaptic inhibition of Ia terminals to soleus and quadriceps motoneurones may contribute to the stiff gait of patients with spinal cord lesions or stroke.

Parkinson's disease

There is evidence for a decrease in presynaptic inhibition. Of particular interest was the finding that in those patients who were examined on and off L-dopa medication, the amount of presynaptic inhibition increased with L-dopa treatment along with improvement in bradykinesia and walking speed.

Dystonia

The radial-induced D1 inhibition of the FCR H reflex is decreased in all types of dystonia. The more severe the dystonia the more marked the decrease in presynaptic inhibition. This was observed on both sides of patients with simple writer's cramp, and seems therefore to be related to the primary neuronal dysfunction.

REFERENCES

Aimonetti, J. M., Vedel, J. P., Schmied, A. & Pagni, S. (2000a). Distribution of presynaptic inhibition on type-identified motoneurones in the extensor carpi radialis pool in man. *Journal of Physiology (London)*, **522**, 125–35.

(2000b). Mechanical cutaneous stimulation alters Ia presynaptic inhibition in human wrist extensor muscles: a single motor unit study. *Journal of Physiology (London)*, **522**, 137–45.

Andén, N. E., Jukes, M. G., Lundberg, A. & Vyklický, L. (1966). The effect of DOPA on the spinal cord. 3. Depolarization evoked in the central terminals of ipsilateral Ia afferents by volleys in the flexor reflex afferents. *Acta Physiologica Scandinavica*, **68**, 322–36.

Aniss, A. M., Diener, H. C., Hore, J., Gandevia, S. C. & Burke, D. (1990). Behavior of human muscle receptors when reliant on proprioceptive feedback during standing. *Journal of Neurophysiology*, **64**, 661–70.

Artieda, J., Queseda, P. & Obeso, J. A. (1991). Reciprocal inhibition between forearm muscles in spastic hemiplegia. *Neurology*, **41**, 286–9.

Ashby, P., Verrier, M. & Carleton, S. (1980). Vibratory inhibition of the monosynaptic reflex. In *Progress in Clinical Neurophysiology*, vol. 8, ed. J. E. Desmedt, pp. 254–62. Basel: Karger.

Aymard, C., Katz, R., Lafitte, C. *et al.*, (2000). Presynaptic inhibition and homosynaptic depression: a comparison between lower and upper limbs in normal subjects and patients with hemiplegia. *Brain*, **123**, 1688–702.

Aymard, C., Baret, M., Katz, R., Lafitte, C., Pénicaud, A. & Raoul, S. (2001). Modulation of presynaptic inhibition of Ia afferents during voluntary wrist flexion and extension in man. *Experimental Brain Research*, **137**, 127–31.

Barnes, C. D. & Pompeiano, O. (1970a). Inhibition of monosynaptic extensor reflex attributable to presynaptic depolarisation of the group Ia afferent fibres produced by vibration of a flexor muscle. *Archives Italiennes de Biologie*, **108**, 233–58.

(1970b). Presynaptic and postsynaptic effects in the monosynaptic reflex pathway to extensor motoneurones following vibration of synergic muscles. *Archives Italiennes de Biologie*, **108**, 259–94.

Berardelli, A., Day, B. L., Marsden, C. D. & Rothwell, J. C. (1987). Evidence favouring presynaptic inhibition between antagonist muscle afferents in the human forearm. *Journal of Physiology (London)*, **391**, 71–83.

Binder, M. D., Kroin, J. S., Moore, G. P. & Stuart, D. G. (1977). The response of Golgi tendon organs to single motor unit contractions. *Journal of Physiology (London)*, **271**, 337–49.

Burke, D. & Ashby, P. (1972). Are spinal 'presynaptic' inhibitory mechanisms suppressed in spasticity? *Journal of the Neurological Sciences*, **15**, 321–6.

Burke, D., Hagbarth, K.-E., Löfstedt, L. & Wallin, B. G. (1976). The response of human muscle spindle endings to vibration of non-contracting muscles. *Journal of Physiology (London)*, **261**, 673–93.

Burke, D., Gracies, J. M., Mazevet, D., Meunier, S. & Pierrot-Deseilligny, E. (1994). Non monosynaptic transmission of the cortical command for voluntary movement in man. *Journal of Physiology (London)*, **480**, 191–207.

Butchart, P., Farquhar, R., Part, N. J. & Roberts, R. C. (1993). The effect of age and voluntary contraction on presynaptic inhibition of soleus muscle Ia afferent terminals in man. *Experimental Physiology*, **78**, 235–42.

Calancie, B., Broton, J. G., Klose, K. J., Traad, M., Difini, J. & Ayyar, D. R. (1993). Evidence that alterations in presynaptic inhibition contribute to segmental hypo- and hyperexcitability after spinal cord injury in man. *Electroencephalography and Clinical Neurophysiology*, **89**, 177–86.

Capaday, C. & Stein, R. B. (1986). Amplitude modulation of the soleus H-reflex in the human during walking and standing. *Journal of Neuroscience*, **6**, 1308–13.

(1987) Difference in the amplitude of the human soleus H-reflex during walking and running. *Journal of Physiology (London)*, **392**, 513–22.

Capaday, C., Lavoie, B. A. & Cormeau, F. (1995). Differential effects of a flexor nerve input on the soleus H-reflex during standing and walking. *Canadian Journal of Physiology and Pharmacology*, **73**, 436–49.

Carpenter, D., Engberg, I. & Lundberg, A. (1966). Primary afferent depolarization evoked from the sensorimotor cortex. *Acta Physiologica Scandinavica*, **59**, 126–42.

Cavallari, P. & Katz, R. (1989). Pattern of projections of group I afferents from forearm muscles to motoneurones supplying biceps and triceps muscles in man. *Experimental Brain Research*, **78**, 465–78.

Chen, R. S., Tsai, C. H. & Lu, C. S. (1995). Reciprocal inhibition in writer's cramp. *Movement Disorders*, **10**, 556–61.

Childers, M. K., Biswas, S. S., Petroski, G. & Merveille, O. (1999). Inhibitory casting decreases a vibratory inhibition index of the H-reflex in the spastic upper limb. *Archives of Physical Medicine and Rehabilitation*, **80**, 714–16.

Coppin, C. M., Jack, J. J. B. & MacLennan, C. R. (1970). A method for the selective electrical activation of tendon organ afferent fibres from the cat soleus muscle. *Journal of Physiology (London)*, **210**, 18P–20P.

Crone, C. & Nielsen, J. (1989a). Spinal mechanisms in man contributing to reciprocal inhibition during voluntary dorsiflexion of the foot. *Journal of Physiology (London)*, **416**, 255–72.

(1989b). Methodological implications of the post-activation depression of the soleus H-reflex in man. *Experimental Brain Research*, **78**, 28–32.

De Gail, P., Lance, J. W. & Neilson, P. D. (1966). Differential effects on tonic and phasic reflex mechanisms produced by vibration of muscle in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **29**, 1–11.

Delwaide, P. J. (1973). Human monosynaptic reflexes and presynaptic inhibition. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 508–22. Basel: Karger.

(1993). Pathophysiological mechanisms of spasticity at the spinal cord level. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 296–308. Berlin: Springer.

Delwaide, P. J. & Pennisi, G. (1994). Tizanidine and electrophysiologic analysis of spinal control mechanisms in humans with spasticity. *Neurology*, **44**, S21–7; S27–8.

Delwaide, P. J., Pepin, J. L. & Maertens de Noordhout, A. (1993). The audiospinal reaction in Parkinsonian patients reflects functional changes in reticular nuclei. *Annals of Neurology*, **33**, 63–9.

Desmedt, J. E. & Godaux, E. (1978). Mechanism of the vibration paradox: excitatory and inhibitory effects of tendon vibration on single soleus muscle motor units in man. *Journal of Physiology (London)*, **285**, 197–207.

Devanandan, M. S., Eccles, R. M. & Yokota, T. (1965). Muscle stretch and the presynaptic inhibition of the group Ia pathway to motoneurones. *Journal of Physiology (London)*, **179**, 430–41.

Devanandan, M. S., Eccles, R. M. & Stenhouse, D. (1966). Presynaptic inhibition evoked by muscle contraction. *Journal of Physiology (London)*, **185**, 471–85.

Dietz, V., Quintern, J. & Berger, W. (1985). Afferent control of human stance and gait: evidence for blocking group I afferents during gait. *Experimental Brain Research*, **61**, 153–63.

Dietz, V., Faist, M. & Pierrot-Deseilligny, E. (1990). Amplitude modulation of the quadriceps H-reflex in the human during the early stance phase of gait. *Experimental Brain Research*, **79**, 221–4.

Eccles, J. C. (1964). *The Physiology of Synapses*, 316 pp. Berlin: Springer Verlag.

Eccles, J. C., Magni, F. & Willis, W. D. (1962a). Depolarization of central terminals of group I afferent fibres from muscles. *Journal of Physiology (London)*, **160**, 62–93.

Eccles, J. C., Kostyuk, P. G. & Schmidt, R. F. (1962b). Central pathways responsible for depolarization of primary afferent fibres. *Journal of Physiology (London)*, **161**, 237–57.

Eccles, J. C., Schmidt, R. F. & Willis, W. D. (1962c). Presynaptic inhibition of the spinal monosynaptic reflex pathway. *Journal of Physiology (London)*, **161**, 282–97.

Eguibar, J. R., Quevedo, J., Jimenez, I. & Rudomin, P. (1994). Selective cortical control of information flow through different intraspinal collaterals of the same muscle afferent fiber. *Brain Research*, **643**, 328–33.

El-Tohamy, A. & Sedgwick, E. M. (1983). Spinal inhibition in man: depression of the soleus H reflex by stimulation of the nerve to the antagonist muscle. *Journal of Physiology (London)*, **337**, 497–508.

Enriquez-Denton, M., Nielsen, J., Perrault, M., Morita, H., Petersen, N. & Hultborn, H. (2000) Presynaptic control of transmission along the pathway mediating disynaptic reciprocal inhibition in the cat. *Journal of Physiology (London)*, **526**, 623–37.

Faist, M., Mazevet, D., Dietz, V. & Pierrot-Deseilligny, E. (1994). A quantitative assessment of presynaptic inhibition of Ia afferents in spastics. Differences in hemiplegics and paraplegics. *Brain*, **117**, 1449–55.

Faist, M., Dietz, V. & Pierrot-Deseilligny, E. (1996). Modulation of presynaptic inhibition of Ia afferents during human gait. *Experimental Brain Research*, **109**, 441–9.

Faist, M., Ertel, M., Berger, W. & Dietz, V. (1999). Impaired modulation of quadriceps tendon jerk reflex during spastic gait: differences between cerebral and spinal lesions. *Brain*, **122**, 567–79.

Ferris, D. P., Aagaard, P., Simonsen, E. B., Farley, C. T. & Dyhre-Poulsen, P. (2001). Soleus H-reflex gain in humans walking and running under simulated reduced gravity. *Journal of Physiology (London)*, **530**,167–80.

Fetz, E. E., Jankowska, E., Johannisson, T. & Lipski, J. (1979). Autogenetic inhibition of motoneurones by impulses in group Ia muscle spindle afferents. *Journal of Physiology (London)*, **293**, 173–95.

Frank, K. & Fuortes, M. G. F. (1957). Presynaptic and postsynaptic inhibition of monosynaptic reflexes. *Federation Proceedings*, **16**, 39–40.

Gillies, J. D., Lance, J. W., Neilson, P. D. & Tassinari, C. A. (1969). Presynaptic inhibition of the monosynaptic reflex by vibration. *Journal of Physiology (London)*, **205**, 329–39.

Gracies, J. M., Pierrot-Deseilligny, E. & Robain, G. (1994). Evidence for further recruitment of group I fibres with high stimulus intensities when using surface electrodes in man. *Electroencephalography and Clinical Neurophysiology*, **93**, 353–7.

Hagbarth, K.-E. & Eklund, G. (1966). Motor effects of vibratory muscle stimuli in man. In *Muscular Afferents and Motor Control*, ed. R. Granit, pp. 177–86. Stockholm: Almqvist & Wiksell.

Hongo, T., Jankowska, E. & Lundberg, A. (1972). The rubrospinal tract. III. Effects on primary afferent terminals. *Experimental Brain Research*, **15**, 39–53.

Huang, Y. Z., Edwards, M.J., Bhatia, K. P. & Rothwell, J. C. (2004). One-Hz repetitive transcranial magnetic stimulation of the premotor cortex alters reciprocal inhibition in DYT1 dystonia. *Movement Disorders*, **19**, 54–9.

Hultborn, H., Meunier, S., Morin, C. & Pierrot-Deseilligny, E. (1987a). Assessing changes in presynaptic inhibition of Ia fibres: a study in man and the cat. *Journal of Physiology (London)*, **389**, 729–56.

Hultborn, H., Meunier, S., Pierrot-Deseilligny, E. & Shindo, M. (1987b). Changes in presynaptic inhibition of Ia fibres at the onset of voluntary contraction in man. *Journal of Physiology (London)*, **389**, 757–72.

Hultborn, H., Illert, M., Nielsen, J., Paul, A., Ballegaard, M. & Wiese, H. (1996). On the mechanism of the post-activation depression of the H-reflex in human subjects. *Experimental Brain Research*, **108**, 450–62.

Iles, J. F. (1996). Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb. *Journal of Physiology (London)*, **491**, 197–207.

Iles, J. F. & Pisini, J. V. (1992). Vestibular-evoked postural reactions in man and modulation of transmission in spinal reflex pathways. *Journal of Physiology (London)*, **455**, 407–24.

Iles, J. F. & Roberts, R. C. (1986). Presynaptic inhibition of monosynaptic reflexes in the lower limbs of subjects with upper motoneurone disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **49**, 937–44.

(1987). Inhibition of monosynaptic reflexes in the human lower limb. *Journal of Physiology (London)*, **385**, 69–87.

Katz, R., Morin, C., Pierrot-Deseilligny, E. & Hibino, R. (1977). Conditioning of H-reflex by a preceding subthreshold tendon reflex stimulus. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 575–80.

Katz, R., Meunier, S. & Pierrot-Deseilligny, E. (1988). Changes in presynaptic inhibition of Ia fibres in man while standing. *Brain*, **111**, 417–37.

Koelman, J. H. T. M., Bour, L. J., Hilgevoord, A. A. J., van Bruggen, G. J. & Ongerboer de Visser, B. W. (1993). Soleus H-reflex tests and clinical signs of the upper motor neuron

syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **56**, 776–81.

Lelli, S., Panizza, M. & Hallett, M. (1991). Spinal inhibitory mechanisms in Parkinson's disease. *Neurology*, **41**, 553–6.

Lev-Tov, A. & Pinco, M. (1992). In vitro studies of prolonged depression in the neonatal rat spinal cord. *Journal of Physiology (London)*, **447**, 149–69.

Llewellyn, M., Yang, J. F. & Prochazka, A. (1990). Human H-reflexes are smaller in difficult beam walking than in normal treadmill walking. *Experimental Brain Research*, **83**, 22–8.

Lorenzano, C., Priori, A., Currà, A., Gilio, F., Manfredi, M. & Berardelli, A. (2000). Impaired EMG inhibition elicited by tendon stimulation in dystonia. *Neurology*, **55**, 1789–93.

Lund, S., Lundberg, A. & Vyklický, L. (1965). Inhibitory action from the flexor reflex afferents on transmission to Ia afferents. *Acta Physiologica Scandinavica*, **64**, 345–55.

Lundberg, A. (1998). Introduction. In *Presynaptic Inhibition and Neural Control*, ed. P. Rudomin, R. Romo & L. Mendell, pp. 3–10. New York: Oxford University Press.

Lundberg, A. & Vyklický, L. (1963). Inhibitory interaction between spinal reflexes to primary afferents. *Experientia*, **19**, 247–8.

Marchand-Pauvert, V., Nicolas, G. & Pierrot-Deseilligny, E. (2000). Monosynaptic Ia projections from intrinsic hand muscles to forearm motoneurones in humans. *Journal of Physiology (London)*, **525**, 241–52.

Marchand-Pauvert, V., Nicolas, G., Burke, D. & Pierrot-Deseilligny, E. (2002). Suppression of the H reflex by disynaptic autogenetic inhibitory pathways activated by the test volley. *Journal of Physiology (London)*, **542**, 963–76.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and their Central Action*. London: Arnold.

Meunier, S. & Morin, C. (1989) Changes in presynaptic inhibition of Ia fibres to soleus motoneurones during voluntary dorsiflexion of the foot. *Experimental Brain Research*, **76**, 510–18.

Meunier, S. & Pierrot-Deseilligny, E. (1989). Gating of the afferent volley of the monosynaptic stretch reflex during movement in man. *Journal of Physiology (London)*, **419**, 753–63.

(1998). Cortical control of presynaptic inhibition of Ia afferents in humans. *Experimental Brain Research*, **119**, 415–26.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta, M. (1993). Pattern of monosynaptic heteronymous Ia connections in the human lower limb. *Experimental Brain Research*, **96**, 533–44.

Meunier, S., Garnero, L., Ducorps, A. *et al.* (2001). Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization. *Annals of Neurology*, **50**, 521–7.

Mizuno, Y., Tanaka, R. & Yanagisawa, N. (1971). Reciprocal group I inhibition of triceps surae motoneurones in man. *Journal of Neurophysiology*, **34**, 1010–17.

Morin, C., Katz, R., Mazières, L. & Pierrot-Deseilligny, E. (1982). Comparison of soleus H reflex facilitation at the onset of soleus contractions produced voluntarily and during the stance phase of human gait. *Neuroscience Letters*, **33**, 47–53.

Morin, C., Pierrot-Deseilligny, E. & Hultborn, H. (1984). Evidence for presynaptic inhibition of Ia fibres in man. *Neuroscience Letters*, **44**, 137–42.

Morita, H., Shindo, M., Yanagawa, S., Yoshida, T., Momoi, H. & Yanagisawa, N. (1995). Progressive decrease in heteronymous monosynaptic Ia facilitation with human ageing. *Experimental Brain Research*, **104**, 167–70.

Morita, H., Petersen, N., Christensen, L. O. D., Sinkjær, T. & Nielsen, J. (1998). Sensitivity of H-reflexes and stretch reflexes to presynaptic inhibition in humans. *Journal of Neurophysiology*, **80**, 610–20.

Morita, H., Olivier, E., Baumgarten, J., Petersen, N. T., Christensen, L. O. D. & Nielsen, J. B. (2000a). Differential changes in corticospinal and Ia input to tibialis anterior and soleus motoneurones during voluntary contraction in man. *Acta Physiologica Scandinavica*, **84**, 698–709.

Morita, H., Shindo, M., Ikeda, S. & Yanagisawa, N. (2000b). Decrease in presynaptic inhibition on heteronymous monosynaptic Ia terminals in patients with Parkinson's disease. *Movement Disorders*, **15**, 830–4.

Morita, H., Crone, C., Christenhuis, D., Petersen, N. T. & Nielsen, J. B. (2001). Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity. *Brain*, **124**, 826–37.

Nakashima, K., Rothwell, J. C., Day, B. L., Thompson, P. D., Shannon, K. & Marsden, C. D. (1989). Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. *Brain*, **112**, 681–97.

Nakashima, K., Rothwell, J. C., Day, B. L., Thompson, P. D. & Marsden, C. D. (1990). Cutaneous effects on presynaptic inhibition of flexor Ia afferents in the human forearm. *Journal of Physiology (London)*, **426**, 369–80.

Nakashima, K., Shimoyama, R., Yokoyama, Y. & Takahashi, K. (1994). Reciprocal inhibition between the forearm muscles in patients with Parkinson's disease. *Electromyography and Clinical Neurophysiology*, **34**, 67–72.

Nielsen, J. (1998). *Co-Contraction of Antagonistic Muscles in Man*, 18 pp. Copenhagen: Laegeforeningens Forlag.

Nielsen, J. & Hultborn, H. (1993). Regulated properties of motoneurons and primary afferents: new aspects on possible spinal mechanisms underlying spasticity. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 177–92. New York: Springer Verlag.

Nielsen, J. & Kagamihara, Y. (1993). The regulation of presynaptic inhibition during co-contraction of antagonistic muscles in man. *Journal of Physiology (London)*, **464**, 575–93.

Nielsen, J. & Petersen, N. (1994). Is presynaptic inhibition distributed to corticospinal fibres in man? *Journal of Physiology (London)*, **477**, 47–58.

Nielsen, J. & Sinkjær, T. (2002). Reflex excitation of muscles during human walking. In *Sensorimotor Control of Movement and Posture*, ed. S. C. Gandevia, U. Proske & D. G. Stuart, pp. 369–75. New York: Plenum Publishers.

Nielsen, J., Sinkjær, T., Toft, E. & Kagamihara, Y. (1994). Segmental reflexes and ankle joint muscle stiffness during cocontraction of antagonistic muscles in man. *Experimental Brain Research*, **102**, 350–8.

Nielsen, J., Petersen, N. & Crone, C. (1995). Changes in transmission across synapses of Ia afferents in spastic patients. *Brain*, **118**, 995–1004.

Panizza, M. E., Hallett, M. & Cohen, L. G. (1987). Abnormality of reciprocal inhibition in patients with hand cramps. *Annals of Neurology*, **22**, 146.

Panizza, M. E., Lelli, S., Nilsson, J. & Hallett, M. (1990). H-reflex recovery curve and reciprocal inhibition of H-reflex in different kinds of dystonia. *Neurology*, **40**, 824–8.

Pierrot-Deseilligny, E. (1990). Electrophysiological assessment of the spinal mechanisms underlying spasticity. In *New Trends and Advanced Techniques in Clinical Neurophysiology*, ed. P. M. Rossini & F. Mauguière, pp. 364–73. Amsterdam: Elsevier.

(1997). Assessing changes in presynaptic inhibition of Ia afferents during movement in humans. *Journal of Neuroscience Methods*, **74**, 189–99.

Pierrot-Deseilligny, E. & Bussel, B. (1973). A comparison of H reflex at the onset of a voluntary movement or a polysynaptic reflex. *Brain Research*, **60**, 482–4.

Pierrot-Deseilligny, E., Morin, C., Bergego, C. & Tankov, N. (1981). Pattern of group I fibre projections from ankle flexor and extensor muscles in man. *Experimental Brain Research*, **42**, 337–50.

Priori, A., Berardelli, A., Inghilleri, M., Pedace, F., Giovannelli, M. & Manfredi, M. (1998). Electrical stimulation over muscle tendons in humans. Evidence favouring presynaptic inhibition of Ia fibres due to the activation of group III tendon afferents. *Brain*, **121**, 373–80.

Roberts, R. C., Part, M. J., Farquhar, R. & Butchart, P. (1994). Presynaptic inhibition of soleus Ia afferent terminals in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**, 1488–491.

Rossi, A., Decchi, B. & Ginanneschi, F. (1999). Presynaptic excitability of group Ia fibres to muscle nociceptive stimulation in humans. *Brain Research*, **818**, 12–22.

Rudomin, P. & Schmidt, R. F. (1999). Presynaptic inhibition in the vertebrate spinal cord revisited. *Experimental Brain Research*, **129**, 1–37.

Rudomin, P., Jimenez, I., Solodkin, M. & Duenas, S. (1983). Sites of action of segmental and descending control of transmission on pathways mediating PAD of Ia and Ib afferent fibres in cat spinal cord. *Journal of Physiology (London)*, **50**, 743–69.

Rudomin, P., Jimenez, I. & Enriquez, M. (1991). Effects of stimulation of group I afferents from flexor muscles on heterosynaptic facilitation of monosynaptic reflexes produced by Ia and descending inputs: a test for presynaptic inhibition. *Experimental Brain Research*, **85**, 93–102.

Rudomin, P., Jimenez, I. & Quevedo, J. (1998). Selectivity of the presynaptic control of synaptic effectiveness of group I afferents in the mammalian spinal cord. In *Presynaptic Inhibition and Neural Control*, ed. P. Rudomin, R. Romo & L. Mendell, pp. 282–302. New York: Oxford University Press.

Shindo, M., Yanagawa, S., Morita, H. & Hashimoto, T. (1994). Conditioning effect in single human motoneurones: a new method using the unitary H reflex. *Journal of Physiology (London)*, **481**, 469–77.

Simonsen, E. B. & Dyhre-Poulsen, P. (1999). Amplitude of the human soleus H reflex during walking and running. *Journal of Physiology (London)*, **515**, 929–39.

Sinkjær, T., Andersen, J. B. & Larsen, B. (1996). Soleus stretch reflex modulation during gait in man. *Journal of Neurophysiology*, **76**, 1112–20.

Stein, R. B. (1995). Presynaptic inhibition in humans. *Progress in Neurobiology*, **47**, 533–44.

Tsai, C. H., Chen, R. S. & Lu, C. S. (1997). Reciprocal inhibition in Parkinson's disease. *Acta Neurologica Scandinavica*, **95**, 13–18.

Taylor, S., Ashby, P. & Verrier, M. (1984). Neurophysiological changes following traumatic spinal lesions in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 1102–8.

Vagg, R., Mogyoros, I., Kiernan, M. C. & Burke, D. (1998). Activity-dependent hyperpolarisation of human motor axons produced by natural activity. *Journal of Physiology (London)*, **507**, 919–25.

Valls-Solè, J., Alvarez, R. & Tolosa, E. S. (1994). Vibration-induced presynaptic inhibition of the soleus H reflex is temporarily reduced by cortical stimulation in human subjects. *Neuroscience Letters*, **170**, 149–52.

Verschueren, S. M.P., Swinnen, S. P., Desloovere, K. & Duysens, J. (2003). Vibration-induced changes in EMG during human locomotion. *Journal of Neurophysiology*, **89**, 1299–307.

Wood, S. A., Gregory, J. E. & Proske, U. (1996). The influence of muscle spindle discharge on the human H reflex and the monosynaptic reflex in the cat. *Journal of Physiology (London)*, **497**, 279–90.

Yang, J. F., Stein, R. B. & James, K. B. (1991). Contribution of peripheral afferents to the activation of the soleus muscle during walking in humans. *Experimental Brain Research*, **87**, 679–87.

Zehr, E. P. & Stein, R. B. (1999). Interaction of the Jendrassik maneuver with segmental presynaptic inhibition. *Experimental Brain Research*, **124**, 474–80.

Zengel, J. E., Reid, S. A., Sypert, W. & Munson, J. B. (1983). Presynaptic inhibition, EPSP amplitude, and motor-unit type in triceps surae motoneurons in the cat. *Journal of Neurophysiology*, **49**, 922–31.

9

Cutaneomuscular, withdrawal and flexor reflex afferent responses

Like muscle afferents, cutaneous afferents are not homogeneous, but the reflex pathways fed by the different types of cutaneous afferent have been documented less well than those fed by muscle afferents. Cutaneous afferents are responsible for a wide range of sensations, but most are also capable of modulating motor behaviour through spinal, supraspinal and transcortical pathways. There is a tendency for clinicians to group all cutaneous afferents together, and this creates confusion, leads to the usage of different terms for the same function and the same term for different functions, and makes the systems appear more complex than necessary. There is heterogeneity in: (i) the type of receptor (e.g. mechanoreceptor, thermoreceptor, nociceptor), (ii) the peripheral afferents (which range from large myelinated Aβ afferents to slow unmyelinated C afferents), (iii) the spinal pathways fed by the afferents (few or many interneurones), (iv) their central projection (spinal, supraspinal, transcortical), (v) the importance of the cutaneous contribution (predominantly 'private' vs. shared pathways), and (vi) their functional role (contributing to the normal usage of the limb or responsible for withdrawal from a noxious agent).

This heterogeneity is reflected in the terminology: 'flexor' or 'withdrawal' reflexes are considered nociceptive responses (though mechanoreceptors may play a role in their generation), whereas 'cutaneomuscular' reflexes refer to responses involved in the control of normal movement. A thesis of this book, addressed in many chapters, is that cutaneous afferents may have a proprioceptive role, perhaps as important for some movements as that played by muscle spindle afferents, whether that influence is mediated by a primarily 'private' pathway or by modulating the activity of some other system. This chapter will consider the following.

Withdrawal responses

These responses have a spinal pathway and are commonly but erroneously thought to involve a flexor synergy activated by a nociceptive stimulus. Withdrawal reflexes have a specific organisation, are reasonably stereotyped, and are elicited by convergence of noxious and tactile stimuli (cf. p. 387).

Cutaneomuscular responses

These responses are elicited by tactile stimuli, vary with task and contribute to the control of normal movement. Their late components are generally more significant than their early spinal components, but the latency of the late components is so long that involvement of transcortical pathways is likely (cf. pp. 421–4).

Short-latency FRA responses

These responses provide a good example of a reflex evoked through a multisensory system with wide convergence of many different afferents on common interneurones. Because the resulting reflexes can be evoked by afferents which *may* evoke the flexion reflex, the corresponding pathways were named FRA (flexor reflex afferent) pathways. There are alternative pathways for these afferents, and pathways mediating short-latency FRA reflexes are

believed to be activated during normal movements (cf. pp. 389–90).

Long-latency FRA responses

These responses are elicited by the same afferents as early FRA responses, but the transmission in the relevant pathways is inhibited by activation of pathways mediating short-latency FRA reflexes. The organisation of long-latency FRA pathways suggests that they play a role in the generation of locomotor stepping activity (cf. pp. 390–1).

Contributions to 'proprioceptive' reflexes

The above responses can be generated by stimulating cutaneous afferents in isolation. In addition, cutaneous afferents contribute to shaping the motor output through their extensive convergence on interneurones interposed in pathways fed by muscle afferents or corticospinal volleys (cf. Chapters 3–7 and 10), and onto PAD interneurones mediating presynaptic inhibition of muscle afferents (cf. Chapters 7–8).

Because of this heterogeneity, withdrawal reflexes (pp. 399–414), and cutaneous reflexes from mechanoreceptors (pp. 414–32) are treated separately, except for the background from animal experiments (pp. 385–91), the methodology (pp. 391–9) and the changes in patients (pp. 432–8).

Background from animal experiments

Initial findings

Investigations of spinal reflexes received impetus from the work of Sherrington (1906, 1910) on the nociceptive flexion reflex. He showed that, in the spinalised decerebrate animal, noxious skin stimuli excite flexors and inhibit extensors in the ipsilateral hindlimb (the flexion reflex), accompanied by excitation of extensors and inhibition of flexors in the contralateral limb (the crossed extension reflex). He proposed that the function of the flexion reflex was 'to withdraw the limb from injurious agents' (Creed *et al.*, 1932), while posture was stabilised by the crossed extension reflex. He had already noted that light pressure on the plantar surface of the foot elicited the extensor thrust, introducing the concept of 'local sign'. The nociceptive withdrawal (flexion) reflex was subsequently shown to be polysynaptic (for references, see Hunt & Perl, 1960), and this was confirmed by intracellular recordings from motoneurones (R. M. Eccles & Lundberg, 1959). The extensive convergence on common interneurones of cutaneous, joint and high-threshold muscle afferents led to the concept of multisensory FRA pathways (R. M. Eccles & Lundberg, 1959; Holmqvist & Lundberg, 1961). Further investigations showed that administration of DOPA in the acute spinal cat suppressed short-latency FRA responses, releasing transmission in a long-latency FRA pathway, which had a half-centre organisation, capable of generating alternating activation of extensors and flexors (Jankowska *et al.*, 1967a,b).

Cutaneous responses mediated through 'private' pathways

It is often difficult to decide whether an action evoked by cutaneous volleys is mediated through a largely 'private' pathway or by a common FRA pathway for two reasons: (i) low-threshold cutaneous afferents contribute to FRA responses, and (ii) effects mediated through specialised cutaneous pathways may have a pattern (flexion reflex in the hindlimb) roughly similar to that of FRA responses. However, when cutaneous and FRA volleys elicit different effects in the same motoneurone(s), there is evidence for a specialised cutaneous pathway.

Reflexes elicited by low-threshold cutaneous afferents

The toe extensor reflex of the cat

This is the most clear-cut example of a specialised cutaneous reflex. Gentle pressure on the central plantar cushion (dashed area in the sketch of Fig. 9.1(*a*)) elicits in the *acutely spinalised* cat a strong

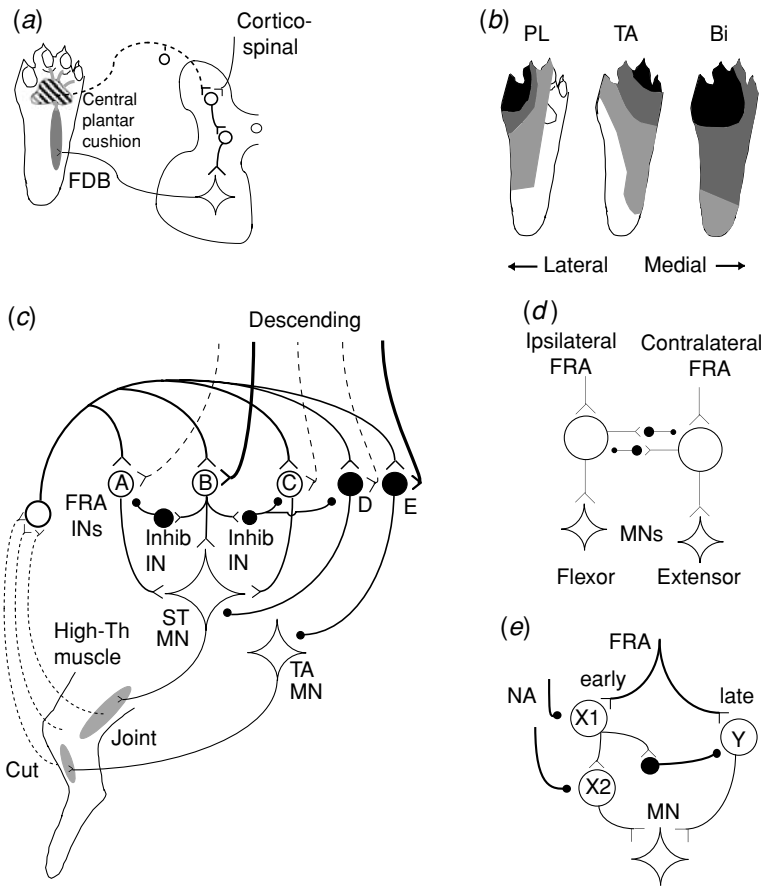


Fig. 9.1. Some spinal pathways fed by cutaneous afferents in the cat. (*a*) Stimulation of slowly adapting mechanoreceptors from the central plantar cushion of the pad activates flexor digitorum brevis (FDB), through an oligosynaptic pathway, which receives corticospinal facilitation. (*b*) Different receptive fields in the plantar skin of the cat for withdrawal reflexes in the peroneus longus (PL), tibialis anterior (TA) and biceps femoris (Bi), with areas evoking 70–100% (black), 30–70% (dark grey) and 0–30% (pale grey) of maximal responses. (*c*)–(*e*) Sketches showing presumed pathways mediating FRA responses. In these diagrams each interneurone (IN) may represent a chain of INs. (*c*) Sketch illustrating how, during movement, short-latency FRA pathways could provide selective reinforcement of the descending voluntary command. High-threshold muscle (High-Th muscle), joint and cutaneous (Cut) (thin dotted lines) afferents converge onto common first-order FRA INs, which excite different chains of alternative excitatory ('A', 'B', 'C') and inhibitory ('D') INs projecting to motoneurones (MN) of the semitendinosus (ST). During movement, there is descending activation (continuous thick lines) of chains 'B' and 'E' and, through inhibitory interactions (Inhib IN), there is inhibition of transmission in the other FRA excitatory ('A' and 'C') and inhibitory ('D') pathways (for TA MNs only descending inhibitory pathways ['E'] are represented). The ensuing movement gives rise to an impulse flow in FRA which is channelled back into the reflex already activated, so that its activity is reinforced and prolonged (see p. 389). (*d*) Mutual inhibition between chains of INs mediating long-latency excitation to flexors and extensor MNs from ipsilateral and contralateral FRAs, respectively (see pp. 390–1). (*e*) Inhibition of pathways mediating long-latency FRA reflexes by pathways mediating short-latency reflexes: noradrenergic (NA) paths activated by DOPA inhibit the short-latency reflex pathway ('X'), thereby releasing transmission in the long-latency reflex pathway ('Y') from an inhibitory control exerted from pathway 'X'. The short-latency pathway 'X' is subdivided into 'X1' and 'X2' to accommodate the finding that the NA pathway may block the short-latency reflex actions on MNs when there is still an inhibitory transmission on the long-latency pathway. From data in Engberg (1964) (*a*), and modified from Schouenborg (2002) (*b*), Lundberg (1973, 1979) ((*c*), (*d*)), and Baldissera, Hultborn & Illert (1981) (*e*), with permission.

response in the plantar flexors of the toes (i.e. the physiological toe extensors), in particular the flexor digitorum brevis (Engberg, 1964). This reflex is due to the activation of slowly adapting mechanoreceptors and is mediated through an oligosynaptic pathway (Egger & Wall, 1971; see the sketch in Fig. 9.1(*a*)). However, the pathway is distinct from FRA pathways, since FRA volleys (from high-threshold muscle and joint afferents) evoke the usual inhibition of physiological extensors in flexor digitorum brevis motoneurones.

Cutaneous reflexes during locomotion

Cutaneous reflexes during locomotion are also mediated through specialised pathways. In chronic spinal cats walking on a treadmill, tactile stimuli applied to the dorsum of the paw evoke short-latency responses involving the flexors during the swing phase, but the extensors during the stance phase (Forssberg, Grillner & Rossignol, 1975, 1977). The responses in knee muscles are stronger and have shorter latencies than those of ankle and hip muscles. This pattern and timing of activation (i) distinguish the above responses from FRA-induced responses, which are stereotyped and synchronous in all flexors, and (ii) appear appropriate during gait. Isolated knee flexion early in swing is sufficient to overcome the obstacle touched by the pad dorsum, whereas the increased extension during stance acts to shorten this phase and accelerate the following flexion. The hindlimb flexion producing this 'stumbling corrective reaction' is completed by plantar flexion of the toes mediated by disynaptic pathways (see R. E. Burke, 1999).

Reflexes in the forelimb

In the forelimb of the cat, low-threshold cutaneous afferents project to segmental interneurones interposed in proprioceptive pathways (cf. Introduction, and Hongo *et al.*, 1989) and to C3–C4 propriospinal neurones (cf. Alstermark & Lundberg, 1992; Chapter 10, p. 453), and also feed 'private' pathways. Thus, stimulation of the skin of the forefoot pad evokes highly specialised reflexes in digit motoneurones, with excitation as in the hindfoot, associated with strong disynaptic inhibition of neighbouring motoneurones, presumably designed for discrete movements of the different digits (Sasaki *et al.*, 1996).

Withdrawal reflexes

In contrast with the classical view that the withdrawal reflexes of the hindlimb were a stereotyped 'nociceptive flexion reflex' in which all physiological flexors were activated while extensors were inhibited, Hagbarth (1952) demonstrated that extensor muscles are activated by noxious stimuli applied to the overlying and adjacent skin. This extensor activation is appropriate to avoid the stimulus. Accordingly, a specific relationship between receptive field, activated muscle(s) and the resulting reflex withdrawal has been revealed both in the rat and the cat (for review, see Schouenborg, 2002).

(i) Each muscle or group of muscles has a separate cutaneous receptive field corresponding to the skin area withdrawn by contraction of the particular muscle group. This is illustrated for the receptive fields for withdrawal reflexes involving the peroneus longus, tibialis anterior and biceps of the cat in Fig. 9.1(*b*).

(ii) Nociceptors and, to a lesser extent, slowly adapting low-threshold mechanoreceptors provide the afferent input to withdrawal reflex pathways.

(iii) The dorsal horn interneurones receiving converging inputs from nociceptive and tactile afferents that elicit the withdrawal reflex are specific for each muscle, and under differential supraspinal control.

Projections to motoneurones innervating slow- and fast-twitch motor units

A differentiation between FRA pathways and specialised cutaneous pathways has also been possible in the motoneurones innervating fast-twitch motor units of triceps surae. Their motoneurones are excited from cutaneous afferents but inhibited from other FRA afferents, specifically joint and high-threshold muscle afferents (R. E. Burke, Jankowska & ten Bruggencate, 1970).

Descending projections to specialised cutaneous pathways

A descending action on specialised reflex pathways from skin has been inferred because facilitation of cutaneous effects may occur without concomitant changes in the FRA effects evoked from high-threshold muscle afferents. This is the case for the following.

(i) Rubrospinal facilitation of low-threshold cutaneous excitation of extensor motoneurones innervating fast motor units (cf. above) (Hongo, Jankowska & Lundberg, 1969).

(ii) Corticospinal facilitation of interneurones in the cutaneous reflex pathway to toe extensors (Engberg, 1964). Because of this convergence, descending excitation of the relevant interneurones may receive feedback reinforcement by impulses evoked from the plantar cushion during contact with the ground (see Fig. 9.1(*a*), and Lundberg, 1973).

(iii) Convergence of cutaneous and corticospinal inputs on common interneurones in pathways to distal forelimb motoneurones, which occurs at two levels: cutaneous modulation of corticospinal volleys mediated through C3–C4 propriospinal neurones (cf. above), and corticospinal facilitation of cutaneous reflexes mediated by interneurones located in brachial segments (C7–C8). There are disynaptic reflex pathways (mediating both excitation and inhibition to motoneurones) that operate only with conjoint cutaneous and corticospinal inputs (Sasaki *et al.*, 1996). Some cutaneous receptors can be activated during movement without contact with an external object (Hulliger *et al.*, 1979). Lundberg (1973) speculated that the information from skin receptors may play a significant role in controlling hand movements in primates, both by modulating the cortical command relayed by common interneurones and by activating segmental reflex pathways to motoneurones. The increased presynaptic inhibition of cutaneous afferents observed during the dynamic phase of wrist flexion-extension movements in the awake monkey could function to gate out inappropriate reflex responses from peripheral receptors and sharpen the resulting exteroceptive information (Seki, Perlmutter & Fetz, 2003).

FRA reflex pathways

Characteristics of FRA pathways

Flexor reflex afferents (FRA)

FRA include group III and, in the cat, group II muscle afferents, joint afferents and low- and high-threshold cutaneous afferents. Afferents of the FRA group may use 'private' pathways which are not part of the common FRA system, as discussed above for specialised cutaneous pathways and in Chapter 7 for group II pathways. There are two reflex patterns from the FRA: the short-latency (early) reflexes found in the acute spinal cat, and the long-latency (late) reflexes, which appear in acute spinal cats after the administration of DOPA or 5-HTP. In this chapter, 'reflex actions from the FRA' denotes the former action when not otherwise stated.

Grouping FRA together

There are multiple reasons to group these afferents together (cf. Lundberg, 1973, 1979, 1982):

(i) They have a common action on motoneurones, i.e. ipsilateral flexion and contralateral extension in the spinal animal.

(ii) In all cases, the reflex actions are drawn from a wide receptive field, which, for muscle afferents, includes both flexors and extensors.

(iii) They converge on common interneurones interposed in reflex pathways to motoneurones.

(iv) They act together on a variety of ascending spinocerebellar pathways (Lundberg, 1959), and this may be explained because the descending excitation of FRA interneurones (see below) requires information regarding activity in FRA pathways.

(v) Transmission in all FRA pathways is similarly influenced by brainstem lesions. Following

intercollicular decerebration, FRA excitation of flexors and inhibition of extensors is suppressed, and following an additional midline low-pontine lesion, stimulation of FRA evokes inhibition in both flexor and extensor motor nuclei. Following spinal transection, the classical 'flexor reflex pattern' with facilitation of flexors and inhibition of extensors appears. These findings strongly suggest that there are '*alternative*' spinal pathways to motoneurones with wide multisensory convergence from all FRAs, a concept of importance for the possible role of early FRA pathways in normal movement (cf. below).

(vi) Transmission in short-latency FRA pathways is facilitated by a number of descending tracts (corticospinal, rubrospinal, vestibulospinal), and depressed by monoaminergic pathways from the brainstem.

Criticism of the FRA concept

The FRA concept provoked criticism (in particular, see Matthews, 1972; Binder *et al.*, 1982), mainly related to the terminology. The term FRA is probably a misnomer that has outlived its usefulness (Lundberg, 1979), but unfortunately it has been ratified by use.

Pathways mediating short-latency FRA reflexes

New perspective on the FRA concept

The FRA concept received a new dimension when Lundberg (1973, 1979) formulated the hypothesis that, during normal movement, pathways mediating short-latency FRA reflexes could provide selective reinforcement of the voluntary command from the brain. The hypothesis relied on experimental evidence for the following findings.

(i) There are alternative FRA pathways to the flexion reflex (see above).

(ii) There are inhibitory interactions between alternative FRA pathways ('Inhib IN' in Fig. 9.1(*c*)).

(iii) Muscle contraction secondary to stimulation of α efferents activates the FRA system (see Lundberg, 1979).

Possible functional role

The hypothesis is outlined in the sketch in Fig. 9.1(*c*) (in which circles represent *chains* of interneurones). Lundberg postulated that the descending command activates one of the several alternative excitatory FRA pathways to motoneurones (e.g. of semitendinosus) ('B' rather than 'A' and 'C' in Fig. 9.1(*c*)). Through inhibitory interactions, transmission in the other FRA excitatory pathways to the same motoneurones is inhibited ('A' and 'C' in Fig. 9.1(*c*)), as is transmission in the inhibitory FRA pathways to the same motoneurones ('D' in the sketch in Fig. 9.1(*c*)). Movement activates muscle receptors of the contracting muscle, related joint and surrounding skin, many of which belong to the FRA system. This sensory activity will be channelled back into the reflex path already activated by descending tracts ('B' in Fig. 9.1(*c*)), because transmission in the other pathways is inhibited. A diffuse feedback system with a multisensory input may therefore be used to reinforce and prolong the descending command. The movement may have been initiated by corticospinal activation of motoneurones, as occurs in primates, but the feedback would help maintain the contraction, if the descending command facilitates interneurones of the FRA pathway. Parallel descending excitation of FRA pathways mediating inhibition to other motoneurone pools (e.g. tibialis anterior in Fig. 9.1(*c*)) might then be used to prevent contraction of muscles not required in a given movement.

Convergence of nociceptive afferents on FRA interneurones

Convergence would facilitate correction of a movement as it approached its limits and became harmful. Due to spatial facilitation the required nociceptive input need only be minor, so that the correction could become effective before injury or pain occurred (see Schomburg, 1990).

Presynaptic inhibition of FRA

The positive feedback provided by the excitatory FRA machinery requires control. Presynaptic inhibition could play a crucial role in this. The FRAs produce primary afferent inhibition of their own terminals (Eccles, Kostyuk & Schmidt, 1962), 'which suggests a negative feedback control of transmission from the FRAs so that excess activity automatically curtails transmission' (Lundberg, 1979).

FRA-induced excitation of other pathways

Strong excitatory effects from the FRAs have been described on interneurones belonging to different reflex pathways: reciprocal Ia inhibition (Chapter 5, p. 199), Ib (Chapter 6, pp. 247–8) and group II (Chapter 7, pp. 291–2). These findings suggest that facilitation of impulse transmission in the FRA pathways evoked by the active movement might have a widespread effect on spinal circuitry (Lundberg, Malmgren & Schomburg, 1987).

Pathways mediating long-latency FRA reflexes

With DOPA, short-latency FRA reflexes are depressed and replaced by long-latency responses

Short- and long-latency FRA reflexes can have a similar pattern of excitation of flexors from ipsilateral FRAs and of extensors from contralateral FRAs, with inhibition of antagonistic motoneurones. However, several lines of evidence indicate that the short- and long-latency FRA responses are mediated through different pathways (cf. Lundberg, 1979; Schomburg, 1990).

(i) Primary afferent depolarisation is exerted mainly on FRA terminals before DOPA, and on Ia terminals after DOPA.

(ii) Late IPSPs evoked after DOPA are mediated via interneurones of reciprocal Ia inhibition, while IPSPs evoked before DOPA are mediated via a private inhibitory pathway.

(iii) Interneurones which mediate long-latency FRA responses do not respond to FRA stimulation before DOPA.

Mutual inhibition between long-latency FRA pathways to flexors and extensors

This mutual inhibition is very effective. Thus, transmission of the late EPSPs evoked by the ipsilateral FRAs to flexor motoneurones is strongly inhibited by activation of the pathway that conveys late excitation to extensor motoneurones from the contralateral FRAs, and vice versa, as outlined in Fig. 9.1(*d*). The strong mutual inhibition between neurones exciting muscles with opposite function is reminiscent of the half-centre organisation postulated by Graham Brown (1914) to give alternating activation of extensors and flexors during locomotion. Accordingly, when DOPA is given after pretreatment by nialamide, stimulation of the FRA produces alternating flexor and extensor activation, dependent on the half-centre organisation of the late FRA pathways (see Lundberg, 1979).

There is inhibition of pathways mediating long-latency FRA reflexes by pathways mediating short-latency FRA reflexes

After DOPA, prolonging a train of FRA volleys delays the onset of the long-latency response, which then appears only after the end of the stimulus train. This finding has been taken as evidence that the same FRA pathway provides excitation of the short-latency FRA pathway ('X' in Fig. 9.1(*e*)) and inhibition of the long-latency FRA pathway ('Y' in Fig. 9.1(*e*)). By causing release of transmitter from a noradrenergic pathway, DOPA would inhibit pathway X, thereby releasing transmission through the pathway Y (cf. Lundberg, 1979). After DOPA, short-latency reflex actions to motoneurones are blocked, but short-latency pathways still have an inhibitory action on the long-latency pathway, as suggested by the finding that the late response only appears after the end of the stimulus train. A possible functional outcome of the inhibition of long-latency FRA pathways by short-latency FRA pathways would be the prompt interruption of locomotor activity that occurs in all phases of stepping when high-threshold cutaneous afferents are stimulated (Viala, Orsal & Buser,

1978). It has been suggested (Lundberg, 1979) but so far without experimental evidence that there is also inhibition from the long-latency to the short-latency FRA pathway, so that, once the former is activated to give locomotor activity, the latter is suppressed.

Conclusions

Cutaneous volleys contribute to many spinal reflexes.

(i) They modulate transmission in pathways which receive their main input from muscle afferents through convergence on the interneurones intercalated in these pathways and on PAD interneurones mediating presynaptic inhibition of primary afferent terminals.
(ii) Low-threshold mechanoreceptors may evoke specialised reflex responses.
(iii) Withdrawal reflexes are evoked by nociceptive afferents but with excitatory convergence from tactile afferents from a specific cutaneous receptive field. Stimulation of these fields produces withdrawal of the area from the potentially injurious stimulus.
(iv) The responses mediated through short-latency FRA pathways are evoked mainly from afferents activated during normal movement, though nociceptive afferents may also contribute. These responses may provide positive feedback designed to prolong and reinforce the voluntary command from the brain.
(v) The half-centre organisation of pathways mediating long-latency FRA responses might be responsible for the alternating activation of flexors and extensors during locomotion.

Methodology

Underlying principles

Although the reflex responses evoked by tactile and nociceptive stimuli are carried by different peripheral afferents and have different central circuits, similar general principles apply to all cutaneous reflexes.

(i) Some reflexes may be documented by recording responses when the subject is relaxed.
(ii) The reflex effects of cutaneous volleys may be tested using the H reflex, the on-going EMG or PSTHs of single motor units.
(iii) Cutaneous volleys may be produced by electrical or mechanical stimuli.
(iv) Temporal summation or spatial and temporal summation may be required to cause the response to appear consistently.
(v) Cutaneous reflexes are more sensitive than H reflexes to repetition rate, such that irregular stimuli at very low rates are advised, particularly at rest.
(vi) Spinal responses may be distinguished from transcortical responses on latency grounds, and/or because similar responses are obtained in subjects with complete spinal transection.
(vii) In practice, whether the stimulus elicits a tactile sensation or pain is often used to document which afferents are activated and to distinguish responses produced by stimulation of low-threshold cutaneous afferents from withdrawal reflexes. However, it must be remembered that an electrical stimulus sufficiently strong to activate nociceptive afferents will also activate mechanoreceptive afferents.

Stimuli

Electrical stimuli

Electrical stimuli to cutaneous nerves

Electrical stimuli can be applied to cutaneous nerves, which are generally stimulated where the nerve is superficial, through bipolar surface electrodes with the cathode proximal. The more commonly stimulated nerves are the sural nerve behind or just below the lateral malleolus, the superficial peroneal nerve on the dorsal side of the foot proximal to the extensor digitorum brevis, the superficial radial nerve on

the inferior part of the radial edge of the forearm, the digital nerves of the fingers and toes using ring electrodes.

Electrical stimulation may also be delivered directly to the skin

Direct cutaneous stimulation may be delivered through plate electrodes placed over the skin, at a site where there is no muscle beneath the skin, to avoid stimulation of muscle afferents. Stimuli can also be delivered through pairs of needle electrodes inserted into the skin.

Withdrawal reflexes

Withdrawal reflexes are elicited by painful stimuli applied to a nerve or to skin. Temporal summation will facilitate the appearance of withdrawal reflexes (cf. Fig. 9.2(*i*)–(*k*)), but the critical parameter is the intensity of the stimulus, which must recruit small afferents (see Hugon, 1973; Willer, 1977). The intensity of stimulation may be expressed with respect to the threshold for perception or to the threshold for pain. The latter is the same as the threshold for the nociceptive reflex (see Fig. 9.2(*l*)–(*m*); Willer, Roby & Le Bars, 1984). There is a specific organisation of the withdrawal reflexes related to the stimulated skin field (cf. p. 407).

Cutaneomuscular responses from low-threshold mechanoreceptors

These responses are produced by stimuli that produce a tactile sensation. Single shocks of weak intensity may have little effect, particularly when applied to skin, and most authors use trains of stimuli applied to nerves. The trains must be short (e.g. 3–5 shocks at 300 Hz) to allow interpretation of latency measurements. The stimulus intensity is expressed as a multiple of the threshold for perception (× PT) for the radiating cutaneous paraesthesiae in the territory of the nerve. At rest, the reflex response is suppressed at repetition rates above 0.1–0.2 Hz, even more so than the H reflex. In contracting muscles, the suppression is less, and rates of 1–3 Hz provide the optimal trade-off between reflex attenuation and the need to average more responses.

Mechanical stimuli

Mechanical stimuli have been used to provide information about (i) the responses elicited in forearm and hand muscles from low-threshold mechanoreceptors activated under natural conditions, and (ii) the mechanisms underlying the reflex responses tested in routine clinical examination.

Natural stimulation of cutaneous afferents from the fingers

Natural stimulation may be produced using a small probe to indent the skin or a controlled puff of air. An analysis of the cutaneous receptors responsible for cutaneomuscular responses in hand muscles has been undertaken by McNulty & Macefield (2002). Rapidly adapting type I and II units (FAI, FAII) were activated by stroking across the receptive field of the unit, while slowly adapting receptors were stimulated by constant indentation of the receptive field of the unit. Recordings from *single* cutaneous afferents allowed a further characterisation of the corresponding receptors, since FAI afferents have a characteristic bursting discharge (see the inset in Fig. 9.10(*f*)), FAII a highly variable discharge rate, and SAII a regular discharge in response to sustained skin stretch.

Plantar responses

Plantar responses are evoked by firm stroking of the lateral plantar surface of the foot, a stimulus that produces spatial and temporal summation of inputs. Attention is focused clinically on the response of the toe 1 because the normal plantar flexion (physiological extension) may be replaced by dorsiflexion to produce Babinski's sign of pyramidal tract dysfunction (cf. Fig. 9.5; pp. 433–4; Babinski, 1898; see van Gijn, 1996 for further references).

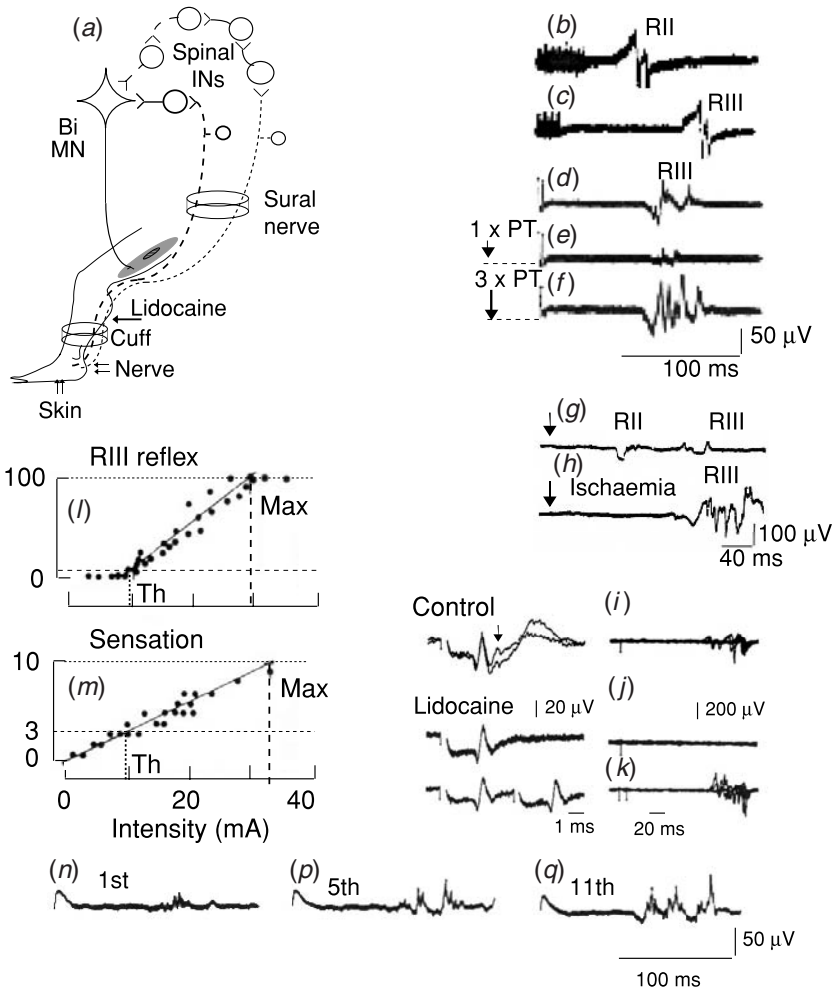


Fig. 9.2. RII and RIII reflexes in the short head of the biceps femoris. (*a*) Sketch of the presumed pathways. Aβ (dashed line) and Aδ (thin dotted line) afferents in the sural nerve activate biceps (Bi) motoneurones (MN) through different chains of interneurones (IN). (*b*)–(*k*) and (*n*)–(*q*) Reflexes elicited by sural stimulation in the Bi at rest. (*b*) RII reflex elicited by stimuli evoking a tactile sensation (train of 13 shocks, 400 Hz). (*c*) RIII reflex elicited by a stronger train evoking a pain sensation (the response being limited to Bi). (*d*)–(*f*) Modulation of the RIII reflex ((*d*), control reflex) by a preceding (50 ms, vertical arrows) conditioning stimulation of Aβ (*e*) and Aδ (*f*) afferents in the sural nerve. (*g*), (*h*) Reflex responses recorded in the Bi after sural stimulation (train of 10 shocks, 300 Hz, 10 mA) in a control situation (*g*) and during ischaemia blocking large Aβ fibres (*h*) (arrows indicate the time of stimulation). (*i*)–(*k*) Effects of lidocaine infiltration on sural volleys (left traces) and Bi activity (right traces) after sural stimulation (40 mA). (*i*) Control recordings (the arrow highlights the Aδ wave), and effects of a single (*j*) and a double (*k*) shock (100 Hz) 10 minutes after lidocaine. (*l*), (*m*) The size of the RIII reflex in the Bi (*l*) (as a percentage of its maximum, Max) and the intensity of the sensation (*m*) (on a 0–10 scale where 3 and 10 are the threshold of pain and intolerable pain, respectively) plotted against the intensity of the sural nerve stimulation (train of 10 shocks, 300 Hz). (*n*)–(*q*) Facilitation of the RIII reflex in the Bi by repeating the stimulation to the sural nerve (single shock, 3.5 × PT) every 2 s: records show the first (*n*), fifth (*p*) and eleventh (*q*) reflex of the same series. Modified from Hugon (1973) ((*b*)–(*f*), (*n*)–(*q*)), Willer (1977) ((*g*), (*h*)), Willer, Roby & Le Bars (1984) ((*l*), (*m*)), and Willer, Boureau & Albe-Fessard (1978) ((*i*)–(*k*)), with permission.

Abdominal reflexes

Abdominal reflexes are evoked by a rapid stroke with a blunt pin on the abdominal skin, again a stimulus that produces spatial and temporal summation of inputs. The latency of the response increases and the amplitude decreases with repetition due to rapid habituation of the reflex (see Fig. 9.3(*l*)–(*n*); Kugelberg & Hagbarth, 1958).

Responses recorded at rest

Withdrawal reflexes

Provided that the stimulus is painful, withdrawal reflexes can be recorded consistently at rest, particularly in the lower limb. The electrophysiological analysis of withdrawal reflexes in human subjects began with Pedersen (1954).

The RIII response of the short head of the biceps femoris

The RIII reflex is elicited by a stimulus to the sural nerve that produces pain (Fig. 9.2(*c*); Hugon, 1973; Willer, 1977), and is a good tool for the investigation of the pathways mediating withdrawal reflexes in humans. The reflex is mediated by small myelinated Aδ afferents (see p. 400). With sural stimulation, the nociceptive response first appears in biceps femoris (Hugon, 1973). If the stimulus intensity is sufficiently strong, the RIII reflex may be elicited by a single shock (Fig. 9.2(*i*)). Lower intensities are sufficient to evoke the nociceptive reflex when a train is delivered but they then also produce pain (Willer, Boureau & Albe-Fessard, 1978, and Fig. 9.2(*j*), (*k*)). At threshold, the response occurs with a latency of 120–130 ms, but this decreases to ~80–90 ms when the stimulus intensity (or the number of shocks in the train) is increased. As discussed on p. 401, such a latency is compatible with a spinal reflex.

Other withdrawal reflexes

Withdrawal reflexes may be elicited in all lower limb muscles when the adequate receptive field is stimulated (Hagbarth, 1960), and their particular pattern is considered on pp. 401–7. Noxious responses are often investigated in the tibialis anterior to stimulation of the medial aspect of the sole of the foot at the apex of the plantar arch (Shahani & Young, 1971), or of the medial plantar nerve of the foot (Meinck, Benecke & Conrad, 1983). Here again, increases in stimulus strength result in increases in the reflex amplitude and duration, and decreases in latency (Fig. 9.3(*b*)–(*e*)), to as little as 50–60 ms at the higher intensities. Increases in stimulus strength also result in the appearance of a late response (Fig. 9.3(*e*)), the origin of which is discussed on pp. 410–11. Abdominal skin reflexes are considered trunk defence reflexes (Kugelberg & Hagbarth, 1958; p. 402). Withdrawal reflexes have been studied less in the upper limb than in the lower limb. Trains of ten painful stimuli at 4–6 × PT to the fingers will produce reflex responses in most muscles investigated (Floeter *et al.*, 1998), with a latency <100 ms (Fig. 9.6(*b*)). Here again, habituation is prominent.

Responses elicited by stimuli evoking a tactile sensation

Reflex responses are not easily evoked at rest by stimulation of tactile cutaneous (Aβ) afferents, and temporal summation is usually required.

The RII response elicited in the short head of the biceps femoris by stimulation of the sural nerve

This is the most consistent cutaneous reflex produced at rest by stimulation of tactile afferents (Fig. 9.2(*b*); Hugon, 1973; cf. p. 414). The reflex elicited by weak electrical stimulation requires the temporal summation produced by trains of 6–10 shocks. The minimal latency of the reflex is about 40 ms and is consistent with a *spinal* pathway (cf. Hugon, 1973; Willer, 1977; pp. 418–19). The RII reflex is not easily observed unless the subject is relaxed, and better results are often obtained during a second session when the subject is familiar with the experimental conditions. The reflex is very sensitive to habituation.

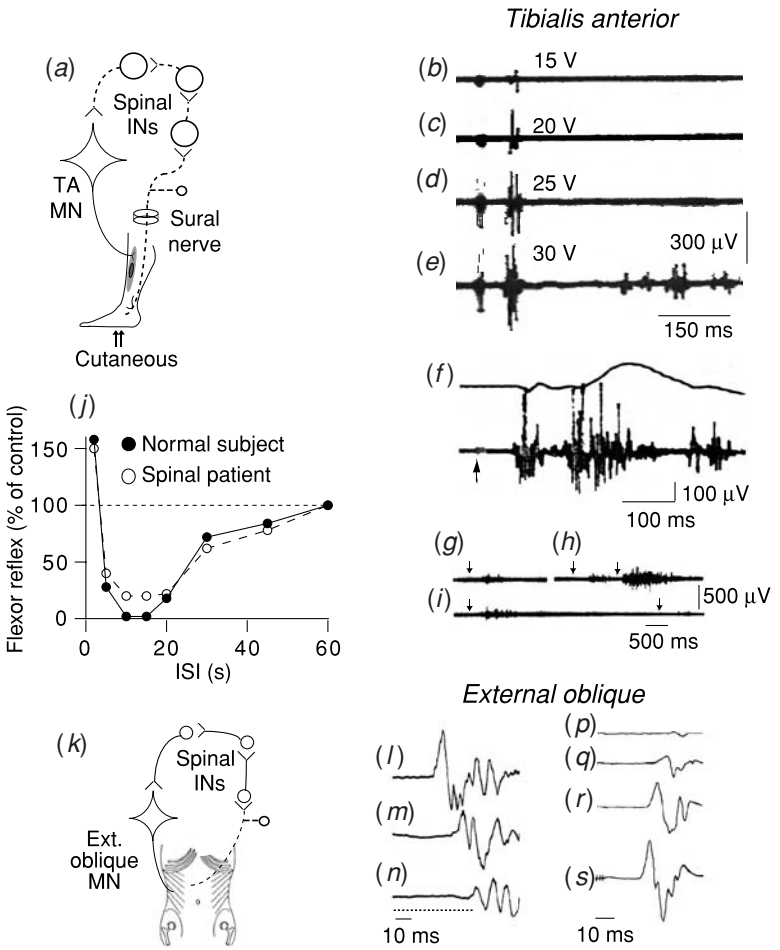


Fig. 9.3. Withdrawal reflexes in the tibialis anterior and external oblique. (*a*) and (*k*) Sketch of the presumed pathways. (*a*) Cutaneous volleys from the sole of the foot excite tibialis anterior (TA) motoneurones (MN) through a chain of interneurones (IN). (*k*) Cutaneous volleys from the abdominal skin excite external oblique MNs through a chain of INs. (*b*)–(*i*) Reflexes are elicited in TA at rest by trains of stimuli (0.1 ms square waves, 20 ms, 500 Hz) delivered by intradermal stimulation of the medial sole (at the apex of the plantar arch). (*b*)–(*e*) Flexor reflexes elicited in TA by stimuli of increasing strength. (*f*) Combined EMG and mechanogram (upper trace), depicting movement at the ankle produced by the flexor reflex, in response to a supramaximal stimulus (arrow). (*g*)–(*i*) Effects of repeating the stimulus train (arrows indicate the time of the stimuli): (*g*) Control response; (*h*), (*i*) the responses to two trains of stimuli given 1 s (*h*) and 4.2 s (*i*) apart. (*j*) Excitability curve in a normal subject (●) and a patient with complete spinal transection (○): the size of the conditioned flexor reflex, expressed as a percentage of the conditioning reflex is plotted against the ISI between the two reflexes. (*l*)–(*s*) Abdominal reflexes elicited by different types of skin stimulation in the external oblique. (*l*)–(*n*) Reflexes following the first (*l*), fifth (*m*) and fifteenth (*n*) rapid stroke (thick dotted line) produced with a blunt pin, showing the habituation of the response. (*p*)–(*s*) Progressive decrease in latency and increase in amplitude following electrical stimuli of increasing strength (train of three shocks) of the abdominal skin. With the highest intensity (*s*), the latency is only 24 ms, implying a central delay of 3.5–5 ms. Modified from Shahani & Young (1971) ((*b*)–(*j*)), and Kugelberg & Hagbarth (1958) ((*l*)–(*s*)), with permission.

Reflexes are rarely evoked by Aβ afferents in other muscles

However, in some subjects, sural nerve stimulation has produced RII reflexes in tibialis anterior (Hugon, 1973) and peroneus longus (Aniss, Gandevia & Burke, 1992), and stimulation of the ulnar nerve at the wrist has produced reflexes attributed to cutaneous afferents in the flexor carpi ulnaris (Fig. 9.10(*b*); Cambier, Dehen & Bathien, 1974).

Modulation of motoneurone excitability

The reflex effects of cutaneous afferents may be documented by recording the modulation of the monosynaptic reflex, the PSTHs of single units or the voluntary on-going EMG activity.

Modulation of the monosynaptic reflex

Changes produced by cutaneous volleys in the amplitude of the H reflex or tendon jerk allow one to distinguish between volleys without effect on the excitability of the motoneurones, those which evoke only subliminal excitation of the motoneurones when applied alone, and those which inhibit the motoneurones. Thus, Fig. 9.4(*b*)–(*d*) shows that painful stimulation of the sural nerve facilitates the tendon jerk of the biceps femoris at an ISI corresponding to the latency of the RIII reflex and, at the same latency, profoundly inhibits the tendon jerk of quadriceps, the soleus tendon jerk and the soleus H reflex (Hugon, 1973).

Modulation of the on-going EMG

This method allows one to record rapidly the full time course of the inhibitory and excitatory effects. Modulation of a few sweeps of on-going tonic EMG activity may be sufficient to reveal the receptive fields of nociceptive reflexes (cf. pp. 404–5). Averaging the rectified on-going EMG provides reasonable temporal resolution of the cutaneous-induced responses and has been used to document the organisation of withdrawal reflexes. Gassel & Ott (1970) showed that the cutaneous modulation of the rectified on-going EMG of triceps surae closely paralleled the recovery curve of the Achilles tendon jerk, and Meinck *et al.* (1981, 1983a, b, 1985) detailed the organisation of noxious responses in the tibialis anterior of normal subjects and spastic patients. However, the method has been used mainly to explore the relatively weak responses to tactile cutaneous inputs in the upper and lower limbs (cf. pp. 414–15). Spike-triggered averaging of the EMG against the discharge of a single cutaneous afferent requires the use of microneurography to record the discharge of a single cutaneous afferent, but it has proved possible to investigate the reflex effects evoked by natural stimulation of identified cutaneous mechanoreceptors (see above).

Modulation of the PSTHs

Modulation of the PSTHs of single units by cutaneous volleys is of prime importance, because cutaneous afferents have been shown to have different effects on motoneurones of different types (cf. pp. 424–7).

Critique of the tests to study cutaneous effects

Nature of the stimuli

Mechanical stimuli

With mechanical stimuli, it is possible to activate only mechanoreceptors and, with stronger stimuli, to reproduce the conditions in which plantar responses or abdominal skin reflexes are tested in the clinical examination. Similarly, withdrawal responses may be evoked by natural stimuli such as pinch or pinprick. However, in general, the spatial and temporal summation required to produce the reflex responses do not allow accurate measurement of latencies.

Radiant heat

Radiant heat can be a noxious stimulus that can be precisely localised and timed (cf. Ellrich, Steffens &

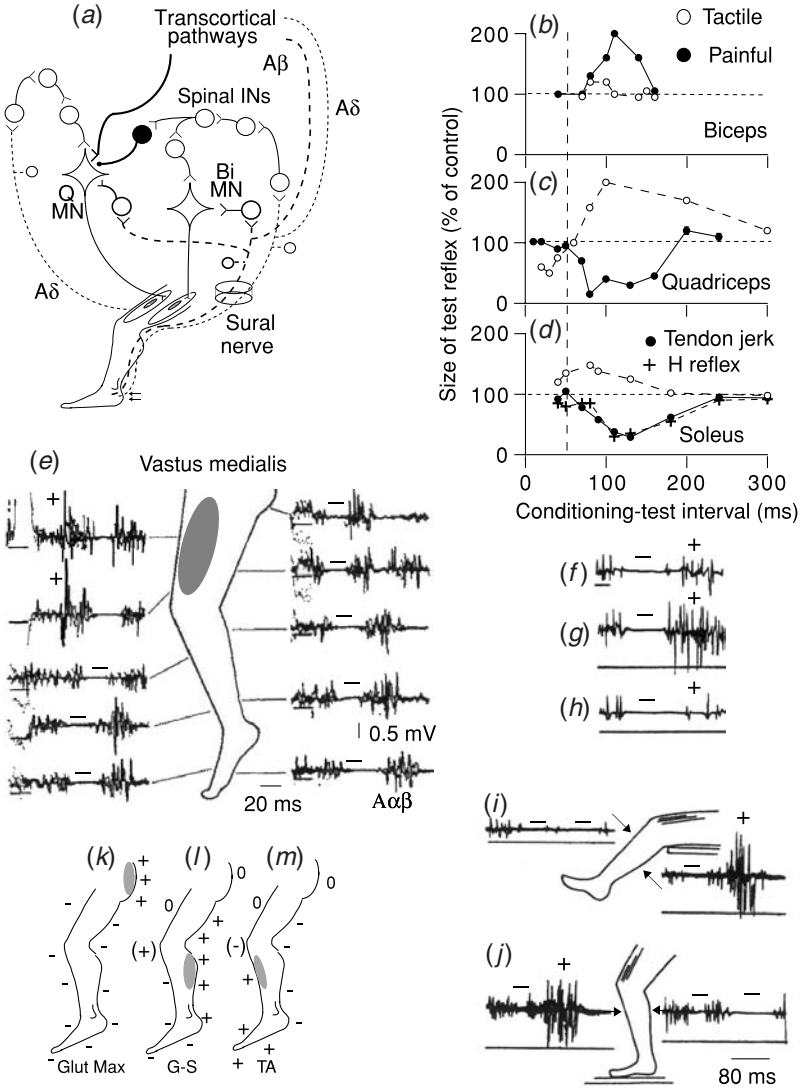


Fig. 9.4. Pattern of cutaneous reflexes in the lower limb. (*a*) Sketch of the presumed pathways. Aβ (dashed line) and Aδ (dotted line) afferents in the sural nerve and from the skin of the anterior aspect of the thigh activate excitatory and inhibitory spinal interneurones (IN) and transcortical pathways to biceps (Bi) and quadriceps (Q) motoneurones (MN). (*b*)–(*d*) The amplitude of the tendon jerk in biceps (*b*), Q (*c*) and soleus (*d*) at rest (as a percentage of the unconditioned value) is plotted after sural stimulation eliciting a tactile sensation (○) or pain (●) against the ISI (+, soleus H reflex after painful stimulation). The vertical dashed line is the latency after which a Aβ volley could act through a transcortical pathway (see p. 418). (*e*)–(*j*) Modulation of the on-going voluntary EMG of the vastus medialis (VM) by noxious stimuli (black bars under records show the duration of the stimulus train). (*e*), Effects of trains (20 ms) from various skin areas: excitatory (+) and inhibitory (−, silent period) responses (three to five sweeps superimposed in each record). (*f*)–(*h*) In the position indicated in (*i*), effects of a short train ((*f*), 30 ms) and a long train ((*g*), (*h*) the duration of which [outlasting the sweep] is determined by the withdrawal movement), in a control situation (*g*) and during hypnotic analgesia (*h*). (*i*), (*j*) Early and late responses of the VM to noxious skin stimuli on the calf and the front of the leg (arrows) in sitting (*i*) and standing (*j*) position. (*k*)–(*m*) Diagrams showing the inhibitory and excitatory responses (estimated as in (*e*)) for gluteus maximus (Glut Max (*k*)), gastrocnemius-soleus (G-S, (*l*)) and tibialis anterior (TA, (*m*)). Modified from Hugon (1973) ((*b*)–(*d*)), and Hagbarth & Finer (1963) ((*e*)–(*m*)), with permission.

Schomburg, 2000), but the stimulus necessary to produce withdrawal reflexes are of high intensity and may damage the skin.

Electrical stimuli

Electrical stimuli are artificial and, when stimulating a nerve trunk, other afferents are almost certainly activated, e.g. joint afferents when stimulating the sural or digital nerves, and muscle and joint afferents when stimulating the tibial nerve at the ankle or its distal plantar branches. Caution should be observed in interpreting the evoked responses. For example, spindle afferents from plantar muscles project to lower limb motor nuclei, and produce strong monosynaptic Ia, non-monosynaptic group I and group II excitation in tibialis anterior motoneurones (cf. Table 2.1, Fig. 10.14(*b*), Table 7.3), a motoneurone pool which is often used to investigate cutaneous pathways in the lower limb. The RII-like response produced in forearm muscles by stimulation of the ulnar nerve is subject to the same criticism, because ulnar nerve stimulation also activates muscle group I and group II afferents from the intrinsic muscles of the hand, afferents that have potent excitatory projections to motoneurones of wrist flexors (cf. Chapter 7, p. 305). Despite these drawbacks, electrical stimulation is the only method that allows accurate measurement of response latencies and is therefore usually preferred.

Recording the responses

Responses recorded at rest

A recording at rest is made under conditions similar to those of the routine clinical examination. However, only excitatory responses can be so disclosed.

Modulation of the average rectified EMG

This is the most commonly used method, because it rapidly reveals the full-time course of excitatory and inhibitory effects produced by the cutaneous volley. The temporal resolution of the method is limited, but this is of less importance here, because there are many uncertainties about the number of interneurones in the pathway to the motoneurone, and millisecond precision is not required. The technique is suitable for comparing the reflex effects of cutaneous volleys in different motor tasks, at equivalent levels of background EMG activity (cf. p. 414 and pp. 427–30). However, there are drawbacks to the technique.

(i) Volition may bias the transmission in the reflex pathways.

(ii) Cutaneous afferents may have opposite effects on slow-twitch and fast-twitch motor units (cf. pp. 424–7), so that the EMG recorded during a strong contraction may contain a mixture of opposite responses.

Modulation of the monosynaptic reflex at rest

This technique does not introduce volitional bias. However, besides their effects on motoneurones, cutaneous volleys can produce changes in the excitability of PAD interneurones transmitting presynaptic inhibition of Ia terminals mediating the afferent volley of the monosynaptic reflex: (i) depression by low-threshold cutaneous volleys (cf. p. 420), and (ii) activation by pathways transmitting late FRA effects (cf. p. 408). In addition, a monosynaptic reflex cannot be obtained in all muscles, and plotting the recovery curve of the H reflex or tendon jerk reflex takes a long time because cutaneous effects are long lasting. This is distinctly inconvenient when investigating patients.

Recordings of single units

PSTHs of single units should be recorded because of the opposite effect of some cutaneous stimuli on slow- and fast-twitch motor units. However, it is difficult to keep the same motor unit recording during a withdrawal reflex, and no data are available on the projections of nociceptive afferents to different types of motoneurones.

Conclusions

The method should be adapted to the type of study undertaken.

(i) When nociceptive reflexes are used to scale pain, i.e. assessing the effects of other stimuli or drugs on pain and/or monitoring patients with pain, volitional biases should be eliminated and noxious (RIII) responses should be studied at rest.

(ii) Task-related changes in exteroceptive pathways are best investigated with the modulation of the on-going EMG activity, because this rapidly provides the full time course of cutaneous-induced excitatory and inhibitory effects. However, such studies should be complemented by studies of the modulation of monosynaptic reflexes to estimate the extent of volitional bias and, when possible, by studies on single units to see whether the distribution of the cutaneous input is homogeneous or not among the different units in the tasks tested. Once again, this emphasises the necessity of using different methods in studies on human subjects.

Organisation, connections and physiological implications of withdrawal reflexes

Withdrawal reflexes are the traditional reflexes produced by cutaneous afferents in the standard neurological examination. The protective nature of these reflexes has long been appreciated. In 1899, Collier proposed that the function of the flexion reflex of the leg was to withdraw the foot from an offending object. Pioneering EMG studies by the Scandinavian school in the early 1960s demonstrated that the protective function of withdrawal reflexes was considerably more refined than had previously been assumed (see pp. 401–7), and recent investigations have confirmed a modular organisation of these reflexes in normal humans, much as has been described in animal experiments (see p. 407). There are two classes of withdrawal reflexes in the lower limbs: the early reflexes occurring with a latency less than 100 ms, reflexes which are almost certainly spinal, and the long-latency responses (see Figs. 9.3(*e*), (*f*), 9.4(*f*)–(*j*), 9.7(*b*)–(*j*)). In this chapter, 'withdrawal reflexes' denote the former when not otherwise stated. Long-latency reflexes are considered separately on pp. 407–11. Conclusions about the pathways underlying withdrawal reflexes (in particular the involvement of long-latency responses) rely on results recorded in patients with complete spinal cord transection. These latter results are therefore considered in the subsections discussing the spinal pathways mediating withdrawal reflexes.

Afferent pathway of withdrawal reflexes

The afferent pathway of the RIII reflex of the short head of the biceps femoris to stimulation of the sural nerve has been investigated in detail (Willer, 1977, 1983; Willer, Boureau & Albe-Fessard, 1978).

Parallel between pain sensation and the RIII reflex

Stimulation of the sural nerve

The close parallel between pain sensation and the size of the RIII reflex is illustrated in Fig 9.2(*l*), (*m*) (Willer, Roby & Le Bars, 1984), illustrating the effects of a train of ten shocks applied to the sural nerve on the area of the RIII reflex of the biceps femoris (*l*) and on the sensation (*m*), scaled from 0 (no sensation) to 10 (intolerable pain). The reflex threshold and the liminal pain sensation, described as a sharp pinprick localised to the point of stimulation (occurring at ~3 on the scale sensation, Willer, 1977), occur at the same stimulus intensity (~10 mA). Increasing stimulus intensity produces a continuous and almost linear increase in both the reflex size and the pain sensation up to a maximum, corresponding to the threshold for intolerable pain, above which further increases in stimulus intensity no longer enhance the RIII reflex or the pain sensation.

Stimuli delivered to the skin

When the stimulus is delivered to the skin in the receptive field of the sural nerve instead of the nerve,

the thresholds for the reflex and the pain sensation are reduced to ~5 mA, and curves similar to those in Fig. 9.2(*l*), (*m*) will be recorded, though shifted to the left (Willer, 1977). This shift has been attributed to an inhibitory action of low-threshold afferents in the trunk nerve on transmission in the pathway of the withdrawal reflex (cf. pp. 411–12).

Afferent volleys involved in producing the RIII reflex and pain

Role of Aδ fibres

The role of Aδ fibres in the production of the RIII reflex has been demonstrated by Willer, Boureau & Albe-Fessard (1978), who recorded the reflex in the biceps femoris and the neurogram in the sural nerve (right and left traces in Fig. 9.2(*i*)–(*k*)). With single shocks of 0.5 ms duration, the first wave to appear in the neurogram was characteristic of large-diameter fast-conducting low-threshold afferents (Aβ, 55–60 m s^{-1}). At the maximal Aβ amplitude, the sensation was not painful and no RIII response was recorded. Pain and the RIII reflex appeared at high stimulus intensities of 40–50 mA, when a small delayed response could be recorded in the neurogram (arrow in Fig. 9.2(*i*)), indicating the recruitment of high-threshold Aδ fibres with conduction velocities of 17–28 m s^{-1}. That the recruitment of Aδ fibres was necessary to evoke both the RIII reflex and pain was confirmed by their disappearance after a lidocaine block of small afferents (Fig. 9.2(*j*)). Similarly, it is probable that the afferent fibres responsible for abdominal skin reflexes are within the Aδ range, since their conduction velocity has been estimated to be ~20–30 m s^{-1} (Kugelberg & Hagbarth, 1958).

Possible contribution of Aβ fibres

Aβ fibres may contribute to both the RIII reflex and pain, provided that they are repetitively stimulated (Willer, Boureau & Albe-Fessard, 1978). Thus, 10 min after a lidocaine block of the Aδ fibres, pain and the RIII reflex could be produced by double-shock stimulation activating only Aβ fibres, although not by a single shock (Fig. 9.2(*j*), (*k*)). Accordingly, it was found that stimulation of the sural nerve by a train at 15 mA, far below the electrical threshold of Aδ fibres, produced both an RIII reflex and a pain sensation which increased with the number of pulses in the conditioning train.

Central pathway of early withdrawal responses

The precise number of interneurones intercalated in polysynaptic 'flexion reflex' pathways is unknown, even in the acute spinal cat, and these 'chains of interneurones' contrast with the well-identified oligosynaptic pathways responsible for the reflex effects of low-threshold muscle afferents. The problem in determining the pathway and central delay of the withdrawal reflex is even more acute in humans because of the length of the afferent pathway and the relatively slow conduction of human afferents compared with those of the cat. It is therefore not surprising that a crucial question about the central pathway of human withdrawal responses is the extent to which withdrawal responses are spinal reflexes.

Central delay

Superficial abdominal reflexes

Abdominal reflexes have been unequivocally demonstrated to be spinal. With strong stimuli their latency may be as short as 24 ms (Fig. 9.3(*s*)), with a minimal central delay of 3–5 ms, and this excludes a supraspinal pathway (Kugelberg & Hagbarth, 1958).

The central delay of the withdrawal reflexes of the limbs is less well defined

(i) The gradual decrease in the latency of the inhibition of knee extensors when the nociceptive stimulus is moved up the limb has been one of the first arguments in favour of a spinal pathway for the withdrawal response (Hagbarth, 1960).

Thus, Fig. 9.4(*e*) shows that the latency of the initial inhibition of the on-going EMG of the vastus medialis decreases from about 65 to 35 ms when the noxious stimulus train is moved from the foot to the perineal or ischial region. This would correspond to a conduction velocity of 33–40 m s^{-1}, further suggesting that afferents larger than Aδ size are involved in the production of withdrawal responses. When allowance was made for a period of temporal summation and the efferent conduction time, Hagbarth (1960) concluded that the central delay 'can hardly permit participation of pathways higher than spinal in the basic reflex arcs'.

(ii) The RIII reflex of the biceps femoris after sural nerve stimulation is the best documented withdrawal response and has a minimal latency of ~80 ms. Given (i) the long conduction time of the slow Aδ volley over the long distance from the ankle to the spinal cord (~40–50 ms and ~110 cm, respectively), and (ii) the necessity for temporal summation at interneuronal level, such a latency is compatible with a polysynaptic spinal pathway (Hugon, 1973, Willer, 1983). However, the exact central delay remains unknown, and it could be argued that 80 ms is also the latency of transcortical responses elicited by Aβ fibres (see pp. 421–3), which may evoke the RIII reflex (see above).

(iii) Withdrawal reflexes evoked in the tibialis anterior appear to be spinal on latency grounds. Shahani &Young (1971) reported a minimal latency of 50–60 ms after stimulation of the sole of the foot, but the afferent volley was not recorded, and it is conceivable that the high intensity intradermal stimulation activated afferents from plantar muscles. However, a recent investigation using weak stimulus intensities has confirmed that the minimal latency of the withdrawal reflex in the tibialis anterior may be as early as 65 ms (Andersen, Sonnenborg & Arendt-Nielsen, 1999).

(iv) In the upper limb, the latency of the nociceptive silent period in the abductor pollicis brevis is 43 ms (see Kofler, 2003; Fig. 9.6(*g*)), significantly earlier than the transcortical response mediated through Aβ fibres (see pp. 421–3), and this is evidence in favour of a spinal pathway.

Patients with complete spinal transection

Reflexes with similar features can be recorded in the tibialis anterior and the biceps femoris in patients with complete spinal transection, and this is often used as an argument for a spinal origin of withdrawal reflexes in normal subjects (Shahani & Young, 1971; Hugon, 1973; Willer & Bussel, 1980; Roby-Brami & Bussel, 1987). The existence of such reflexes in these patients does demonstrate that there is a spinal pathway capable of mediating the RIII reflex in humans, but the similarity of the latencies does not imply that the responses are mediated by the same pathway in normal awake subjects and spinal patients (see pp. 407–11).

Conclusions

It is probable that the early withdrawal responses of lower limb muscles are spinal in awake normal subjects. However, some uncertainties remain:

(i) In investigations using stimulation of the tibial nerve at the ankle or of its branches, particularly the medial plantar nerve, group II muscle afferents probably contribute to the responses in the tibialis anterior (cf. p. 398).

(ii) Because of the need for temporal summation, the exact central latency of these reflexes is uncertain, and so is the number of interneurones intercalated in the relevant pathway(s).

(iii) The nature of these pathways (specific or FRA-like) also remains an open question, although there is increasing evidence that there is a highly specialised modular organisation of withdrawal reflex pathways (see p. 407).

Functional organisation of early withdrawal reflexes

In the 1910s, emphasis was placed on the segmental organisation of the skin withdrawal reflexes (Walshe,

1914). However, as pointed out by Kugelberg (1962), EMG studies have shown little evidence for segmental boundaries (see below). It is clear that early withdrawal reflexes are not organised on an anatomical (segmental) basis, but on a functional basis designed to produce rapid movement away from an offending object. The 'local sign' is an important feature of withdrawal reflexes everywhere (on the trunk as well as in the limbs), and is a consequence of this protective function.

Trunk skin reflexes

Trunk skin reflexes are considered first, because from their relatively simple organisation it is easy to understand the general functional organisation underlying withdrawal reflexes. Although the abdominal skin reflex is regarded as a nociceptive reflex, the reflex may be elicited by stimuli of innocuous quality, such as touch, probably because of the convergence of tactile and nociceptive inputs from the same skin field onto common interneurones, much as described in the rat (see p. 387). These reflexes have been investigated in detail by Kugelberg & Hagbarth (1958) and an example of abdominal reflexes in the external oblique is illustrated in Fig. 9.3(*l*)–(*n*) and (*p*)–(*s*) using mechanical and electrical stimulation, respectively. Abdominal skin reflexes show little evidence of any segmental boundaries and radiate over several segments ipsilaterally and, to a lesser extent, contralaterally, although the response with the lowest threshold and the shortest latency is confined to the ipsilateral segments in the immediate vicinity of the stimulus. 'A painful stimulus applied to the abdominal skin during steady contraction of the erector spinae muscles evokes a reflex contraction of abdominal muscles with reciprocal inhibition of the activity in the erector spinae muscles. . . . In fact, a stimulus applied at any point on the circumference of the trunk produces a contraction pattern with withdrawal from the offending stimulus. Thus, the abdominal skin reflexes are but one manifestation of a defence mechanism of the trunk which functionally connects each skin area with the appropriate withdrawal and protection muscles' (Kugelberg, 1962).

Plantar responses

Because of the clinical importance of plantar responses evoked from the sole of the foot, their refinement with respect to the area of the stimulus, and the considerable literature devoted to them, they are considered apart from the other withdrawal responses in the lower limb.

Involvement of the extensor hallucis longus

Different results concerning the involvement of the extensor hallucis longus have been obtained using mechanical and electrical stimulation of the hollow of the foot.

(i) Mechanical stimulation produced by the point of a safety-pin on the lateral plantar surface and lateral surface of the foot was used by Landau & Clare (1959) to analyse plantar responses, grading the stimulation by varying the pressure of the pin. They showed that at threshold, in normal adults, the response in the flexor hallucis brevis (a physiological extensor) appeared before that in the tibialis anterior (Fig. 9.5(*b*), (*c*)). Increasing the pressure caused a general flexion reflex of the lower limb to develop, with responses in the extensor hallucis brevis, semitendinosus and tensor fasciae latae (Fig. 9.5(*e*)). The crucial point of their description was that, whatever the stimulus strength, the response spared the extensor hallucis longus (a physiological flexor, Fig. 9.5(*e*), (*f*)), explaining the normal plantar flexion of toe 1.

(ii) Noxious electrical stimuli were applied to the skin of the hollow of the foot to produce a general flexion reflex of the ankle, knee and hip by Kugelberg, Eklund & Grimby (1960) and Grimby (1963). This flexion reflex was accompanied by activation of muscles responsible for dorsiflexing toe 1 and those for plantar flexion more or less simultaneously at a latency of 70–80 ms. However, the plantar flexors were activated more strongly so that the net force moved the toe down.

Functional organisation with respect to the receptive field

The organisation is sketched in Fig. 9.5(*j*)–(*l*), and was investigated in detail using strong electrical

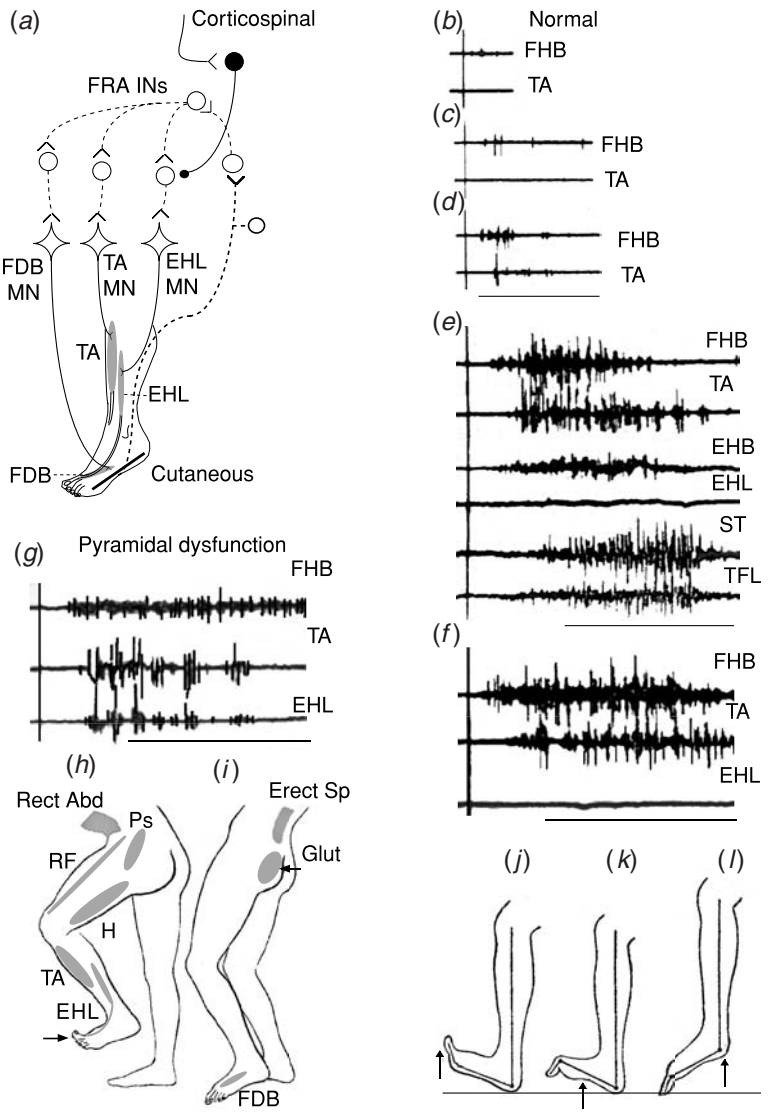


Fig. 9.5. Responses evoked by mechanical stimulation on the lateral plantar surface of the foot. The Babinski sign. (*a*) Sketch of the presumed pathways. Cutaneous afferents from the lateral part of the sole of the foot activate a chain of interneurones (IN), which mediate excitation to extensor hallucis longus (EHL), tibialis anterior (TA) and flexor digitorum brevis (FDB) motoneurones (MN). Transmission in the pathway to EHL MNs is normally tonically inhibited from the corticospinal tract. (*b*)–(*g*) EMG responses elicited by mechanical stimulation of the lateral plantar surface of the foot in various muscles: FHB, TA, extensor hallucis brevis (EHB), EHL, semitendinosus (ST), tensor fasciae latae (TFL). Moment of contact: vertical continuous line. (*b*)–(*e*) Responses obtained by increasing pressure in the same normal subject. (*f*), (*g*) Responses in the FHB, TA and EHL are compared in another normal subject (*f*) and in a tetraplegic patient ((*g*), two months after the injury). Horizontal calibration: 1s. (*h*)–(*l*) Schematic drawing of withdrawal reflexes after electrical stimulation (arrows) on the ball of the great toe ((*h*), flexion reflex with contraction of the EHL, TA, hamstrings [H], rectus femoris [RF], psoas [Ps], rectus abdominis [Rect Abd]), on the buttock ((*i*) extension reflex with contraction of gluteus maximus [Glut], erector spinae [Erect Sp] and FDB), and on different parts of the sole of the foot ((*j*)–(*l*)). Modified from Landau & Clare (1959) ((*b*)–(*g*)), Kugelberg, Eklund & Grimby (1960) ((*h*), (*i*)), and Kugelberg (1962) ((*j*)–(*l*)), with permission.

stimuli applied to various areas of the sole of the foot (Kugelberg, Eklund & Grimby, 1960; Grimby, 1963). As stated by Kugelberg (1962), 'the reflex defence system for the plantar surface of the toes and foot is designed primarily to protect the foot when the subject is in the upright position, e.g. during walking, running and jumping, when the chances of an injury to the foot are the greatest'.

(i) The ball of the toes is the only area for which flexion of all lower limb muscles is the adequate protection movement. Accordingly, stimulation of the ball of toe 1 in a normal subject will elicit reflex contraction of both the extensor hallucis longus and brevis with dorsiflexion of toe 1, withdrawing it from the offending stimulus (Fig. 9.5(*j*), (*h*)).

(ii) A stimulus to the hollow of the foot and the surrounding areas produces the normal plantar reflex, i.e. plantar flexion of the toes with flexion at the ankle, knee and hip. This is the adequate movement for protection of this area. When the subject is standing upright, plantar flexion of the toes would raise the sole from the ground (Fig. 9.5(*k*)) and so long as the toes are in contact with the ground would assist in the general withdrawal movement.

(iii) When the stimulus is applied to the heel, there is a plantar flexion of the toes and extension of the ankle (Fig. 9.5(*l*)). This pattern, combined with flexion at the knee and hip, represents the most effective withdrawal response to protect the heel.

Maturation of plantar responses

In 1898, Babinski drew attention to the presence of an upward response of toe 1 in the newborn, a phenomenon that had not escaped the renaissance artist, Botticelli (see Lance, 2002). In normal neonates, stimulation of the sole of the foot produces a flexion synergy with an upward response of the toes, which is much brisker than in adults. As the pyramidal system matures, the response of the toes becomes reversed at a variable age from 7 months to a year or more, and the entire flexion reflex becomes less brisk. In most normal adults all that is left is a subtle contraction of proximal muscles, particularly of the tensor fasciae latae (see van Gijn, 1996). In this respect, the normal response in clinical investigation is closer to that illustrated in Fig. 9.5(*d*) than that of Fig. 9.5(*e*), which may have been produced by a more painful stimulus.

Other withdrawal responses than plantar responses in the lower limb

The principles underlying the general organisation of withdrawal reflexes other than plantar responses in the lower limb have been established in a seminal paper by Hagbarth (1960). Noxious electrical stimuli (trains of 5–10 stimuli in 10–20 ms, at 5–10 mA, producing an intense burning sensation) were applied to different areas of the skin of the limb during weak on-going contractions of various lower-limb muscles. This allowed a systematic analysis of the receptive fields for withdrawal responses in individual muscles.

Receptive fields for individual muscles

Figure 9.4(*e*) shows the responses in the vastus medialis, a pure extensor of the knee. Stimuli applied to the leg or the posterior aspect of the thigh caused an initial inhibition, while stimuli to the anterior aspect of the thigh caused an initial reflex discharge. The sketches of Fig. 9.4(*k*)–(*m*) show the results of similar analyses performed for the hip extensor, gluteus maximus, the ankle extensor, gastrocnemius-soleus and the ankle flexor, tibialis anterior. Skin areas which produced primarily excitation are indicated by +, and those which produced inhibition by –. It should be noted that gastrocnemius-soleus responded in a reciprocal manner to tibialis anterior, activated from those skin areas which inhibited the flexor, and vice versa. These results agree fairly well with those obtained in the spinal cat (see p. 387). The weak voluntary contraction used in these experiments probably did not bias the results significantly: noxious stimuli applied to the distal part of the limb produce an early facilitation of the biceps femoris tendon jerk and inhibition of quadriceps and soleus tendon jerks at ISIs corresponding to the latencies of the excitatory and inhibitory responses in the

on-going EMG of these muscles (Hugon, 1973, and Fig. 9.4(*b*)–(*d*), (•)). The organisation of withdrawal reflexes in humans can be summarised by stating that extensor muscles are inhibited from most parts of the limb as part of the flexion withdrawal, but are activated by cutaneous stimuli over the muscle itself. There are reciprocal responses in antagonistic flexor muscles.

The main function of early nociceptive reflexes is protective

The flexion movement which occurs at joints proximal to the stimulus represents the classical flexion reflex, and has an avoidance capacity. The protective function of extension movements at joints distal to the stimulus is also protective if the subject is standing with lower-limb joints in slight flexion. Ankle extension then removes the leg from calf stimulation, and knee extension causes withdrawal from an offending object on the front of the thigh. Similarly, a stimulus to the buttock produces extension of the hip and contraction of the erector spinae, both of which result in withdrawal from the stimulus (see Kugelberg, Eklund & Grimby, 1960; Fig. 9.5(*i*)).

Withdrawal responses in the upper limb

Silent periods in intrinsic muscles of the hand

The most systematic study of silent periods evoked by noxious stimuli in intrinsic muscles of the hand is the recent investigation by Kofler (2003), which also reviews the literature on this topic. The higher the stimulus intensity to the finger tip, the deeper the cutaneous silent period in the abductor pollicis brevis (APB) and the earlier its latency (Fig. 9.6(*d*)–(*g*)). Qualitatively similar results were found in the abductor digiti minimi (ADM) and the first dorsal interosseous (FDI). However, in response to noxious stimulation (20 × PT) to the index and fifth fingers, there is a clear 'local sign' in the silent periods of the three muscles, which are supplied by the same myotome. Stimulation caused an earlier and deeper nociceptive silent period in APB and FDI when applied to the index finger than to finger V, while the reverse occurred with ADM. Again, this indicates a functional organisation of the underlying spinal circuitry which is not based on anatomical metameric boundaries, but on the functional relevance of the responses. Appropriately, there is a similar topographic organisation of tactile cutaneomuscular reflexes, again suggesting convergence of tactile and nociceptive afferents from the same skin field onto common interneurones. The finding that the H reflex and the MEP in the APB are similarly inhibited by noxious cutaneous stimuli indicates that the suppression is due to postsynaptic inhibition of motoneurones, not to presynaptic inhibition of the contraction-associated Ia afferent activity that helps sustain the voluntary contraction (Manconi, Syed & Floeter, 1998; Fig. 9.6(*h*)–(*m*); cf. Chapter 8, pp. 343–4).

Withdrawal responses elicited at rest

There have been few studies of withdrawal responses in non-contracting muscles of the upper limb. Cambier, Dehen & Bathien (1974) reported that stimulation of Aδ fibres in the ulnar nerve at the wrist evokes a RIII-like reflex, with a minimal latency of 60 ms in the FCU, involving biceps with higher intensities. The question was revisited recently by Floeter *et al.* (1998) using electrical stimulation of the digital nerves. Single shocks did not evoke any reflex at any intensity. A noxious train to the index finger evoked a response in all recorded muscles (Fig. 9.6(*b*)), but the net biomechanical result was flexion of the elbow and extension of the wrist. The shortest latencies were seen in the biceps, ECR and FCR, 60–80 ms after stimulus onset. A response was not seen consistently in intrinsic muscles of the hand and, when present, occurred at a longer latency (80–100 ms). Interestingly, the latency of the response in wrist muscles (ECR and FCR) was shortened by 20–30 ms, when noxious stimulation of the contralateral index finger was delivered 100 ms before the test train. This result supports the view that withdrawal responses are mediated through a spinal mechanism. Changes in the location of the stimulus

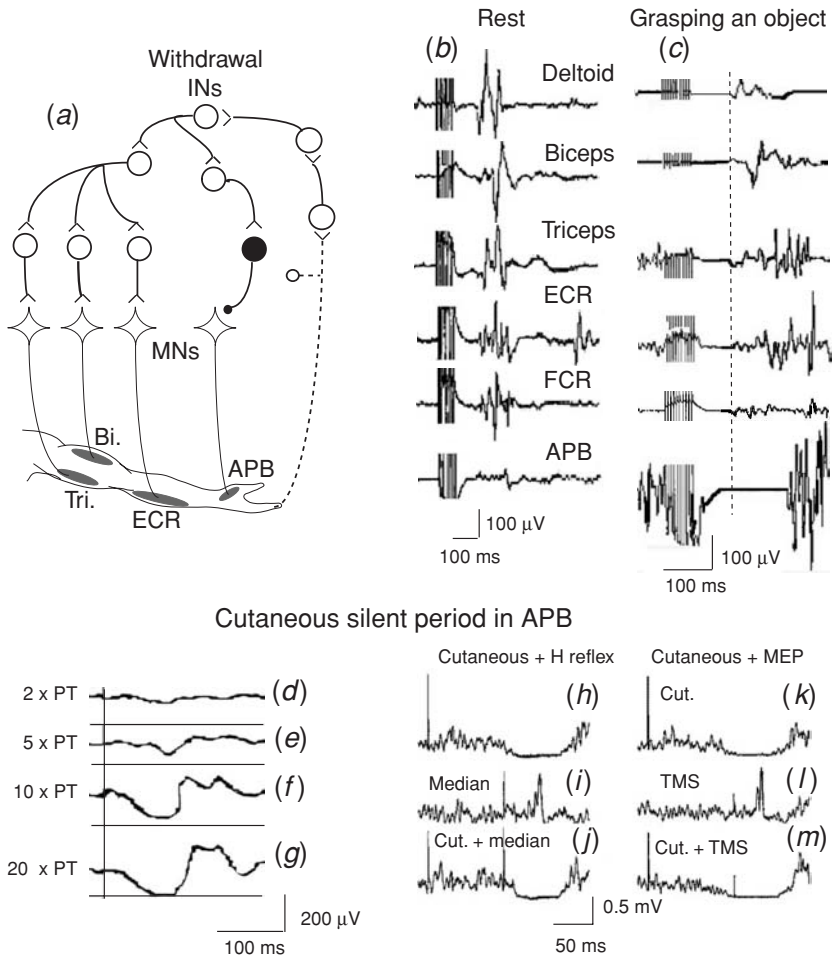


Fig. 9.6. Cutaneous withdrawal reflexes of the upper extremity. (*a*) Sketch of the presumed pathways: cutaneous afferents mediating pain sensation from the index finger excite, through a chain of spinal interneurones (withdrawal IN), motoneurones (MN) innervating proximal muscles (biceps [Bi], triceps [Tri], extensor carpi radialis [ECR]), and inhibit MNs innervating intrinsic muscles of the hand such as abductor pollicis brevis (APB). (*b*), (*c*) EMG responses recorded, from top to bottom, in deltoid, Bi, Tri, ECR, FCR and APB following cutaneous stimulation to the index finger (10 pulses, 300 Hz, at 4 × PT in (*b*) and 6 × PT in (*c*), stimulus artefacts being redrawn and truncated). (*b*) Responses obtained at rest. (*c*) Responses during grasping an object between thumb and forefinger while keeping more proximal muscles relaxed. The onset of EMG activity in proximal muscles (dotted vertical line) occurred when EMG activity was silenced in the intrinsic muscles of the hand. (*d*)–(*m*) Cutaneous silent period in the APB evoked by a single electrical shock. (*d*)–(*g*) Rectified APB EMG (20% of MVC) conditioned by increasing electrical stimulation applied to the tip of the index finger: 2 × PT (*d*), 5 × PT (*e*), 10 × PT (*f*), 20 × PT (*g*). The vertical line indicates stimulus onset, and horizontal lines indicate zero EMG activity. (*h*)–(*m*) Suppression by stimulation (6 × PT) to the fifth finger of various responses in the APB. (*h*), (*k*) Silent period in the on-going EMG. (*i*), (*l*) Control H reflex (*i*) and MEP (*l*), (*j*). (*m*) Cutaneous suppression both of the H reflex (80 ms ISI) and the MEP elicited by TMS (90 ms ISI). The stimulus artefacts in (*i*), (*j*) and (*l*), (*m*) indicate the timing of the median and TMS stimuli, respectively. Modified from Floeter *et al.* (1998) ((*b*), (*c*)), Kofler (2003) ((*d*)–(*g*)), and Manconi, Syed & Floeter (1998) ((*h*)–(*m*)), with permission.

(finger V, palmar or dorsal side of fingers II and III) did not change the responses. Arguably, this may not represent the absence of 'local sign' because, whatever the hand region stimulated, the adequate reaction is to withdraw it.

Relationship between the nociceptive silent period in hand muscles and proximal withdrawal reflexes

This relationship was explored by delivering the noxious stimulus to fingers II or V as the hand grasped an object between thumb and forefinger, while proximal muscles were relaxed (Floeter *et al.*, 1998). As shown in Fig. 9.6(*c*), a silent period was produced in hand muscles at the same time as withdrawal excitation was evoked in forearm and arm muscles. As a result, most subjects transiently lost their grasp on the object, sometimes tossing it away, and moved the arm upwards and outwards.

These nociceptive responses have a protective function

The combination of the withdrawal reflex in proximal muscles and the silent period in hand muscles is appropriate for protecting the hand, opening and withdrawing it when there is an offending stimulus to the fingers. The functional relevance of nociceptive responses is also supported by the finding that the functional unit which is most intimately involved in the prehensile grasp (index and thenar) receives the most powerful inhibition from the index (Kofler, 2003; see above).

Modular organisation of withdrawal reflexes

The above results show a specific organisation of withdrawal reflexes with a 'local sign'. Recent investigations using less painful stimuli at 1.5 × pain threshold applied to 16 different limited areas of the sole of the foot have delineated the organisation of excitatory and inhibitory withdrawal responses evoked in various ankle muscles (Andersen, Sonnenborg & Arendt-Nielsen, 1999; Sonnenborg, Andersen & Arendt-Nielsen, 2000). The results concerning ankle dorsiflexion and plantar flexion seen on pp. 402–4 were confirmed, and it was shown in addition that stimuli to the medial distal sole produce inversion of the foot, while those to the lateral distal sole produce eversion. Thus, it seems that humans have a similar modular organisation of withdrawal reflexes as in the rat (p. 387).

Late withdrawal responses

In normal subjects, late withdrawal responses, at a latency longer than 120 ms, usually follow the early responses, when the stimulus intensity is high (Figs. 9.3(*e*), (*f*), 9.4(*i*), (*j*)). In tibialis anterior, the main mechanical component of the withdrawal movement is produced by the long-latency response (cf. upper trace in Fig. 9.3(*f*); Shahani & Young, 1971). Late responses also occur in the upper limb (e.g. see the response in the ECR in Fig. 9.6(*b*)). Results obtained in patients with complete spinal transection (cf. below) show that humans have a pathway analogous to the long-latency FRA pathway described in the cat (cf. pp. 390–1), but whether long-latency withdrawal responses in normal subjects are transmitted through this pathway is a matter of debate.

Late withdrawal responses in patients with complete spinal cord transection

In patients with complete spinal cord lesions, several arguments suggest the existence of a pathway transmitting long-latency responses, analogous to the long-latency FRA pathway described in the acute spinal cat after DOPA (Roby-Brami & Bussel, 1987, 1990, 1992).

Long-latency flexor reflexes

When such patients are tested more than 6 months after the initial lesion, noxious cutaneous stimuli applied to the nerves of the foot do not produce the same withdrawal responses in flexor muscles as in normal subjects.

(i) In tibialis anterior and, to a lesser extent, in biceps femoris, early responses with a latency less than 120 ms are rare (Fig. 9.7(*c*)–(*f*) and (*g*)–(*j*)).

(ii) Instead, long-lasting long-latency responses appear consistently in the two muscles (Fig. 9.7(*c*)–(*j*)). When both responses are present, the threshold for the late response is lower than that for the early response. The finding that late responses often appear without any early response in homonymous or heteronymous muscles indicates that they are neither afterdischarges (see Creed *et al.*, 1932) nor produced by twitch-induced afferent discharges.

Early FRA pathways inhibit late FRA pathways

A crucial feature of late responses is their increase in latency as the stimulus intensity increases (Fig. 9.7(*c*)–(*j*)), or the stimulus train is prolonged. The latter point is illustrated in Fig. 9.7(*b*), which shows that the onset of the late reflex is delayed after the end of the stimulus train regardless of its duration. This is reminiscent of the long-latency FRA response observed in the acute spinal cat injected with DOPA (see Lundberg, 1979; pp. 390–1), and the above results could be explained by inhibition of transmission in late FRA pathways by activation of early FRA pathways, even though this was insufficient to produce an overt early FRA response. Thus, the primary change in the spinal cord following the chronic spinal lesion could be decreased excitability of pathways mediating early responses. This would account for (i) the depression of early flexion reflexes with respect to normal subjects, and (ii) the resulting release of transmission in late FRA pathways (pathway 'Y' in Fig. 9.1(*e*)). However, even though the activation of early FRA pathways is insufficient to evoke the early flexion reflex, the late response might still be inhibited by activation of early pathways, and this would occur with a shorter central delay than the late reflex itself. Through pathway 'X1' in the sketch of Fig. 9.1(*e*), this inhibitory effect would prevent the late reflex from manifesting itself until the inhibition ceased. As a result, there would be an increase in latency of the late response when the conditioning train was prolonged, much as occurs in the DOPA-treated cat.

Presynaptic inhibition of Ia terminals

Stimulation of contralateral high-threshold cutaneous afferents has complex effects on the soleus H reflex (Fig. 9.7 (*k*)). There is an early peak of facilitation at the same latency as the early ipsilateral response of flexor muscles, corresponding to the crossed extensor reflex. This is followed by a late long-lasting but weak facilitation at ISIs of 200–700 ms, and then by inhibition. The late facilitation is weak, because it is the result of two opposite effects: (i) a post-synaptic excitation, which is the counterpart in contralateral extensors of the ipsilateral long-latency excitation of flexors, and (ii) increased presynaptic inhibition of Ia terminals mediating the afferent volley of the soleus H reflex, demonstrated using the heteronymous facilitation of the H reflex (Chapter 8, pp. 345–6). These results provide a further similarity to the late FRA responses observed in the DOPA-treated cat, in which there is long-latency long-lasting postsynaptic excitation of contralateral extensors, together with a long-lasting primary afferent depolarisation of Ia terminals of both sides (Lundberg, 1979).

Stimulation of contralateral high-threshold cutaneous afferents depresses the late ipsilateral flexor reflex

When stimulation of contralateral afferents conditions the ipsilateral reflex in tibialis anterior, the early flexor response is not affected, while the late response disappears almost completely (Fig. 9.7(*l*), (*m*)). This inhibition is not due to inhibition of the target motoneurones, because the tibialis anterior H reflex is not inhibited, or to presynaptic inhibition of cutaneous terminals mediating the flexor reflex response, because the early response is not modified. The most parsimonious explanation is therefore mutual inhibition between the chains of interneurones mediating long-latency ipsilateral and contralateral FRA effects, much as described in the DOPA-treated cat (see Lundberg, 1979; Fig. 9.1(*d*)).

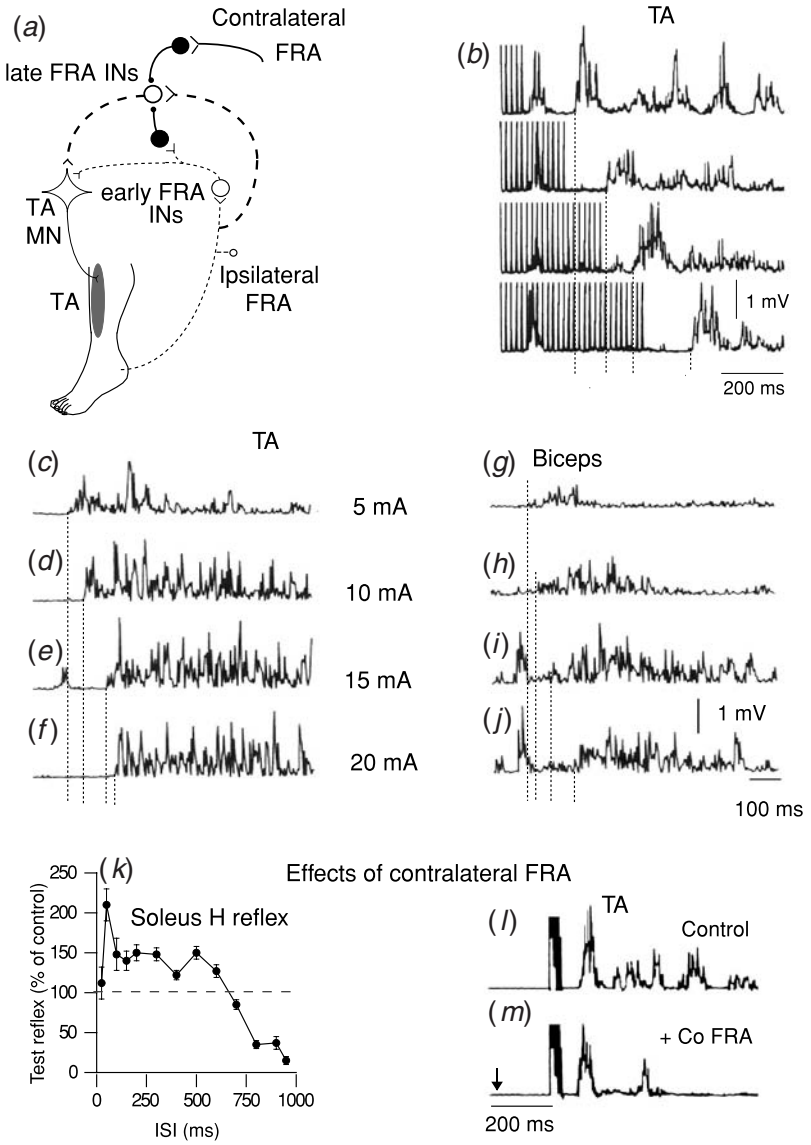


Fig. 9.7. Late flexion reflex in paraplegic patients. (*a*) Sketch of the presumed pathways: ipsilateral flexor reflex afferents (FRA) activate a chain of early FRA interneurones (INs) (thin dotted line) and a chain of late FRA INs (thick dashed line). Late FRA INs are inhibited by early FRA INs and by contralateral FRA. (*b*) Rectified EMG responses in tibialis anterior (TA) to stimulus trains (70 Hz, 50 mA) of increasing duration (60, 160, 260, 360 ms from top to bottom) to the tibial nerve (the stimulus artefacts being redrawn and truncated). (*c*)–(*j*) Rectified EMG responses (average of three sweeps) elicited simultaneously in TA ((*c*)–(*f*)) and biceps femoris ((*g*)–(*j*)) to stimulation of the sural nerve (trains of 10 shocks, 300 Hz) of increasing intensity: 5 mA ((*c*), (g)), 10 mA ((*d*), (*h*)), 15 mA ((*e*)–(*i*)), 20 mA ((*f*)–(*j*)). Vertical dotted lines in (*b*)–(*j*) highlight the increase in latencies of the late responses when the stimulus train was prolonged (*b*), or the stimulus intensity increased ((*c*)–(*j*)). (*k*)–(*m*) Effects of stimulation of the contralateral FRA (train of ten shocks to the sural nerve, 300 Hz, 50 mA) on the soleus H reflex (*k*) and the early and late flexor reflexes elicited in TA by ipsilateral stimulation of the sural nerve ((*l*), (*m*)), train of ten shocks, 300 Hz, 10 mA). (*k*) The size of the H reflex (expressed as a percentage of its unconditioned value) is plotted against the ISI. Each point is the mean of five measurements, vertical bars ±1 SEM. (*l*)–(*m*) Flexor reflexes in the TA in a control situation (*l*) and when stimulation of contralateral FRA (*m*) occurs 200 ms earlier (arrow). Modified from Roby-Brami & Bussel (1987) (*b*), and Bussel *et al.* (1989) ((*c*)–(*m*)), with permission.

Conclusions

Several lines of evidence suggest that the human spinal cord contains a pathway analogous to the long-latency FRA pathway revealed in the acute spinal cat by the administration of DOPA. The finding that, in patients with complete spinal cord transection, long-latency responses only appear in patients with chronic lesions, when early responses are attenuated or have disappeared (cf. p. 433), favours the view that transmission in long-latency pathways can be inhibited by pathways mediating the early effects.

Late responses in normal subjects are not spinal in origin

The late responses seen in normal subjects do not have the characteristics of long-latency reflexes described in patients with spinal cord transection and they are probably not spinal. Several features suggest that they involve supraspinal pathways.

Absence of characteristics of long-latency FRA-like responses

(i) Late responses of normal subjects are always associated with an early response, and the threshold of the late response is higher than that of the early response (Shahani & Young, 1971; Meinck, Benecke & Conrad, 1983). By contrast, in patients with spinal cord transection, the threshold of the early response is the higher, and the depression of transmission in the pathway of the early responses seems to be a prerequisite for the long-latency responses.

(ii) The latency of late responses decreases when the stimulus strength is increased (Shahani & Young, 1971). In spinal patients, increasing stimulus strength or the duration of the conditioning train increases the latency of the late response, a particularly strong argument in favour of a transmission of the late response though long-latency FRA pathways (Roby-Brami & Bussel, 1987; cf. p. 408).

Plasticity of late responses

Hagbarth & Finer (1963) performed experiments in which the noxious stimulus was continued up to the withdrawal movement which terminated the stimulus by removing the limb from the electrode. They so demonstrated that the avoidance capacity of withdrawal reflexes in a new situation depends on late not early responses.

(i) In the sitting position drawn in Fig. 9.4(*i*), a stimulus on the calf must cause a contraction of knee extensors to move the leg away from the stimulus. However, according to the results shown in Fig. 9.4(*e*), the initial reflex effect of a brief calf stimulus is inhibition of the activity in the vastus medialis, which would allow knee flexion with movement of the leg towards the stimulus (Fig. 9.4(*f*)). The same early effect was observed in experiments in which the stimulating current was continuous and the subject could avoid it only by removing the leg from the electrodes (which initially were in contact with the skin, but not attached to it). However, when continuous stimulation was applied, there was an extension of the knee due to a strong late discharge in the vastus medialis at a latency of 120 ms (Fig. 9.4(*g*)).

(ii) During hypnotic analgesia, the late discharge (and the resulting knee extension) disappeared, while the early inhibition was hardly influenced by suggestion (Fig. 9.4(*h*)).

(iii) The influence of the initial position on the early and late responses of the vastus medialis to continuous noxious stimulation applied to the front of the leg and the calf was determined when the subject was sitting and standing (Fig. 9.4(*i*)–(*j*)). Whatever the posture, both stimuli produced initial inhibition, an inappropriate response to calf stimulation in sitting position (*i*) and to stimulation of the front of the leg when standing (*j*) because such responses would move the leg towards the offending the stimulus. In both cases the appropriate movement occurred because a large late response compensated for the initial inappropriate response.

(iv) Training experiments were performed in which the subject could turn off a continuous unpleasant stimulus only by performing a movement towards the electrodes. The sign of the late response was reversed after a few trials, but not that of the early response even after training for a month.

The above results show that, while early responses are fixed, withdrawal responses can adapt to a new situation by a change in the sign of the late response. It was suggested that early responses are hardwired in the spinal cord, whereas the late responses of normal subjects involve supraspinal centres and have developed largely through experience (Hagbarth & Finer, 1963).

Interactions between different inputs in withdrawal reflex pathways

Besides the inhibition of the transmission in long-latency FRA pathways by activity in early FRA pathways, and the mutual inhibition of pathways mediating ipsilateral and contralateral long-latency reflexes seen above, various peripheral and descending inputs have been shown to modulate the transmission in withdrawal reflex pathways.

Effects of painful homonymous cutaneous volleys

The effects of repeated stimulation are complex with facilitation at short ISIs and suppression at long ISIs.

Facilitation at short ISIs

Repeated painful cutaneous volleys at intervals below 3 s facilitate the withdrawal reflex in biceps femoris and tibialis anterior (Hugon, 1973; Shahani & Young, 1971). Thus, when a painful electrical stimulus to the sural nerve at 3.5 × PT is repeated every 2 s, the amplitude and duration of the RIII reflex in biceps femoris increases progressively, in parallel with the pain sensation, while its latency decreases (cf. Fig. 9.2(*n*)–(*q*) where the eleventh reflex of the series is larger than the fifth, which is itself larger than the first). The tibialis anterior withdrawal reflex elicited by stimulation of the medial aspect of the sole of the foot is similarly facilitated, with decreased latency, by a stimulus delivered 1 ms earlier (Shahani & Young, 1971; Fig. 9.3(*h*)).

Suppression at long ISIs

At ISIs longer than 3–4 s, facilitation is replaced by suppression, with decreased amplitude and duration and increased latency of the response (Shahani & Young, 1971; Fig. 9.3(*i*), (*j*)). Thereafter the response comes back to its control value by 60 s (Fig. 9.3(*j*)).

Underlying mechanisms

The mechanisms responsible for the modulation of withdrawal reflexes by preceding painful volleys are probably spinal, because similar results have been recorded in spinal patients with a complete spinal transection, both in the biceps femoris (Hugon, 1973) and the tibialis anterior (Shahani & Young, 1971; Dimitrijević & Nathan, 1968, 1971; Hornby *et al.*, 2003; Fig. 9.3(*j*)). The facilitation of the RIII reflex in the short head of biceps at short ISIs is not accompanied by a facilitation of the tendon jerk of this muscle at corresponding ISIs (Hugon, 1973). This indicates that the 'sensitisation' at short ISIs was exerted at a premotoneuronal level. The simplest explanation would be that facilitation at short ISIs and depression at long ISIs reflect post-activation facilitation and depression of transmission at the synapse of cutaneous afferents with interneurones. Depression, at least, has been described in dorsal horn interneurones activated by low-threshold cutaneous afferents (Hammar, Slawinska & Jankowska, 2002).

Effects of other peripheral inputs

Depression by tactile cutaneous volleys

Tactile cutaneous volleys depress the biceps femoris RIII reflex (Hugon, 1973), as illustrated in Fig. 9.2(*d*), (*e*), where tactile stimulation of the sural nerve at 1 × PT, 50 ms before the test stimulus, suppressed the withdrawal reflex almost completely. Accordingly, before ischaemic blockade of large Aβ fibres, the RIII reflex was small and preceded by the RII response elicited by tactile afferents, whereas after the block and the resulting disappearance of the RII reflex, the same stimulus evoked a much larger RIII

response (Fig. 9.2(*g*), (*h*); Willer, 1977). The depression of RIII by tactile afferents is maximal at ISIs of 100–300 ms and lasts for several hundreds of milliseconds (Hugon, 1973). A similar depression, though weaker and briefer, is observed after stimulation of tactile afferents in the superficial peroneal nerve. This depression could result from postsynaptic inhibition of interneurones mediating RIII effects by low-threshold cutaneous afferents, as has been described in the cat lumbosacral cord (Hongo, Jankowska & Lundberg, 1966). However, the long-lasting time course of the depression rather suggests presynaptic inhibition of cutaneous terminals by the conditioning cutaneous volley, a phenomenon that is potent in the cat (Eccles, Kostyuk & Schmidt, 1962).

Facilitation by non-noxious thermal stimuli

Stimuli produced by a CO_2 laser and evoking a sensation of warmth in the skin field of the sural nerve facilitate the RIII reflex of the biceps femoris. This facilitation has two peaks, at ISIs of 500 and 1100 ms, due to the convergence of Aδ and C fibres emanating from warmth receptors and from nociceptive afferents onto common interneurones (Plaghki *et al.*, 1998).

Descending effects

There is no direct evidence for descending control of pathways mediating withdrawal reflexes in humans. However, several arguments indicate the existence of descending controls.

(i) The attenuation of early withdrawal reflexes in patients with chronic spinal cord injury, when compared with normal subjects (pp. 407–8), indicates that the spinal lesion has deprived the relevant pathways of a tonic excitatory drive and/or removed tonic inhibitory control of a spinal inhibitory circuit. This could involve the monoaminergic inhibition from the brainstem described in the cat (see Lundberg, 1982; Fig. 9.1(*e*)).

(ii) The findings that early withdrawal reflexes may be modified by habituation and attention, and may be susceptible to hypnotic suggestion indicate a descending control of the pathways mediating such reflexes in the trunk and lower limbs (Kugelberg & Hagbarth, 1958; Hagbarth & Finer, 1963).

(iii) There are depressive effects of heterotopic noxious stimuli applied to a remote part of the body such as the hand or face on early withdrawal reflexes (Willer, Roby & Le Bars, 1984). These effects are not seen in patients with complete transection of the cervical spinal cord and could be another example of descending control of spinal withdrawal pathways (Roby-Brami *et al.*, 1987).

Changes in withdrawal reflexes during motor tasks

Voluntary contraction

Changes in withdrawal reflexes during voluntary contraction have been poorly documented, and would deserve to be revisited.

Cutaneous reflexes of the trunk

The cutaneous reflexes of the trunk evoked by a given stimulus may be altered by a change in posture or an appropriate voluntary contraction. The reflex alteration involves the latency and size of the reflex discharge, but occasionally there may be a reversal of the reflex effect (Kugelberg & Hagbarth, 1958).

Nociceptive inhibition of the soleus H reflex

Inhibition of the soleus H reflex produced by noxious stimulation of toe 1 or toe 5 has been compared at rest and during voluntary contractions of the soleus and tibialis anterior (Pierrot-Deseilligny *et al.*, 1973). As illustrated in Fig. 9.8(*b*), (*c*), the inhibition was more marked at rest with stimulation of toe 5. During tonic voluntary contractions of soleus or tibialis anterior, the inhibition from toe 5 was reduced (*b*), but the inhibition from toe 1 was not modified (*c*). These results indicate that changes in withdrawal responses of the distal extremity during voluntary contractions are determined more by the site of the noxious stimulus ('local sign') than by the muscle involved in the contraction. Given the absence of

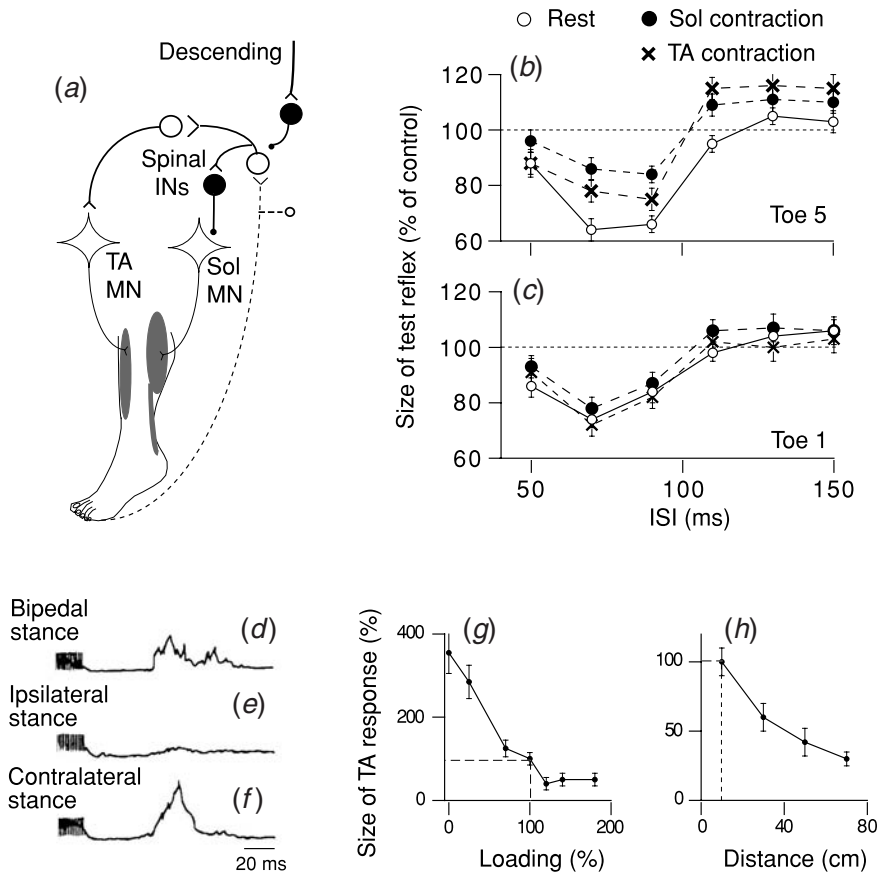


Fig. 9.8. Task-related nociceptive reflexes in the lower limb. (*a*) Sketch of the presumed pathways. Nociceptive afferents from the ball of the toes and the sole of the foot activate chains of spinal interneurones (IN) with excitatory projections to tibialis anterior (TA) motoneurones (MN) and inhibitory projections to soleus (Sol) MNs. (*b*), (*c*) Modulation of the Sol H reflex by noxious stimulation (10 shocks, 300 Hz, 2 × PT) applied through ring electrodes to the fifth (*b*) and the first (*c*) toe. The amplitude of the test reflex (expressed as a percentage of its unconditioned value) is plotted against the ISI (measured from the onset of the train) at rest (○), and during tonic contraction of either soleus (●) or tibialis anterior (×). (*d*)–(*h*) Modulation of the rectified on-going TA EMG by electrical stimulation of the sole of the foot (10 shocks, 500 Hz, 1.2 × pain threshold). (*d*)–(*f*) Results are compared during bipedal stance (*d*), and unipedal stance on either the ipsilateral leg (*e*) or the contralateral leg (*d*). (*g*), (*h*) The area of the rectified TA response (expressed as a percentage of control value in bipedal stance with an interfoot distance of 10 cm) is plotted against the loading of the ipsilateral leg ((*g*) 100%: symmetrical bipedal stance) or the lateral distance between the two feet (*h*). Each symbol is the grand average of results obtained in 12 ((*b*), (*c*)) or 6 ((*g*), (*h*)) normal subjects. Vertical bars ±1 SEM. Modified from Pierrot-Deseilligny *et al.* (1973) ((*b*), (*c*)), and Rossi & Decchi (1994) ((*d*)–(*h*)), with permission.

changes in the inhibition from toe 1, it is unlikely that the changes from toe 5 during contraction were produced by a specific effect of the contraction-induced afferent discharge only on the responses from toe 5. These changes are likely to result from a descending control, and can be interpreted in terms of the requirements of unilateral stance or asymmetrical loading. The lateral part of the sole of the foot, including toe 5, bears much of the load during unilateral or asymmetrically loaded stance, and postural instability is compensated for by adaptive contractions, involving soleus and tibialis

anterior. Inhibition of withdrawal reflexes from the supporting area would prevent them from conflicting with the support role, as discussed below.

Postural tasks

Reflex responses evoked in tibialis anterior by a noxious stimulus applied to the medial anterior part of the sole have been explored while the subjects maintained different postures during upright stance (Rossi & Decchi, 1994). Standing on one leg resulted in a significant decrease in the withdrawal reflex of the ipsilateral tibialis anterior, whereas a significant facilitation was observed when the subject was standing on the contralateral leg (Fig. 9.8(*d*)–(*f*)). A progressive depression of the withdrawal response was observed when the subject gradually shifted body weight from one leg to the other: the more loaded the ipsilateral leg, the smaller the response (Fig. 9.8(*g*)). Similar depression was observed in symmetrical bilateral stance when the interfoot distance was increased so that the hips were more abducted, and the load was greater on the mechanoreceptors of the stimulated area, the medial anterior part of the sole (Fig. 9.8(*h*)). Thus, the withdrawal responses of tibialis anterior are suppressed when the supporting function of the leg increases. The function of this suppression is clearly to prevent the response from jeopardising stance. It was proposed that the load to which the limb is subjected is measured from the activity of peripheral mechanoreceptors, and forms the basis on which the reflex is regulated at a spinal and/or supraspinal level.

Organisation, connections and physiological implications of cutaneomuscular reflexes evoked by non-noxious stimuli

The different responses

Reflex responses evoked by low-threshold cutaneous afferents can be documented by different methods (cf. pp. 394–6), but each has drawbacks. *A priori*, only the early responses occurring with latencies compatible with a spinal pathway fall within the field of a book centred on spinal circuitry. However, there must be some discussion of long-latency transcortical responses, in part because some have long been considered spinal reflexes.

RII reflex at rest

RII reflex

The RII reflex elicited at rest in the short head of the biceps femoris by low-intensity stimuli to the sural nerve at the ankle (Fig. 9.2(*b*)) is the most consistent example of a cutaneomuscular reflex recordable at rest (see Hugon, 1973; p. 394), and in the following 'RII reflex' refers to this particular response when not otherwise stated. A RII-like response may be occasionally recorded in other muscles (cf. p. 396; Fig. 9.10(*b*)). Recording these reflexes at rest, without volitional bias, represents the purest way to investigate 'private' cutaneous spinal pathways.

However, RII-like reflexes suffer several drawbacks

(i) They can be evoked only in some muscles.

(ii) They cannot be evoked consistently in all subjects.

(iii) They always require temporal summation (using long trains) which makes the estimation of the central delay difficult.

(iv) They provide no insight into the inhibitory effects of the input.

Cutaneomuscular reflexes during voluntary contraction

Modulation of the on-going EMG

The technique of modulating the on-going EMG activity by tactile cutaneous volleys was introduced by Gassel & Ott (1970) for triceps surae and by Caccia *et al.* (1973) for hand muscles. This technique has since been used extensively to investigate human pathways mediating effects produced

by low-threshold cutaneous afferents. The resulting responses are denoted in the following as 'cutaneomuscular reflexes'. They have been documented in many limb muscles. The technique is simple and the cutaneomuscular reflexes so produced are consistently recorded in most normal subjects.

Upper-limb responses

In the upper limb, the typical pattern is a triphasic response with a modest early (E1) excitation at a latency of ~30–35 ms, followed by an inhibition (I1) and by a large long-latency excitation (E2). This is illustrated in 9.10*E*, which shows the response produced in the first dorsal interosseous (FDI) by a single shock at 2 × PT to the digital nerves of the index finger (Jenner & Stephens, 1982). Similar responses have been recorded in many hand and forearm muscles: abductor digiti minimi, extensor digitorum communis, flexor digitorum superficialis (Evans, Harrison & Stephens, 1989), forearm extensors and flexors (Issler & Stephens, 1983). E1 response habituates rapidly (Harrison, Norton, & Stephens, 2000), and this could explain why it is not always seen in normal subjects (Chen & Ashby, 1993; Hallett *et al.*, 1994; Floeter *et al.*, 1998).

Lower-limb responses

In the lower limb, cutaneomuscular reflexes have a much less stereotyped pattern. Single shocks at 2 × PT to the digital nerves of toe 2 produce a consistent excitation at spinal latency (E1) only in the extensor digitorum brevis (Fig. 9.9(*b*)) followed by a long-latency excitation (E2), which is the only response consistently recorded in the other tested muscles (soleus, tibialis anterior, quadriceps; Gibbs, Harrison & Stephens, 1995). Sural nerve stimulation using five shocks at 300 Hz and 2 × PT evokes quite variable short-latency responses at ~50 ms or less in the different muscles: excitation in the peroneus longus and the gastrocnemii, and inhibition in both the soleus and tibialis anterior (Fig. 9.9(*c*)–(*g*); Aniss, Gandevia & Burke, 1992). These early responses are followed by a long-latency excitation which, in soleus, becomes obvious only with stronger stimulus intensities (4 × PT). Early inhibition and late facilitation have also been found in tibialis anterior after stimulation of the superficial peroneal nerve at the ankle (Nielsen, Petersen & Fedirchuk, 1997).

Difficulties in interpretation

Low-threshold cutaneous afferents have effects mediated through 'private' circuits and can modulate the transmission in other pathways activated during the voluntary contraction (see pp. 419–21). A further difficulty arises because the cutaneous input has opposite effects on motoneurones innervating slow- and fast-twitch motor units (cf. pp. 424–7). Finally, the contraction introduces a voluntary bias, and there are important task-related changes in the modulation of the on-going EMG (cf. pp. 427–30).

Modulation of the monosynaptic reflex

Lower limb

The dominant effect of sural nerve stimulation using a train of 3–10 shocks at 2–2.5 × PT is facilitation occurring at ISIs longer than 50 ms in all tested motor nuclei (e.g. Fig. 9.4(*b*)–(*d*), (○)): soleus, tibialis anterior, quadriceps and biceps femoris (Hugon, 1973; Delwaide, Crenna & Fleron, 1981; Delwaide & Crenna, 1984; Nielsen, Petersen & Fedirchuk, 1997). There are, however, more modest preceding effects, which are considered on p. 419.

Upper limb

Mechanical stimulation of the fingertip produces a biphasic modulation of the flexor carpi radialis (FCR) H reflex, with weak short-latency inhibition appearing at 2 × PT, followed some 3–4 ms later by a potent facilitation appearing just above 1 × PT (Cavallari & Lalli, 1998). Qualitatively similar results were obtained whether the stimulus was applied to the skin of the palmar or the dorsal surface of the finger (Fig. 9.10(*c*)). The same early inhibition and subsequent potent facilitation have now been observed

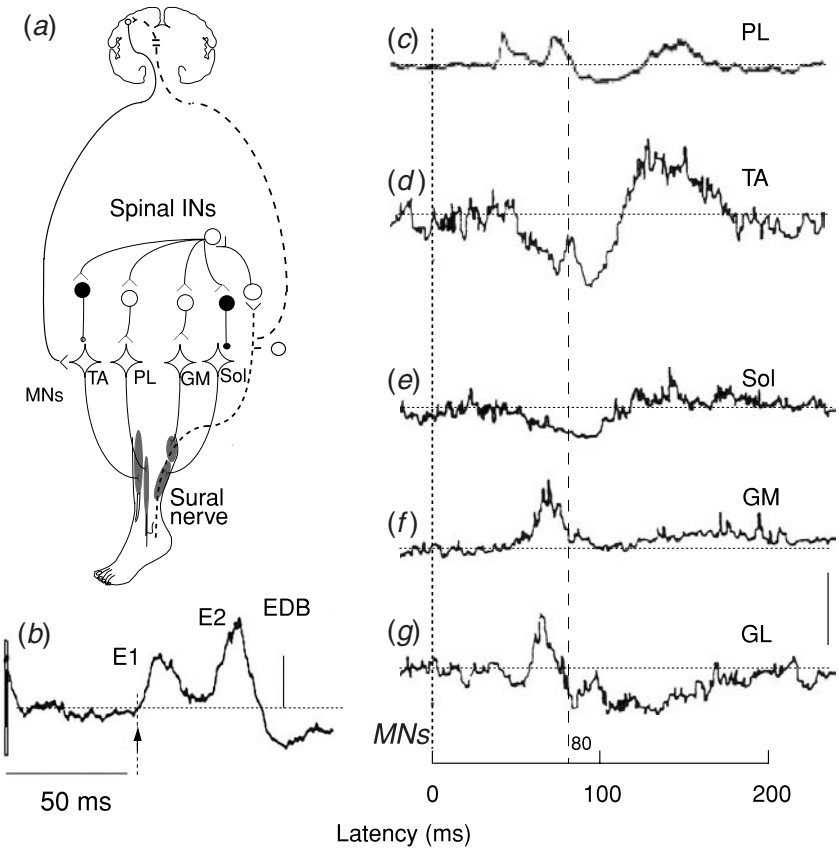


Fig. 9.9. Cutaneomuscular reflexes evoked by low-threshold cutaneous afferents in the lower limb. (*a*) Sketch of the presumed pathways. Cutaneous afferents excite peroneus longus (PL) and gastrocnemius medialis (GM), and inhibit soleus (Sol) and tibialis anterior (TA) motoneurones (MN) through spinal interneurones (INs), and excite TA MNs through a transcortical pathway. (*b*)–(*g*) Cutaneomuscular responses evoked by stimulation of low-threshold cutaneous afferents in various muscles. (*b*) Modulation of the on-going EMG (contraction 20% of MVC) in the extensor digitorum brevis (EDB) by a single shock to toe 2 (2 × PT, 1024 sweeps). The arrow and vertical dotted line indicate the latency of E1. (*c*)–(*g*) All responses were evoked by sural nerve stimulation (train of three shocks, 500 Hz, 2 × PT), during a background voluntary contraction of the target muscle (30% of MVC). Responses are in PL ((*c*), 500 sweeps), TA ((*d*), 500 sweeps), Sol ((*e*), 250 sweeps), GM ((*f*), 250 sweeps), and gastrocnemius lateralis (GL, (*g*), 250 sweeps). Vertical calibration: 10 μV (*b*), 250 μV (*c*), 200 μV ((*d*)–(*g*)). The vertical thick dotted line and thin dashed line in (*c*)–(*g*) indicate the onset of the stimulus train, and the limit below which the responses may be considered as spinal, respectively. Modified from Jenner & Stephens (1982) (*b*), and Aniss, Gandevia & Burke (1992) ((*c*)–(*g*)), with permission.

in PSTHs of single FCR units after mechanical or electrical stimulation of the skin of the palmar side of the index finger (Fig. 9.10(*d*); G. Lourenço, R. Espoti & P. Cavallari, personal communication). The brief latency and short duration of the inhibition exclude a presynaptic inhibitory mechanism. Since the reflex inhibition occurs *at rest*, it presumably results from IPSPs in motoneurones. This inhibition differs from the *disfacilitation* that occurs with inhibition of propriospinally mediated excitation of motoneurones in a number of respects: (i) brief latency; (ii) the target muscle (FCR instead of ECR); (iii) the subsequent potent facilitation; and (iv) that it can be elicited from both sides of the hand. Propriospinally

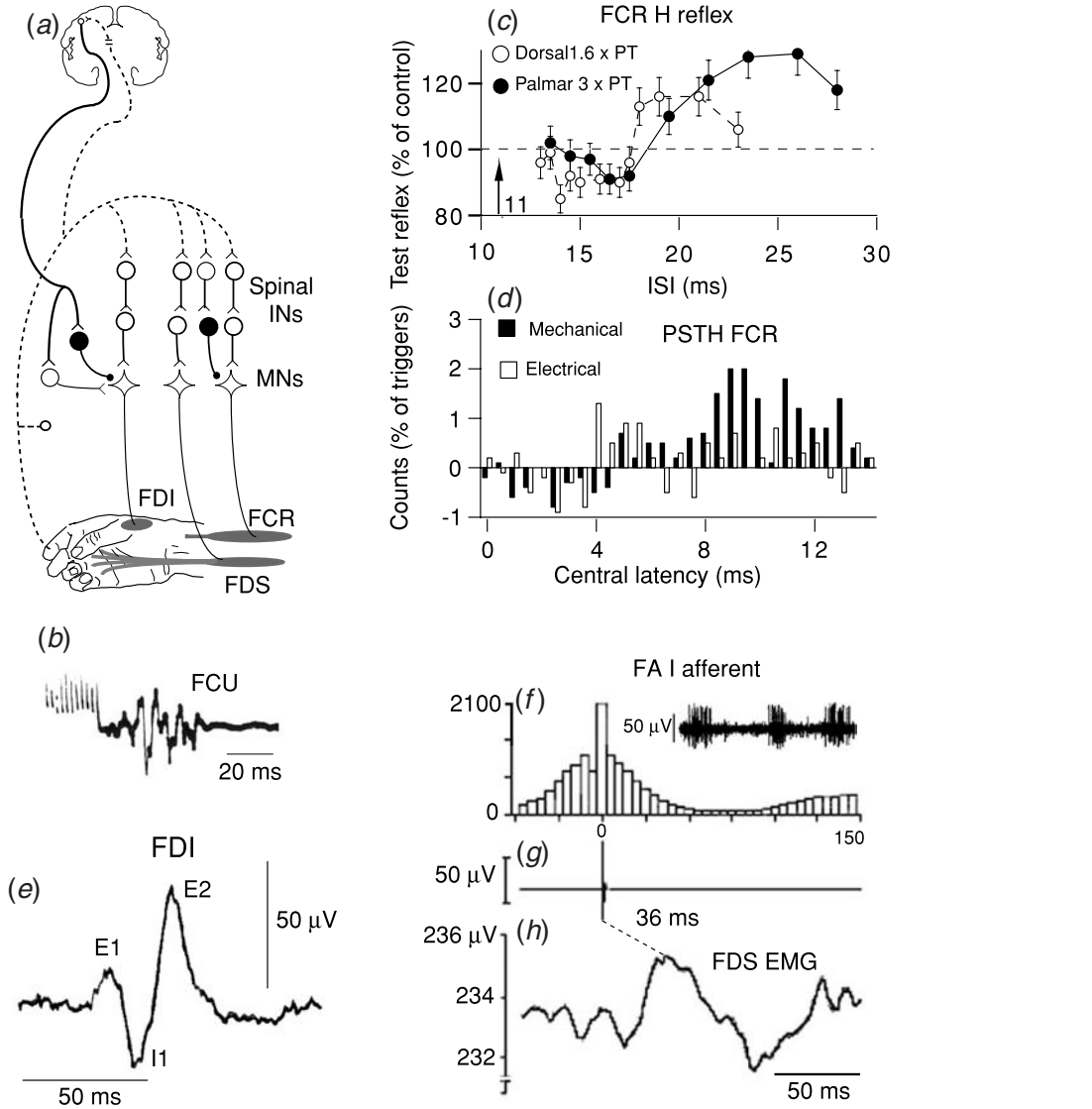


Fig. 9.10. Spinal reflex effects evoked by low-threshold cutaneous afferents in the upper limb. (*a*) Sketch of the presumed pathways. Cutaneous afferents through spinal interneurones (INs) excite flexor digitorum superficialis (FDS) and first dorsal interosseus (FDI) motoneurones (MNs), both excite and inhibit flexor carpi radialis (FCR) MNs, and both excite and inhibit FDI MNs through a transcortical pathway. (*b*) RII reflex elicited at rest in the flexor carpi ulnaris (FCU) by ulnar nerve stimulation (train 10 shocks, 500 Hz, 3 mA). (*c*) The FCR H reflex (expressed as a percentage of its control value) is plotted against the ISI after mechanical stimulation of the palmar aspect (●, 3 × PT) and the dorsal aspect (○, 1.6 × PT) of the index finger. The arrow at 11 ms indicates the arrival of the cutaneous volley at motoneuronal level. (*d*) PSTHs of a single FCR unit after mechanical (■) and electrical (□) stimulation (2 × PT) of the palmar pulp of the index finger. The zero on the abscissa corresponds to the expected time of arrival of the cutaneous volley at motoneuronal level. (*e*) Modulation of on-going EMG activity of FDI by a single electrical stimulus (2 × PT) delivered to the index finger (1024 sweeps). (*f*)–(*h*) EMG events time-locked to the discharge of a single FAI cutaneous afferent activated by repeated indentation of the receptive field of the afferent, as revealed by spike-triggered averaging. (*f*) Autocorrelogram of the afferent discharge with inset showing the neurogram produced by three skin strokes. (*g*) Averaged nerve action potential. (*h*) Averaged EMG (9718 sweeps), which was root-mean square processed, sampling over a sliding window (5 ms). Dashed line highlights the peak of the short-latency reflex. Modified from Cambier, Dehen & Bathien (1974) (*b*), Cavallari & Lalli (1998) (*c*), G. Lourenço, R. Espoti & P. Cavallari (personal communication) (*d*), Jenner & Stephens (1982) (*e*), and McNully & Macefield (2002) ((*f*)–(*h*)), with permission.

mediated excitation from one muscle is selectively suppressed from the skin field that would encounter the target at the end of movements produced by that muscle (cf. Chapter 10, p. 478).

The modulation of the H reflex or tendon jerk has limitations

Low-threshold cutaneous volleys may alter the size of the H reflex (i) by altering presynaptic inhibition of Ia afferents mediating the test volley (see Chapter 8, p. 350), and (ii) by modifying transmission in non-reciprocal group I (Ib) pathways activated by the test volley for the H reflex (cf. Chapter 6, Fig. 6.7(*c*) and pp. 267–8). In addition, because of the differential effect of the cutaneous input on early and late recruited motoneurones, opposite effects might occur with reflexes of different size (cf. pp. 425–6; Fig. 9.12(*h*)).

Afferent conduction

Given the low threshold of the RII reflex (5 mA, Willer, 1977), there is little doubt that the responsible cutaneous afferents in the sural nerve are within the large-myelinated Aβ range. Accordingly, stimuli evoking the responses discussed in this section generally require an intensity of 2–2.5 × PT, and produce a non-painful tactile sensation, even when a long train is delivered. The mean conduction velocity for the fastest of these afferents is 51 m s^{-1} (range 45–62) in the distal lower limb (Willer, Boureau & Albe-Fessard, 1978). Afferents are faster in the upper limb (Macefield, Gandevia & Burke, 1989), where individual axons may have conduction velocities up to 80 m s^{-1} (see Johansson & Vallbo, 1983).

Central pathway of short-latency responses occurring at 'spinal latency'

Three questions arise concerning the central pathway of the effects produced by stimulation of low-threshold cutaneous afferents.

(i) Is the response mediated through a spinal or a transcortical pathway?

(ii) If spinally mediated, is it through an oligosynaptic pathway or a long chain of interneurones?

(iii) Is it mediated through a 'private' cutaneous pathway or does it reflect a change in transmission in another spinal pathway?

Spinal origin of the early cutaneous-induced effects

The first point to elucidate is whether the response is mediated through a spinal or a supraspinal pathway. It is argued on pp. 421–4 that RII-like reflexes at rest and cutaneomuscular responses occurring after distal stimulation at latencies earlier than 45–50 ms in the upper limb and 70–80 ms in the lower limb may be considered spinal (Deuschl, Schenck & Lücking, 1985; Nielsen, Petersen & Fedirchuk, 1997). For the modulation of the monosynaptic reflex, allowance for the conduction time of the test reflex discharge indicates a similar spinal origin for effects occurring at ISIs of ~30 ms in the upper limb and ~55 ms in the lower limb. On these latency grounds, the following reflex responses are probably spinal:

RII responses evoked at rest

The latency of the biceps femoris RII reflex is variable (40–80 ms) from trial to trial and from subject to subject. This variability is due to the need for temporal summation, which fluctuates with the state of attention-relaxation of the subject and because of habituation. RII reflexes with longer latencies (80 ms) fall within the same range as the earliest ISI for the late diffuse facilitation of the monosynaptic reflex. However, the minimal latency of the RII reflex is 40 ms after the onset of the train (Hugon, 1973; Willer, 1977) and, at threshold, for a minimal stimulus train which would elicit the reflex every second trial, the latency was 35 ms after the last shock of the train (Hugon, 1973). Such an early latency clearly indicates a spinal reflex (see above). The spinal origin of the reflex is also suggested by the finding that similar low-threshold responses occurring with the same

latency can be recorded in patients with complete spinal transection (Hugon, 1973).

Central delay of cutaneomuscular responses

The central delay has been estimated after subtraction of the peripheral afferent and efferent conduction times from the latency of the response. The afferent conduction time was determined by recording the spinal evoked response after cutaneous stimulation at C7 for the upper limb and T12 for the lower limb, and the efferent conduction time was calculated by halving the sum of the latencies of the M and F waves. Using a single conditioning volley, it was demonstrated that the mean central delay of the earliest excitation (E1) in extensor digitorum brevis and the FDI was 2.3 and 4.6 ms, respectively (Figs. 9.9(*b*), 9.10(*e*); Jenner & Stephens, 1982). Such short central delays indicate transmission through an oligosynaptic spinal pathway. Short stimulus trains to the sural nerve produce excitation in the peroneus longus at a latency of 44 ms, which implies an oligosynaptic spinal pathway and, given the necessity of temporal summation, the early inhibition in tibialis anterior and soleus is also consistent with a short spinal pathway (Fig. 9.9(*c*)–(*e*); Aniss, Gandevia & Burke, 1992).

Modulation of monosynaptic reflexes

A spinal mechanism explains the short-latency inhibition (2–3 ms central delay) and following facilitation of the flexor carpi radialis H reflex after stimulation of the fingertip (Cavallari & Lalli, 1998; Fig. 9.10(*c*)). The dominant effect of stimulation of tactile cutaneous afferents in the sural nerve is a diffuse long-latency facilitation, which has been shown to be supraspinal (see pp. 421–4). However, sural stimulation also evokes weak earlier effects with facilitation of flexors (tibialis anterior and biceps) and inhibition of extensors (soleus and quadriceps, see Fig. 9.4(*c*); Hugon, 1973; Delwaide, Crenna & Fleron, 1981). Again the latencies of these early effects, which occur at ISIs of 25–35 ms, are those of a spinal pathway.

Oligosynaptic or polysynaptic nature of spinal pathways mediating early effects

Temporal summation is required to cause the RII reflex to appear at rest, and this renders uncertain speculations about the number of interneurones intercalated between the cutaneous terminals and motoneurones. When the cutaneomuscular response can be obtained with a single shock, a more precise estimate of the central delay is possible, as short as 1–2 ms in some cases, implying an oligosynaptic pathway (Jenner & Stephens, 1982). Spike-triggered averaging of the EMG against natural spike trains of single cutaneous afferents has allowed a spinal reflex pathway to be demonstrated at a single unit level (McNulty & Macefield, 2002). Thus, with an afferent activated from a FAI mechanoreceptor in the skin of the index finger, the latency of the response in the flexor digitorum superficialis was 36 ms (Fig. 9.10(*f*)–(*h*); McNulty & Macefield, 2002). This implicates a spinal pathway but, in the absence of the conduction velocity for the afferent, it does not indicate whether the pathway is oligosynaptic or polysynaptic, though the former is likely given that polysynaptic connections are more difficult to define using spike-triggered averaging.

'Private' pathway or changes in transmission in another pathway?

RII reflex

In the case of responses recorded at rest, such as the RII reflex, the absence of voluntary contraction rules out the possibility that the response to cutaneous stimulation reflects a change in the contraction-induced Ib discharge or in the propriospinally mediated descending activation of motoneurones. The RII reflex is therefore probably mediated through a 'private' cutaneous pathway. The problem with the RII reflex is that, because of the necessity for temporal summation, it is impossible to estimate precisely the number of interneurones intercalated in this 'private' spinal pathway (cf. above).

Cutaneomuscular reflexes

During voluntary contractions, a modulation of the on-going EMG could result from a reflex action affecting the motoneurone discharge directly ('private' pathway) or indirectly by actions on (i) γ motoneurones (Chapter 3, pp. 127–30), (ii) interneurones transmitting the contraction-induced Ib afferent discharge (Chapter 6, pp. 261–3), or (iii) propriospinal neurones relaying the descending command (Chapter 10, pp. 471–4). These different possibilities have been generally neglected and are considered below.

(i) Reflex activation of γ motoneurones by inputs from cutaneous mechanoreceptors has been sought without success in the lower limb of reclining subjects performing isometric voluntary contractions. However, when the subjects were reliant on proprioceptive cues to maintain balance during unsupported standing, it was possible to demonstrate cutaneous activation of γ motoneurones (Chapter 3, pp. 127–9). This could contribute to the task-dependent changes in cutaneomuscular reflexes then observed (cf. pp. 429–30). However, given the delay of transmission across the γ loop, any effect on α motoneurones resulting from cutaneous reflex modulation of γ drive would occur at long latencies, superimposed on supraspinally-mediated effects.

(ii) Cutaneous facilitation of interneurones mediating Ib inhibition to voluntarily activated motoneurones may be observed during voluntary contractions (cf. Chapter 6, p. 262). The sural-induced early inhibition observed in the on-going EMG of the tibialis anterior and soleus could reflect cutaneous facilitation of the transmission of the contraction-induced Ib discharge (Fig. 9.9(*d*), (*e*)). However, cutaneous facilitation of Ib inhibition to voluntarily activated motoneurones has been observed only with afferents from the skin field that would have come into contact with an obstacle during the contraction of the corresponding muscle (cf. Chapter 6, p. 272). This is not the case for the lateral side of the foot innervated by the sural nerve during contraction of the tibialis anterior or soleus.

(iii) Cutaneous inhibition of the propriospinally mediated component of the descending command for movement is responsible for the inhibition of the on-going EMG of wrist extensors and arm muscles occurring with a 4–6 ms central delay after stimulation of cutaneous afferents from the dorsal side of the hand (Chapter 10, pp. 471–4). However, this mechanism cannot account for the inhibition (I1) following the early excitation (E1) in the intrinsic muscles of the hand, because there are no significant projections of C3–C4 propriospinal neurones to these muscles (Chapter 10, p. 460). Nor could this mechanism explain the inhibition of the FCR H reflex *at rest* (pp. 415–18). It also cannot account for the inhibition of the tibialis anterior or soleus documented in Fig. 9.9(*d*), (*e*), because there is no evidence for cutaneous inhibition of lumbar propriospinal neurones (Chapter 10, p. 496).

Presynaptic inhibition of Ia terminals

Depression of presynaptic inhibition of Ia terminals mediating the afferent volley of the test reflex can be produced by low-threshold cutaneous afferents in the upper and lower limbs (cf. Chapter 8, p. 350), and this would facilitate the monosynaptic reflex. Parallel cutaneous inhibition of motoneurones and depression of presynaptic inhibition of Ia terminals would explain why sural stimulation produces profound suppression of the on-going EMG in the tibialis anterior and soleus (Fig. 9.9(*d*), (*e*); Aniss, Gandevia & Burke, 1992) but not the H reflex, which is facilitated in the tibialis anterior and only modestly inhibited in the soleus (Delwaide, Crenna & Fleron, 1981). In contrast, the long-lasting facilitation of the flexor carpi radialis following the initial short-latency inhibition has been reproduced in the PSTHs of single units (Fig. 9.10(*c*), (*d*)), and may be ascribed to a postsynaptic facilitation of the motoneurones.

Conclusions

Short-latency cutaneomuscular reflexes are probably mediated through 'private' spinal pathways.

Cutaneous inhibition of propriospinal neurones may account for the inhibition of the on-going EMG evoked in wrist extensors and arm muscles, but not for the inhibition in hand and leg muscles. Divergent results obtained with the modulation of on-going EMG and the H reflex may be due to the cutaneous depression of PAD interneurones mediating presynaptic inhibition of Ia terminals.

Central pathway for long-latency effects

The conclusion that long-latency responses involve a long-loop pathway relies on: (i) latency, (ii) studies in patients with various lesions in the central nervous system, (iii) studies in children at various stages of the maturation of the pyramidal tract, and (iv) cutaneous modulation of the responses evoked by cortical stimulation.

Latencies of late responses

Pattern of the long-latency facilitation of monosynaptic reflexes

Stimulation of the sural nerve evokes long-latency facilitation of the soleus and tibialis anterior H reflexes, starting at ISIs longer than 50 ms and peaking at ~80–100 ms (Delwaide, Crenna & Fleron, 1981). The absence of reciprocal organisation of this facilitation argues against a spinal mechanism, and this view is supported by further findings (Delwaide & Crenna, 1984).

(i) Sural-induced facilitation of monosynaptic reflexes was seen at an earlier latency in arm muscles than in leg muscles, and at an even earlier latency in the masseter.

(ii) When comparing the effects on the soleus H reflex of cutaneous stimuli applied to various nerves, the closer the stimulus to cerebral cortex, the earlier the facilitation.

The most parsimonious explanation for these data is a common supraspinal centre responsible for the reflex activation of the muscles in a rostrocaudal sequence.

Latencies of late responses are compatible with a transcortical pathway

The nature of this supraspinal pathway is discussed below. Jenner & Stephens (1982) suggested that it could be transcortical, a requirement being sufficient time for conduction of the volley to the cerebral cortex and back. The afferent and efferent conduction times in a transcortical pathway may be inferred from the latencies of the cerebral somatosensory evoked potential and of the MEP following cortical stimulation. Such estimates have been the basis of several investigations:

(i) The difference in the latencies of the short- and long-latency excitatory components in FDI could represent conduction in central pathways to and from cortex. It was 3.5–8.5 ms longer than the minimal time for impulse conduction along a pathway travelling through the dorsal columns to cerebral cortex and returning by way of the corticospinal tract. This extra delay above the sum of estimated afferent and efferent conduction times could represent the time for processing in the sensorimotor cortex. In addition, it was found that the difference in time delay between short- and long-latency excitation in FDI and extensor digitorum brevis muscles was, on average, 12 ms, and this fits well with estimates of the afferent and efferent conduction times for central pathways between the T12 and C7 spinal segments (Jenner & Stephens, 1982).

(ii) More precise investigations have allowed the time for processing in the sensorimotor cortex to be measured. Such studies have (i) confirmed that the timing of the late excitation is compatible with a transcortical pathway, and (ii) assessed accurately the minimal time required for a mediation through a transcortical pathway. This is illustrated in Fig. 9.11(*b*)–(*d*) (Nielsen, Petersen & Fedirchuk, 1997). The difference between the latency of the sural-induced excitation of the on-going tibialis anterior EMG and the sum of the afferent and efferent conduction times leaves ~13 ms for processing in the cerebral cortex (cf. legend of Fig. 9.11(*b*)–(*d*)). Accordingly, the onset of the sural-induced

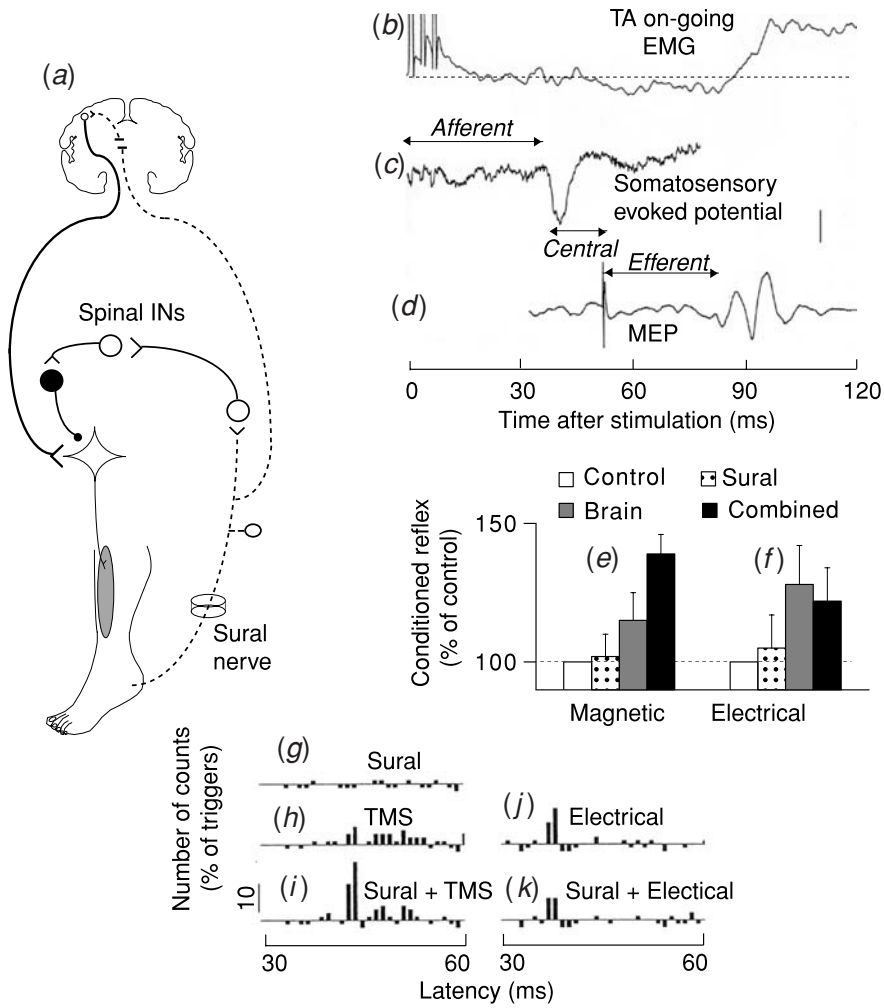


Fig. 9.11. Evidence for transcortical mediation of long-latency excitation in tibialis anterior to sural nerve stimulation. (*a*) Sketch of the presumed pathways. Aβ cutaneous afferents mediate, through spinal interneurones (INs), a short-latency inhibition and, through a transcortical pathway, a long-latency excitation of tibialis anterior (TA) motoneurones (MNs). (*b*)–(*d*) Calculations of afferent and efferent conduction times for a possible transcortical reflex. Sural stimulation (three shocks, 300 Hz, 2.5 × PT) evokes in the rectified on-going TA EMG (average of 100 traces) a late facilitation at 83 ms (*b*), and a somatosensory-evoked cerebral potential at a latency of 38 ms (*c*), while TMS produced a MEP in TA at a latency of 32 ms (*d*). Vertical calibration: 20 μV (*b*), 2 μV (*c*), 500 μV (*d*). The 13 ms difference (83 − [38 + 32]) between the latency of the late sural-induced facilitation and the sum of the minimal afferent and efferent conduction times represents the maximal central delay of the late excitation. (*e*), (*f*) Effects of sural stimulation (three shocks, 300 Hz, 2 × PT) on the TA H reflex at the earliest ISI (50 ms) with sural-induced facilitation when using a stronger (2.5 × PT) stimulation, are compared when conditioned by TMS ((*e*), 50% of the stimulator output, −4 ms ISI with respect to CPN stimulation) or electrical stimulation of the motor cortex ((*f*), 25% of the stimulator output, −3 ms ISI with respect to CPN stimulation): control reflex (□), effects of separate sural (dotted), separate cortical (grey), and combined (■) stimulation. (*g*)–(*k*) PSTHs of a single TA unit (after subtraction of the background firing, 1 ms bin width). Effects produced by separate sural (*g*), separate transcranial magnetic (*h*) and transcranial electrical (*j*) stimulation (same parameters of stimulation as in (*e*), (*f*), and combined stimulation ((*i*), (*k*)). Modified from Nielsen, Petersen & Fedirchuk (1997), with permission.

facilitation of the response evoked by TMS was found at the 50 ms ISI, i.e. 12 ms after the arrival of the cutaneous volley at cortical level (38 ms, Fig. 9.11(*c*)). This corresponds to the central delay of ~10 ms previously reported for cutaneomuscular responses in the upper limb (Deuschl *et al.*, 1989). Overall, it has been found that the minimal latencies of transcortical cutaneomuscular responses in tibialis anterior after sural stimulation and in the thenar muscles after superficial radial stimulation are ~85–90 and 50–55 ms, respectively (Nielsen, Petersen & Fedirchuk, 1997; Deuschl *et al.*, 1989).

Observations in patients

Latency measurements are a necessary criterion but insufficient by themselves to establish transcortical mediation of the late responses. An additional complementary approach has been provided by the study of patients with established neurological lesions that abolished or attenuated the E2 response, but not the spinal E1 response.

Studies in patients with suprasegmental lesions

These studies have shown that the late E2 excitatory cutaneomuscular response requires the integrity of the dorsal columns, the sensorimotor cortex and the corticospinal tract. The E2 response in the FDI muscle is reduced and often delayed in patients with dorsal column lesions, absent in patients with damage to motor cortex, and reduced in amplitude and often delayed in patients with corticospinal tract abnormalities due to upper motor neurone disease (Jenner & Stephens, 1982). Similarly, late E2 responses in the extensor digitorum brevis and tibialis anterior muscles may be absent in patients with lesions of the corticospinal tract (Choa & Stephens, 1981; Rowlandson & Stephens, 1985b).

Studies in patients with mirror movements

Studies in patients with X-linked Kallmann's syndrome and mirror movements (Mayston *et al.*, 1997) have provided further evidence for the transcortical origin of the E2 component, and showed in addition that the inhibitory I1 component, which was initially thought to be spinally mediated, may also be transmitted through a transcortical pathway (see also Carr *et al.*, 1993). In these studies, unilateral stimulation of the digital nerves produced a unilateral E1 spinal response but bilateral I1 and E2 responses in the first dorsal interosseous. The bilateral responses were attributed to the novel branched projections from the ipsilateral motor cortex, characteristic of these patients.

Maturation

Short- (E1) and long- (E2) latency responses to cutaneous stimulation have been studied in forearm flexors and extensors and in lower limb muscles of children of different ages (Issler & Stephens, 1983; Rowlandson & Stephens, 1985a). The main findings are illustrated in Fig. 9.13(*n*)–(*r*) for the forearm extensors: (i) initially, there is only a large E1 response, and this decreases progressively over the first year of life (*n*)–(*p*); (ii) E2 appears in the second year of life; and (iii) during the school years, E2 increases still further in size at the expense of E1 (*q*)–(*r*). These changes parallel the maturation of the corticospinal tract and the acquisition of motor skills, and provide further evidence that long-latency cutaneous reflexes have a transcortical origin and are important in the acquisition of motor skills.

Which supraspinal pathway?

Alternative possibilities to transcortical pathways

The above findings argue that the late excitatory cutaneomuscular reflex is mediated through a suprasegmental pathway, but there were originally questions about the nature of the pathway. Different alternative hypotheses had been proposed.

(i) The possibility of an effect mediated through *long propriospinal pathways* linking upper and lower limb motor nuclei (Kearney & Chan, 1979) did not take into account the modulation in the masseter or data in patients.

(ii) Data from patients also argue against a role for a *spino-bulbo-spinal pathway*, which has been described in the cat (Shimamura, Mori & Yamauchi, 1967). Such a pathway had been raised by Meier-Ewert *et al.* (1973) to account for the modulation of the on-going EMG of different muscles in a rostro-caudal sequence after stimulation of the skin of the forehead or of the fingers.

(iii) Delwaide & Crenna (1983, 1984) suggested that the response was similar to a *startle response* after, e.g. an auditory stimulus, a view that has been challenged by Nielsen, Petersen & Fedirchuk (1997).

Definitive evidence for a transcortical pathway

This evidence has come from experiments using motor cortex stimulation, as illustrated in Fig. 9.11(*e*)–(*k*) (Nielsen, Petersen & Fedirchuk, 1997). The effects of a sural volley were compared on the facilitation evoked in the H reflex and in the PSTHs of single units of the tibialis anterior by magnetic or electrical stimulation of the motor cortex. Sural stimulation, adjusted to be insufficient by itself to facilitate tibialis anterior motoneurones, increased the facilitation of the H reflex produced by TMS (*e*) and the peak of cortical excitation evoked by TMS in the PSTHs (*i*), but did not enhance the facilitation evoked by electrical stimulation of the motor cortex ((*f*), (*k*)). A differential effect of the sural volley on the responses evoked by magnetic and electrical stimulation implies that motor cortex excitability has been affected by the conditioning cutaneous stimulation (Chapter 1, p. 44). Similarly, a superficial radial volley increases the facilitation evoked from motor cortex on the flexor carpi radialis H reflex only with TMS and not with transcranial electrical stimulation (Deuschl *et al.*, 1991).

Conclusions

Measurements of afferent and efferent conduction times and of the central delay of the late excitation are compatible with a transcortical pathway. Observations in patients have shown that the late excitation requires transmission of afferent impulses through the dorsal columns, a relay in the sensorimotor cortex and then descending transmission along the corticospinal tract. Finally, cutaneous facilitation of the responses evoked by TMS, but not of those produced by electrical stimulation, has demonstrated a transcortical pathway for the late responses. However, it must be emphasised that the above demonstration of a transcortical pathway does not exclude the possibility that spinal pathways also contribute to these responses. Indeed, in patients with complete spinal transection, reflexes in the tibialis anterior and biceps femoris evoked by weak sural stimuli at short latency, with the characteristics of RII reflexes in normal subjects, may have a long duration overlapping with the latency of transcortical responses in normal subjects (Hugon, 1967, 1973). Similarly, a contribution of spino-bulbo-spinal pathways cannot be ruled out.

Projections of cutaneous afferents to different types of motoneurones

Evidence for a different effect on motoneurones of different type

In the cat, stimulation of the sural nerve produces IPSPs in small motoneurones of triceps surae, i.e. those with a high input resistance (type S motoneurones), and EPSPs in large motoneurones with a low input resistance (type F motoneurones) (R. E. Burke, Jankowska & ten Bruggencate, 1970; R. E. Burke, 1981). The findings in humans are consistent with the cat data, i.e. of cutaneous effects of opposite sign on early-recruited motoneurones innervating slow-twitch motor units (inhibition) and late-recruited motoneurones innervating fast-twitch units (facilitation).

First dorsal interosseous (FDI) conditioned by electrical stimuli

Differential effects of low-threshold cutaneous afferents on low- and high-threshold motor units of human subjects were first shown by J. A. Stephens and colleagues in the FDI, using long trains of non-painful cutaneous stimuli delivered through

ring electrodes to the digital nerves of the index finger. The stimulation had opposite effects on motor units recruited at small and large contraction forces (low- and high-threshold units, respectively) during slowly increasing ramp contractions. Cutaneous stimulation raised the recruitment threshold of units normally recruited at low contraction strengths and reduced the threshold of units normally recruited at high contraction strengths (Fig. 9.12(*b*), (*c*); Stephens, Garnett & Buller, 1978; Garnett & Stephens, 1981). This result was confirmed by showing that the mean interval between single motor unit spikes in low-threshold units was increased by a similar stimulation, while it was reduced in high-threshold units (Fig. 9.12(*d*), (*e*); Datta & Stephens, 1981). Cutaneous afferents from the index finger can therefore shift the weighting of synaptic input associated with a voluntary contraction to favour the recruitment of the more powerful fast-twitch units in FDI.

FDI conditioned by natural stimuli

The results of Stephens and colleagues were confirmed and extended by Kanda & Desmedt (1983), using natural cutaneous stimulation, and this is of greater functional relevance. The findings are illustrated in Fig. 9.12(*f*), (*g*). During a standardised ramp contraction, one motor unit (MU1) was recruited at a lower threshold than the other (MU2). However, when the distal phalanx of the thumb was flexed so that there was skin contact between fingertips and the subject made slight to-and-fro palpation movements, motor unit 2 fired in isolation, even though the contraction force was barely at threshold for the first unit during ramp contraction. Impressive as this finding is, it is possible that the role of FDI was different in the two tasks, and that this might have required a change in descending drives and spinal circuitry.

Effect of sural stimulation on tibialis anterior motoneurones

Sural nerve stimuli below pain threshold produce inhibition in the PSTHs of early-recruited motoneurones and excitation in the PSTHs of late-recruited motoneurones of tibialis anterior (Fig. 9.12(*i*),(*j*); Nielsen & Kagamihara, 1993). Because of these opposite effects on early- and late-recruited motoneurones, unconditioned tibialis anterior H reflexes of small amplitude were inhibited by sural stimulation, whereas those of large amplitude were facilitated (Fig. 9.12(*h*)).

Changes in recruitment gain

Nielsen & Kagamihara (1993) also demonstrated that sural nerve stimulation, that was adjusted to have no effect by itself, significantly increased the amount of heteronymous monosynaptic Ia facilitation of the tibialis anterior H reflex produced by femoral stimulation. However, the sural stimulation did not affect the peak of monosynaptic Ia excitation produced by femoral stimulation in the PSTHs of single motor units in tibialis anterior. Thus, this represents a good example (actually the only one yet described) where the increased monosynaptic reflex facilitation could not be attributed to depression of presynaptic inhibition of Ia terminals mediating the femoral volley. A change in the heteronymous monosynaptic Ia excitation of the H reflex without a parallel change in the monosynaptic Ia excitation of individual motoneurones is characteristic of a change in the recruitment gain of the reflex (see Chapter 8, pp. 346–7): the skewed distribution of cutaneous inputs within the tibialis anterior motoneurone pool, illustrated in Fig. 9.12(*h*)–(*j*), compresses the range of functional thresholds in the motoneurone pool and thereby increases the slope of the input-output relationship of the test reflex (Chapter 1, pp. 18–20; Fig. 1.9).

Functional implications

Significant decreases in the recruitment threshold of high-threshold motor units can be produced by artificial stimuli but also occur during the natural stimulation involved in precision grip and active manipulation (see above). The net result is that prehension and manipulation are assisted and made more reliable: contact of appropriate skin regions

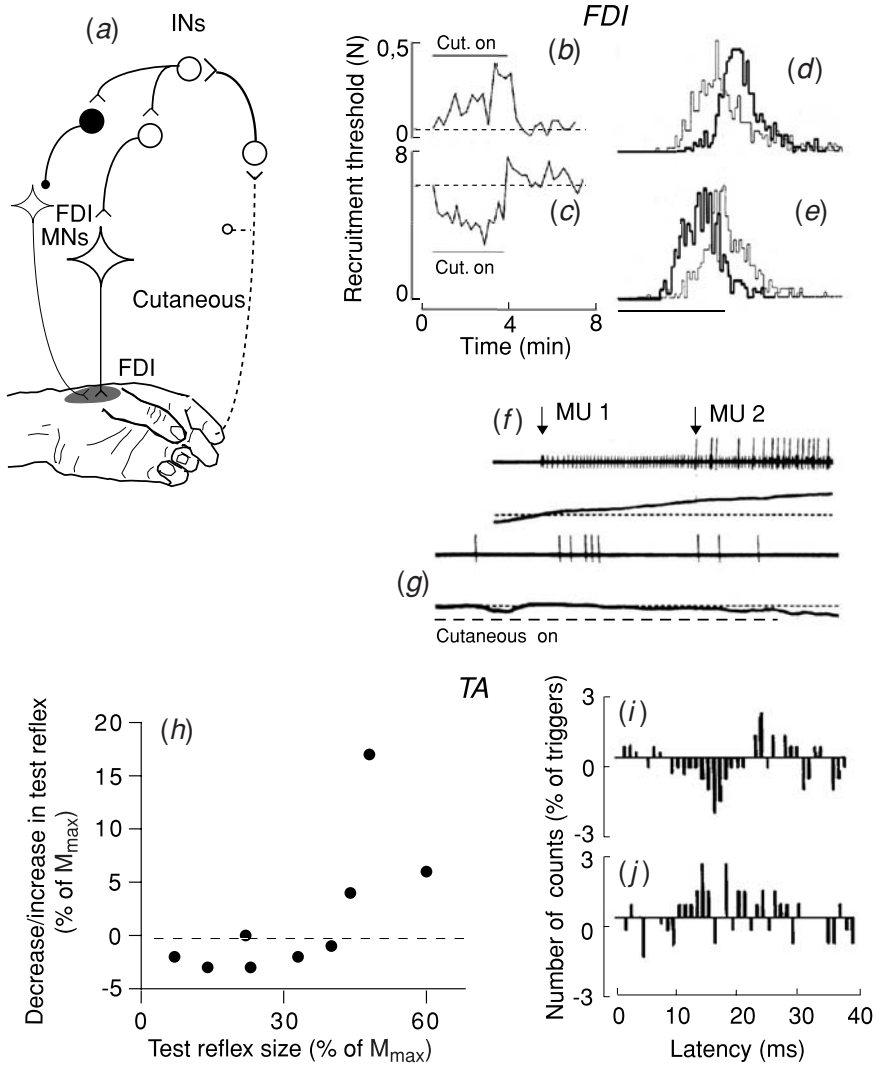


Fig. 9.12. Different projections of cutaneous inputs to low- and high-threshold motor units. (*a*) Sketch of the presumed pathways. Aβ cutaneous afferents inhibit small motoneurones (MN) supplying slow-twitch motor units (MUs) and excite large MNs supplying fast-twitch MUs of the first dorsal interosseus (FDI). (*b*), (*c*) Time course of the changes in recruitment threshold observed for a low-threshold (*b*) and a high-threshold (*c*) MU in the FDI during continuous electrical stimulation (4 × PT, horizontal bar, Cut. on) of the digital nerves of the index finger (control situation: dotted line). (*d*), (*e*) Histograms of the interspike intervals of a low-threshold ((*d*), recruitment threshold <1.5 N) and high-threshold ((*e*), recruitment threshold >1.5 N) MU are compared in a control situation (thin line) and after cutaneous stimulation (thick line) applied to the digital nerve of the index finger (3 × PT) timed to arrive at the spinal cord 5–15 ms after the onset of the measured interspike interval. (*f*), (*g*) Action potentials of single MUs (1 and 2, upper trace) and abduction force (lower trace). (*f*) During a ramp contraction, MU 1 is recorded at a lower threshold (horizontal dotted line) than MU 2. (*g*) The contact of the thumb with index tip in natural palpation (dashed horizontal line) facilitates the recruitment of MU 2, while the force is barely at threshold of MU 1. (*h*)–(*j*) Effect of sural nerve stimulation (train of three shocks, 333 Hz, 2.5 × PT) on tibialis anterior (TA) MNs. (*h*) Changes in the TA H reflex (conditioned – control reflex, expressed as a percentage of M_{max}, 11 ms ISI) at the onset of voluntary dorsiflexion are plotted against the size of the unconditioned test reflex. (*i*), (*j*) Changes in the PSTHs of a low- (*i*) and a high- (*j*) threshold MU, recruited at 1 and 25% of MVC, respectively. Abscissa: latency with respect to homonymous monosynaptic Ia latency. Modified from Garnett & Stephens (1981) ((*b*), (*c*)), Datta & Stephens (1981) ((*d*), (*e*)), Kanda & Desmedt (1983) ((*f*), (*g*)), and Nielsen & Kagamihara (1993) ((*h*)–(*j*)), with permission.

with an object will excite high-threshold motoneurones, and thereby make a greater contribution to grip force. Similarly, during locomotion, the cutaneous feedback evoked by foot contact might act to strengthen the on-going motoneuronal activity by changing the recruitment gain within the motoneurone pool(s). This could explain why the EMG activity during gait may only be mimicked by strong tonic contractions (~50% of MVC). However, while these changes will favour the recruitment of high-threshold motor units, the increased slope of the input-output relationship will decrease the ability to make small changes in force in discrete movements, whether in response to descending drives or peripheral feedback.

Pattern and functional role of early responses

Some responses at rest suggest placing reactions

RII response in the biceps femoris

The primary function of the short head of the biceps femoris is not to flex the knee but to produce an external rotation of the leg and foot, and Hugon (1973) therefore did not consider the RII response a 'flexion reflex'. In contrast with a withdrawal response, the RII reflex evoked by low-threshold cutaneous afferents from the lateral aspect of the foot would tend to increase the contact with the stimulus, much as in a 'placing reaction'. In this respect, it may be pointed out that, in the cat, activation of hair receptors in the sural field has been found to evoke polysynaptic excitation of motoneurones of the tenuissimus (Hunt, 1951), which is embryologically homologous to the short head of the biceps.

Early response in peroneus longus

Similarly, a response in the peroneus longus may also be observed occasionally at rest after sural nerve stimulation (Aniss, Gandevia & Burke, 1992). Here again the resulting eversion and abduction of the foot would tend to increase the contact with the stimulus on the lateral side of the foot, and this response may also be considered a placing reaction.

Cutaneomuscular responses in the upper limb

Organisation of cutaneomuscular responses

The absence of reciprocal organisation in spinal cutaneomuscular responses is attested by the finding that in all muscles tested (intrinsic muscles of the hand, long flexors and extensors of the fingers and flexors and extensors of the wrist), the early spinally mediated response is excitation (see p. 415). In addition, spike-triggered averaging has revealed that the excitatory input from single cutaneous afferents in the hand is sufficiently strong to be able to drive motoneurones in hand muscles and in the flexor digitorum superficialis through spinal pathways that probably contain few interneurones (see p. 419).

Task-related changes in cutaneomuscular responses

The amount of cutaneous facilitation of the on-going EMG activity of a given muscle varies with the task that the subject is performing (Evans, Harrison & Stephens, 1989). The main variations involve the transcortical E2 component. Thus, as illustrated in Fig. 9.13(*b*)–(*i*) for cutaneomuscular reflexes elicited in the FDI by a cutaneous stimulus to the index finger, E2 was significantly larger when the subject carried out an isolated finger manoeuvre than during grip. On the other hand, during finger tapping, whatever the involved finger, the E2 response was smaller, probably reflecting gating of the afferent volley within the sensory cortex (Turner, Harrison & Stephens, 2002). In contrast, the amplitude of the spinal E1 response remained relatively constant, except for the ball grip where E1 was increased (Fig. 9.13(*g*)). Similarly, in the extensor digitorum communis, E2 was large during an isolated voluntary extension of the finger, while E1 was somewhat increased during a power grip (Fig. 9.13(*k*)).

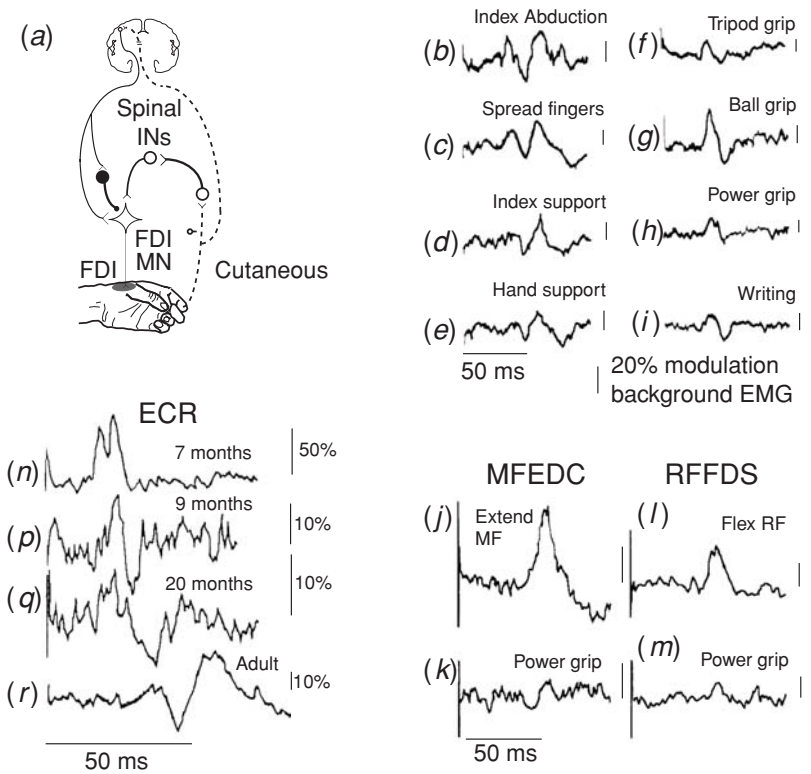


Fig. 9.13. Task-related changes in cutaneous reflex responses in the upper limb and reflex maturation. (*a*) Sketch of the presumed pathways. Aβ cutaneous afferents (thick dashed line) from the skin of the index finger produce a triphasic effect, with early facilitation mediated through spinal interneurones (IN), and inhibition and late excitation, both mediated through a transcortical pathway. (*b*)–(*r*) Modulation of the on-going EMG activity elicited by a single cutaneous volley (2 × PT) delivered via ring electrodes attached on either side of the proximal interphalangal joint of the index finger for the first dorsal interosseus (FDI), the middle finger for middle finger extensor digitorum communis (MFEDC), ring finger for ring flexor digitorum subliminis (RFFDS), and on index and ring fingers for the ECR. For (*b*)–(*m*), vertical calibrations represent a 20% modulation of mean background EMG level. (*b*)–(*m*) Changes in the cutaneous reflexes recorded in the FDI during various tasks in which the same level of EMG activity (~10–20% MVC) was maintained. (*b*)–(*e*) Relatively isolated finger manoeuvres: (*b*) index abduction; (*b*) spread fingers; (*d*) index supporting the weight of the arm; (*e*) all fingers supporting the weight of the arm. (*f*)–(*i*) Different grips: (*f*) tripod grip (holding a pen); (*g*) ball grip; (*h*) power grip (holding a cylinder); (*i*) writing. (*j*), (*k*) Responses in the MFEDC during extension of the middle finger (*j*), or power grip (*k*). (*l*), (*m*) Responses in the RFFDS during flexion of the ring finger (*l*) or power grip (*m*). (*n*)–(*r*) Modulation of the ECR EMG is compared in normal infants of different age: (*n*) 7 months; (*p*) 9 months; (*q*) 20 months; (*r*) adult (32 years). Modified from Evans, Harrison & Stephens (1989) ((*b*)–(*m*)), Issler & Stephens (1982) ((*n*)–(*r*)), with permission.

Functional implications

The pattern of cutaneous facilitation of different distal upper limb motor pools would reinforce the grip after contact with an object, and this suggests that spinal cutaneomuscular reflexes evoked by tactile afferents prevent grasped objects from slipping from the hand. The use of excessive force could then be minimised by the transcortical inhibition (I1), which immediately follows the initial spinally mediated facilitation.

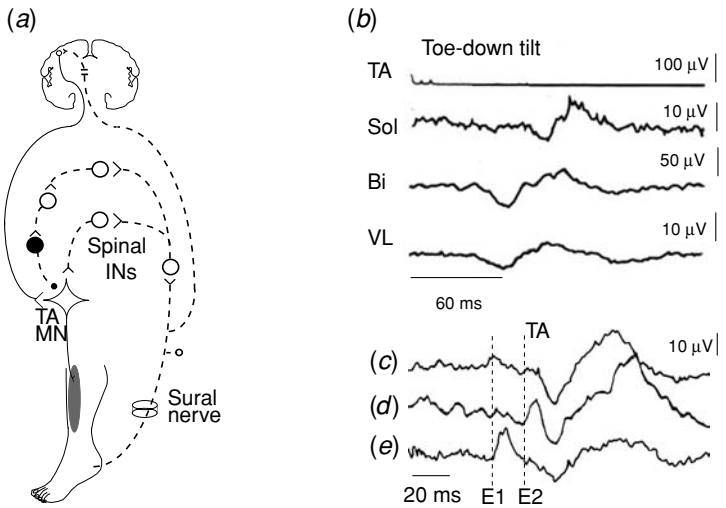


Fig. 9.14. Task-related changes in cutaneous reflex responses in the lower limb. (*a*) Sketch of the presumed pathways from afferents in the sural nerve to tibialis anterior (TA) motoneurones (MN). Aβ cutaneous afferents (thick dashed line) produce a biphasic response, with early facilitation and inhibition mediated through spinal interneurones (INs), and a late transcortical facilitation. (*b*)–(*e*) Effects evoked in the rectified on-going EMG by a train of five shocks (300 Hz) to the sural nerve producing intense paraesthesiae below pain threshold, at a level 2–4 × PT. (*b*) Responses in TA, soleus (Sol), biceps femoris (Bi) and vastus lateralis (VL) during bipedal stance tilted toe-down. (*c*)–(*e*) Comparison of the results obtained in TA during bipedal stance toe-up (*c*), voluntary contraction during unipedal stance on the contralateral leg, with the ipsilateral leg held in flexion (*d*), standing on an unstable support (pedals of an exercise bicycle (*e*)). Background EMG levels were 108, 128 and 132 μV. Vertical dotted lines indicate the latencies of the early (E1) and late (E2) excitations. Modified from Burke, Dickson & Skuse (1991) ((*b*)–(*e*)), with permission.

Cutaneomuscular responses in the lower limb

The pattern of the early cutaneomuscular responses in the lower limb is difficult to interpret

In most voluntarily activated muscles, cutaneous volleys from the digital nerves of the second toe or the sural nerve evoke a response at transcortical latency (E2), followed by an even later excitatory response (Gibbs, Harrison & Stephens, 1995; Burke, Dickson & Skuse, 1991; Aniss, Gandevia & Burke, 1992). Early responses (E1) at spinal latency (~50 ms) are illustrated in Figs. 9.9 and 9.14(*b*): there is excitation in the extensor digitorum brevis, peroneus longus and the gastrocnemii, and inhibition in tibialis anterior, soleus, biceps femoris and vastus lateralis. An early inhibition of the soleus H reflex has been produced by pressure applied to the sole of the foot and attributed to the activation of slowly adapting cutaneous receptors (Knikou & Conway, 2001). During gait, this inhibition of ankle extensors will be maximal prior to the initiation of swing (toe off), and it could contribute to the timing of the transition from stance to swing during walking (cf. Abbruzzese, Rubino & Schieppati, 1996).

Task-related changes in cutaneomuscular responses

Here again, the more prominent changes involve the E2 responses, which are significantly smaller during postural tasks than during voluntary contraction (Gibbs, Harrison & Stephens, 1995). Thus, the sural-induced E2 response seen in the tibialis anterior when standing on the contralateral leg with the ipsilateral leg voluntarily flexed (Fig. 9.14(*d*)) disappears when standing toe-up on a tilted platform (Fig. 9.14(*c*)). However, there are also changes in

the early responses during postural tasks (Burke, Dickson & Skuse, 1991).

(i) With unstable stance, an early E1 excitatory response appeared at a latency of ~50 ms in the ipsilateral tibialis anterior (Fig. 9.14(*e*)). This finding suggests that an excitatory spinal mechanism is released from a descending inhibitory control when stance is unstable.

(ii) During bipedal stance tilted toe-up, the inhibition of the ipsilateral tibialis anterior is accompanied by facilitation in the contralateral muscle. This seems intuitively reasonable: in bipedal stance, there would need to be compensatory changes in one leg to support the body as reflex actions occurred in the other.

Functional implications

Tilting the platform changes the background activity in soleus and tibialis anterior, and the extent to which stable stance depends on the reflex responses in the two muscles. The changes in E1 and E2 of tibialis anterior in Fig. 9.14(*c*)–(*e*) represent a shift from a long-latency transcortical response (E2) to a spinal response (E1) as stance becomes more unstable. These findings imply that the spinal component (E1) is functionally important in maintaining balance and that the later components are insufficient to achieve this when the motor system is not first primed by the E1 response.

Gait

Reflex responses produced by stimulation of the tibial nerve could be due to activation of muscle afferents from plantar muscles (p. 398). Thus, only the results obtained with stimulation of purely cutaneous nerves (sural, superficial peroneal) are considered below.

Cutaneous responses evoked during the swing phase

The modulation during gait of the reflex responses evoked by low-threshold cutaneous afferents has been extensively investigated by Stein and colleagues (for review, see Zehr & Stein, 1999) and Duysens and colleagues (e.g. Van Wezel, Ottenhoff & Duysens, 1997). From these studies, it has emerged that stimuli to the sural or superficial peroneal nerves can evoke excitatory responses in flexor muscles (tibialis anterior and hamstrings). These responses occur with a latency of ~80–85 ms and have a duration of ~30 ms, but are not closely related to the background EMG activity in any of the nerve/muscle combinations (Van Wezel, Ottenhoff & Duysens, 1997). In striking contrast with the responses to stretch, which are mainly observed during the stance phase of gait (Chapter 11, p. 549), these responses are seen mainly during the swing phase.

Local sign

The reflex responses depend on the stimulated nerve, as would be expected if the location of the stimulus is important for the response (Van Wezel, Ottenhoff & Duysens, 1997). While stimuli to both the sural and peroneal nerves produce large facilitatory responses in hamstrings, they have a different effect on the tibialis anterior. Thus, Fig. 9.15(*b*) shows the excitatory response evoked by sural nerve stimulation on the on-going EMG of tibialis anterior during the early swing phase, 600 ms after heel strike. The time course of this response during the step cycle shows that the excitation appears at the onset of the swing phase (or at the transition from stance to swing), peaks early in swing phase and is replaced by inhibition (cutaneous reversal) at the end of the swing phase (Fig. 9.15(*d*)). In contrast, stimulation of the peroneal nerve suppresses tibialis anterior EMG activity, even in early swing phase.

Evidence for a transcortical response

The onset latency of the excitatory response is ~85 ms, much the same latency as the similar, though smaller, response evoked during voluntary tonic dorsiflexion in the sitting position (Fig. 9.11(*b*)). The latter depends on a transcortical pathway p. 424, and the question then arises whether the

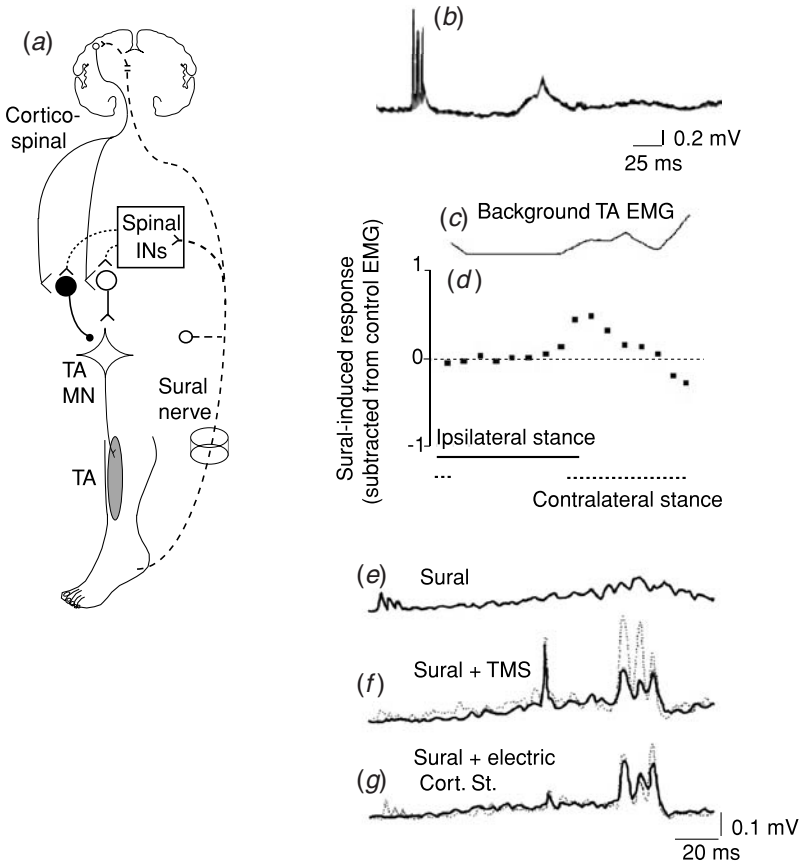


Fig. 9.15. Sural modulation of the on-going EMG of tibialis anterior during walking. (*a*) Sketch of the presumed pathways. Aβ cutaneous afferents in the sural nerve activate, through spinal interneurones (IN) and/or transcortical pathways, excitatory and inhibitory INs projecting to ipsilateral tibialis anterior (TA) motoneurones (MNs). (*b*) Effect of sural stimulation (3 shocks, 300 Hz, 2 × PT), triggered 600 ms after heel strike (early swing) on the on-going TA EMG. (*c*) Background activity of TA throughout the step cycle. (*d*) Modulation by sural stimulation (5 shocks, 200 Hz, 2 × PT) of the on-going TA EMG, measured within a window 80–110 ms after stimulation, throughout the step cycle (mean data from ten subjects). Horizontal continuous and dotted lines indicate the times of ipsilateral and contralateral stance, respectively. (*e*)–(*g*) Effect of sural stimulation (three shocks, 300 Hz, 2.5 × PT, 600 ms after heel strike) on the on-going TA EMG (*e*), the MEP elicited by TMS ((*f*), 60 ms ISI) and by electrical stimulation of the motor cortex ((*g*), 63 ms ISI): averaged (20 sweeps) control (continuous thick line) and conditioned responses (dotted thin line) are superimposed. Modified from Nielsen & Sinkjær (2002) ((*b*), (*e*)–(*g*)), and Van Wezel, Ottenhoff & Duysens (1997) ((*c*), (*d*)), with permission.

sural-induced excitation of tibialis anterior during the early swing phase of gait uses the same pathway. The effects of sural stimulation on tibialis anterior MEPs elicited by magnetic or electrical stimulation of the motor cortex at the time when the cutaneous volley had reached the cortex were used to investigate this possibility (Christensen *et al.*, 1999, and Fig. 9.15(*e*)–(*g*), see also Pijnappels *et al.*, 1998). The sural volley facilitated the MEP elicited by TMS, but did not modify the MEP elicited by electrical stimulation. Such a differential effect implies that motor cortex excitability was affected by the

conditioning cutaneous stimulus (Chapter 1, p. 44), and provides evidence for a transcortical contribution to the sural-induced excitation. However, again, it must be emphasised that the above demonstration of a transcortical pathway does not exclude the possibility that other supraspinal (spino-bulbo-spinal) or even spinal pathways also contribute to these responses (cf. p. 424).

Functional implications

It has been suggested that the *sural* facilitation of flexors is involved in lifting the foot over an obstacle (Yang & Stein, 1990; Duysens *et al.*, 1990). When the foot strikes an obstacle in the transition from stance to swing, it would be useful for an automatic mechanism to help withdraw the limb from the ground through actions at ankle, knee and hip. Later in the swing phase, this response would be inappropriate, as the weight is shifting from the other leg. Then facilitation of tibialis anterior activity is replaced by inhibition, and this would help to place the foot on the ground to avoid stumbling (see Zehr & Stein, 1999; Christensen *et al.*, 2000). On the other hand, the *dorsum of the foot* innervated by the peroneal nerve is most likely to encounter an obstacle during the swing phase. The resulting suppression of the tibialis anterior EMG combined with the excitation of hamstrings is then adequate to clear the foot from the obstacle and prepare the leg to step over it, thus enabling continuation of an on-going walking pattern. Cutaneous reflexes are also evoked in contralateral muscles. It seems therefore that cutaneous reflexes are used during gait, whether running or walking, to move the perturbed leg away from the stimulus, with the general constraint of preserving both the cadence and balance during the step cycle (Tax, Van Wezel & Dietz, 1995; Van Wezel, Ottenhoff & Duysens, 1997).

Why a transcortical component to the response?

Similar reflex responses have been described in the *spinalised* cat during walking, and could play a similar role (see p. 387). Christensen *et al.* (2000) suggest that 'the ease with which the balance may be endangered in bipedal gait by too large or too small responses to cutaneous stimulation has made it necessary to integrate the reflex response at a cortical level rather than or in addition to a spinal level in human subjects. In this way, an inappropriate response may be suppressed, or the information carried out by the cutaneous afferents may be used by the structure responsible for subsequent voluntary corrections of the movement'.

Hopping

During hopping, there is a sural-induced facilitation of the tibialis anterior at the end of the stance phase, as during gait, but no inhibition at the end of the swing phase. This finding indicates that the end-stance facilitation is not specific for alternating gait, and the absence of the end-swing suppressive reflexes may be related to the absence of heel strike in hopping (Hauglustaine *et al.*, 2001).

Conclusions

Cutaneomuscular reflexes evoked through 'private' cutaneous pathways prevent grasped objects from slipping from the hand. In the lower limb, spinally mediated placing reactions tend to increase the contact with the ground, while supraspinally mediated excitatory responses appear in flexor muscles during the swing phase of gait and are involved in lifting the foot over an obstacle. However, the main role of cutaneous afferents in motor control is probably to modulate the transmission in 'proprioceptive' pathways (cf. Chapters 3–10).

Changes in patients and clinical implications

Changes in cutaneous reflexes, in particular in withdrawal reflexes, are of clinical importance in the examination of patients with upper motor neurone disorders. The exaggeration of flexor reflexes and the

release of flexor spasms may, in addition, contribute to the discomfort of these patients.

Complete spinal transection

Early responses are replaced by long-latency withdrawal reflexes

These long-latency responses are mediated through pathways analogous to those transmitting long-latency FRA responses in the DOPA-treated cat. Three phases can be distinguished in the evolution of reflexes in these patients (Hiersmenzel, Curt & Dietz, 2000):

(i) During the initial phase of spinal shock, withdrawal reflexes are abolished.

(ii) Then, during a 'transition phase to spasticity', early withdrawal responses of the same amplitude as in normal subjects reappear. There are no long-latency responses.

(iii) Finally, some 2–6 months after the initial injury when the lesion is chronic, the pattern described by Roby-Brami & Bussel (1987) appears, with suppression of early responses and their replacement by long-latency responses (cf. pp. 407–8). The earliest plantar response after stimulation of the sole of the foot is then recorded in the extensor hallucis longus where it appears with a latency similar to that of long-latency withdrawal responses (Roby-Brami, Ghenassia & Bussel, 1989).

Receptive field

In contrast to the modular organisation of early withdrawal reflexes in normal subjects (see p. 407), late responses in patients with a chronic spinal cord injury have an invariant pattern of flexion, regardless of the stimulus location on the foot or leg (Schmit *et al.*, 2003). The finding that similar responses occur with stimulation of the sural and posterior tibial nerves (Roby-Brami & Bussel, 1987) is of methodological interest: it is not possible to grade the stimulus intensity with respect to the perception (or pain) threshold in these patients, but stimulation of the tibial nerve can be graded with respect to motor threshold, and results so obtained may then be compared across different subjects.

Afferents contributing to the flexion reflex

In these patients, they include cutaneous afferents, since the responses are evoked by sural nerve stimulation (Roby-Brami & Bussel, 1987), but also probably high-threshold muscle afferents (Schmit, McKenna-Cole & Rymer, 2000), much as in FRA-induced reflexes in the spinal cat (see pp. 388–9).

Upper motoneurone lesions other than those due to a complete spinal transection

Upper motoneurone lesions other than those due to a complete spinal transection produce characteristic changes in cutaneous reflexes.

Abolition of normal cutaneous reflexes

Some cutaneous reflexes are abolished by upper motoneurone lesions. The disappearance of cutaneous reflexes on the affected side of patients with hemiplegia was recognised by Jastrowitz in 1875 for the cremasteric reflexes and by Rosenbach in 1876 for the abdominal reflexes (cited by van Gijn, 1996). When the Babinski response is manifest (see below), this is in part because the normal downward movement of the hallux, which is a segmental cutaneomuscular reflex involving the flexor hallucis brevis, disappears after upper motoneurone lesions (cf. van Gijn, 1996). The disappearance of these cutaneous responses after upper motoneurone lesions implies that the relevant pathways normally receive tonic descending excitation from the corticospinal tract.

The Babinski response

The replacement of the normal plantar flexion of toe 1 by dorsiflexion constitutes the Babinski response, a major sign of an upper motor neurone lesion.

The abnormal dorsiflexion response has been documented in EMG recordings

Using natural mechanical stimuli, Landau & Clare (1959) stated that 'the unique feature of the pathological extensor response is the recruitment of extensor hallucis longus into contraction' (see Fig. 9.5(*g*)). However, using electrical rather than mechanical stimuli, Kugelberg, Eklund & Grimby (1960) found that the response involves both dorsiflexors and plantar flexors of toe 1 in normal subjects and in patients with pyramidal lesions, but that the dominant response is in dorsiflexors in the patients so that the toe moves up. The differences in these studies may be due to the different method of stimulation – electrical stimulation is artificial, quite unlike the situation when neurologists test the reflex. In accordance with Landau & Clare (1959), van Gijn (1996) recommends observation of the tendon of the extensor hallucis longus when testing the plantar response.

Pathophysiology of the Babinski response

The pathophysiology of the Babinski response involves the suppression of the normal segmental cutaneomuscular reflex (cf. above) and disinhibition of the flexion withdrawal reflex, with expansion of the receptive field to include the skin of the lateral side of the sole, in addition to the ball of toe 1. Accordingly, the upward response of toe 1 will be accompanied by activation of other muscles of the flexor synergy (see van Gijn, 1996). The Babinski sign is thus an indication of withdrawal of supraspinal control of flexor reflexes in the lower limb. Absence of the downward response of toe 1 is not pathological, unless there is a marked difference between the two sides.

The Babinski response can be equated with transient or permanent dysfunction of the upper motor neurone

The function of the pyramidal tract may be disturbed by structural lesions (of myelin sheaths, axons or both), by epileptic seizures (Babinski, 1898) or by metabolic factors, such as hypoglycaemia. The absence of an expected Babinski sign or an equivocal response is often due to the technique used to elicit the response. A pressure palsy of the peroneal nerve will, of course, weaken dorsiflexion of toe 1. In other cases there may be temporary inexcitability of the segmental reflex pathway. This may be the case in the 'spinal shock' following an acute transverse lesion of the cord, but can also be observed after acute brain lesions such as a large infarct (see van Gijn, 1996).

Withdrawal (flexor) reflexes in the lower limb

Alterations of lower-limb withdrawal reflexes in spasticity

These alterations can be summarised as follows.

(i) Breakdown of the adapted modular organisation of withdrawal reflexes, with appearance of a flexion response whatever the site of stimulation (Kugelberg, Eklund & Grimby, 1960; Dimitrijević & Nathan, 1968; Bathien & Bourdarias, 1972; Fisher, Shahani & Young, 1979).

(ii) Irradiation into muscles normally not involved (Meinck, Benecke & Conrad, 1983) with, for example, widespread irradiation of activity from stimulation of the unaffected side in hemiplegic patients (Dimitrijević, 1973).

(iii) Decreased threshold in patients with incomplete spinal cord lesions and hemiplegic patients (Shahani & Young, 1971; Dimitrijević, 1973).

(iv) Delay or suppression of early reflex components (Dimitrijević, 1973; Fisher, Shahani & Young, 1979; Meinck, Benecke & Conrad, 1983).

(v) Dishabituation of reflex activity (Dimitrijević & Nathan, 1971) and abnormal sensitivity to temporal facilitation (Meinck *et al.*, 1983b).

Flexor spasms

Flexor spasms are due to an overly vigorous reflex response of the isolated spinal cord to segmental inputs. According to Shahani & Young (1973), they are extremely variable, ranging from the brief repetitive firing of single units without any visible contraction

in the limb to sustained firing of many motor units in many muscles with massive movements. They have the same clinical and physiological properties as do evoked flexor reflexes in the same patients. Spontaneous flexor spasms may therefore be considered labile or heightened flexor reflexes, the stimuli for which are not immediately apparent. They occur characteristically following more rostral spinal cord lesions.

Electrical stimulation of the medial plantar nerve

Such stimulation produces a flexor reflex in the tibialis anterior, and has been used in the electrophysiological investigations in spastic patients (Meinck *et al.*, 1983a, b, 1985). Reflex pathways activated by the conditioning volley are complex, because the stimulation activates not only cutaneous afferents but also group I and group II muscle afferents from plantar muscles, and these muscle afferents have strong projections to tibialis anterior motoneurones (cf. p. 398). However, these investigations are of interest because they involve a large number of patients with lesions at various level of the corticospinal tract. With weak stimuli, the early synchronised response observed in normal subjects was not seen; instead long-latency desynchronised activity occurred. With stronger stimuli, the desynchronised activity increased in amplitude and duration, and its latency shortened. These flexor reflexes differed from normal responses: (i) the inhibitory reflex components were replaced by excitation, (ii) the overall reflex discharge was greater, (iii) the reflex responses became grossly desynchronised, and (iv) phasic reflex activity was replaced by tonic activity. Such abnormalities were seen in 98% of the 148 patients investigated (Meinck *et al.*, 1983b), regardless of whether the lesion was at the cerebral, brainstem or spinal level.

Withdrawal reflexes during gait in stroke patients

Studies during gait have revealed three abnormalities: (i) an expansion of the receptive field of tibialis anterior, (ii) a decrease in the reflex activity in soleus and biceps femoris, and (iii) absence of reflex modulation during the step cycle (Spaich, Arendt-Nielsen & Andersen, 2004).

Inhibition of the soleus H reflex

Inhibition of extensors by noxious stimuli to the skin of the foot is the counterpart of the activation of flexors in normal withdrawal reflexes of the foot (cf. pp. 404–5). Inhibition of the soleus H reflex by noxious stimulation to toe 5 has been compared in normal subjects and hemiplegic patients with lesions of the corticospinal tract at various levels of the neuraxis (Pierrot-Deseilligny, Bussel & Morin, 1973). The normal inhibition peaks at 50–70 ms in normal subjects (Fig. 9.8(*b*)) but was reduced in all patients, to a variable degree, according to the site of the lesion. The inhibition disappeared in patients with lesions of the paracentral lobule, was markedly decreased in patients with hemispheric lesions, and moderately decreased in patients with brainstem lesions.

Withdrawal reflexes in the upper limb

In stroke patients, Cambier, Dehen & Bathien (1974) described changes in the nociceptive reflex elicited by stimulation of the ulnar nerve at the wrist, resembling those described in the lower limb: a lower threshold for the reflex which appeared in the biceps, and spread of the response to involve flexors of other limb segments. A recent investigation by Dewald *et al.* (1999) has revealed further abnormalities.

(i) As in the lower limb, the onset latencies of the responses were delayed.

(ii) The normal proximal-to-distal sequence of activation of upper limb muscles after noxious stimulation of the finger was systematically changed, because the responses were more delayed at the shoulder than at the elbow.

(iii) The normal pattern of shoulder extension was changed into shoulder flexion.

Cutaneomuscular responses

Lower limb

Late E2 responses in the extensor digitorum brevis and tibialis anterior muscles are absent in patients with lesions of the corticospinal tract (Choa & Stephens, 1981; Rowlandson & Stephens, 1985b). In addition, during the stance phase of gait in stroke patients, superficial peroneal stimulation suppresses triceps surae and quadriceps EMG, a change that does not occur in normal subjects (Zehr, Fujita & Stein, 1998).

Upper limb

Cutaneomuscular responses in the first dorsal interosseous to stimulation of the digital nerves of the index finger undergo changes previously discussed in patients with upper motoneurone lesions: the late E2 excitation may be abolished and, when present, is attenuated and delayed, the I1 inhibitory response is also attenuated, and the spinally mediated E1 excitation is generally increased (Jenner & Stephens, 1982; Chen *et al.*, 1998). These changes produce a pattern similar to the cutaneomuscular responses observed in the neonate before the pyramidal tract has reached maturity (cf. p. 423). They provide some of the evidence for a transcortical pathway for the late E2 excitation, and raise the possibility that corticospinal drive normally exerts tonic inhibition on the oligosynaptic spinal pathway mediating the E1 response.

Grasp reflex

Whether the grasp reflex observed in patients with frontal lobe lesions depends on cutaneous or muscle afferent inputs had been the subject of debate until Seyffarth & Denny-Brown (1948) showed that it was due to the summation of two local reflexes: an early cutaneous reflex (catching phase) followed by a stretch reflex of finger flexors (holding phase), the latter being ineffective in the absence of the former. Cutaneous participation in the grasp reflex was indicated by the finding that the RII reflex evoked in the flexor carpi ulnaris to stimulation of tactile afferents in the ulnar nerve was increased in a patient with a grasp reflex (Shahani, Burrows & Whitty, 1970). This result was confirmed further in an investigation showing that the RII reflex is increased not only in the flexor carpi ulnaris but also in the biceps, and that, unlike RII in normal subjects, it is not prone to habituation (Cambier, Dehen & Bathien, 1974). The lack of habituation reflects the difficulty observed in these patients in inhibiting a response to tactile stimulation of the palmar side of the hand. In normal subjects, sustained vibration of the skin of the fingers at 100 Hz can produce a reflex contraction of the long finger flexor muscles, a response that nerve block experiments indicated due to activation of rapidly conducting cutaneous afferents (Eklund, Hagbarth & Torebjörk, 1978). Accordingly, the appearance of a grasp reflex in patients represents pathological accentuation of an intrinsically normal reflex response, not the development of a completely different reflex.

Parkinson's disease

Withdrawal reflexes

Withdrawal reflexes produced by noxious stimuli in the lower limb of patients with Parkinson's disease differ from those in normal subjects in five respects.

(i) The threshold of the early component is reduced.

(ii) The normal reciprocal relationships in antagonistic leg motoneurones are disturbed and a great deal of 'co-contraction' is seen, such that stimuli which normally produce reflex activity in extensors (cf. pp. 404–5) now also produce reflex activity in flexors.

(iii) Cutaneous silent periods (cf. Fig. 9.4(*e*)) are abnormally brief or virtually absent.

(iv) Habituation is less evident than normal.

(v) These abnormalities are largely, though not completely, reversed by the administration of DOPA

(Shahani & Young, 1971; Young, 1973; Delwaide, Schwab & Young, 1974).

Early transcortical inhibition

The early inhibitory component of the cutaneomuscular response (I1) in the first dorsal interosseus is decreased in parkinsonian patients (Fuhr, Zeffiro & Hallett, 1992). Given that the I1 component probably uses a transcortical pathway (cf. p. 423), this reduction of I1 inhibition is in keeping with the effects of cutaneous volleys on the MEP evoked by TMS in the abductor pollicis brevis (Delwaide & Olivier, 1990). In normal subjects cutaneous volleys from the index finger produce an inhibition of the MEP at ISIs 18–22 ms, possibly the result of cutaneous inhibition of cortical neurones. This inhibition was reduced and even reversed to facilitation in parkinsonian patients. Both effects (depression of I1 and of the inhibition of the MEP) were partially reversed with dopaminergic treatments. This mechanism could contribute to parkinsonian rigidity.

Peripheral neuropathies

Sural-induced facilitation of the tibialis anterior and biceps femoris EMG observed in normal subjects during the swing phase of gait (see pp. 430–2) is significantly reduced in patients with a sensory neuropathy producing a deficit restricted largely to the loss of large-myelinated Aβ fibres and not Aδ fibres. The abnormally large variability in step cycle duration and the gait impairment seen in these patients has been related to this loss of reflex activity from low-threshold cutaneous afferents (Van Wezel *et al.*, 2000).

Diagnostic uses

Some clinically important tests in the standard neurological examination, such as the Babinski response and the abolition of cutaneous abdominal reflexes, can provide evidence for dysfunction of the corticospinal tract. An understanding of cutaneous reflexes and their supraspinal control is critical for understanding these tests. However, this section has focussed on the clinical relevance of electrophysiological investigations.

Spinal responses

These reflex responses can allow the integrity of different peripheral and segmental pathways to be investigated in tests that complement H reflex studies. While the afferents responsible for the H reflex have the same segment as the innervated motoneurones, this is usually not so with the cutaneomuscular responses, and reflex studies can be useful in differentiating between peripheral nerve and segmental pathologies. For example, stimulating different digits of the hand can create inputs that traverse C6, C7 and C8 to the same motoneurone pool.

Lesions of the transcortical pathway

Abnormality can be manifest in patients with central lesions as attenuation of the E2 and I1 components and/or by prolongation of the interval between the short- and long-latency components. However, the selective involvement of long-latency transcortical responses sparing short-latency spinal responses has not proved a reliable finding in diagnostic tests on individual patients with questionable lesions.

Nociceptive reflexes may be of value in monitoring the effects of medication for pain

Because of the strong correlation between the sural-induced RIII reflex in the biceps femoris and the pricking pain in the receptive field of this nerve (p. 399; Fig. 9.2(*l*), (*m*)), the RIII reflex provides an objective method to assess treatments in patients with pain (Willer, 1983).

Rehabilitation

The ability to activate the lower-limb flexion synergy may be of value in helping restore locomotion in patients with incomplete spinal cord injury (see Barbeau *et al.*, 1999).

Conclusions

Apart from their role in sensation, cutaneous afferents are also capable of modulating motor behaviour through spinal, supraspinal and transcortical pathways. They may play a 'proprioceptive' role of paramount importance, whether that influence is mediated by primarily 'private' pathway or by modulating the activity of spinal pathways fed by muscle afferents and/or descending inputs.

Role of cutaneous reflexes in motor control

Withdrawal reflexes

Early withdrawal reflexes, i.e. responses occurring with a latency of less than 120 ms in the lower limb, are the only responses that are unequivocally mediated through spinal pathways in normal subjects. They are organised to produce rapid movement away from the offending object. The 'local sign' is an important feature of withdrawal reflexes everywhere, on the trunk as well as the limbs, and is a consequence of this protective function.

Late withdrawal reflexes are recorded in patients with complete spinal transection, in whom they have a latency of more than 120 ms and a lower threshold than early withdrawal reflexes. Several features of these late reflexes, in particular that their latency increases as stimulus intensity is increased or the stimulus train prolonged, are reminiscent of the late FRA responses seen in the acute spinal cat treated with DOPA.

Cutaneomuscular reflexes evoked by non-noxious stimuli

Cutaneomuscular reflexes evoked through 'private' cutaneous pathways associate modest early responses mediated by oligosynaptic spinal pathways with large long-latency transcortical excitation. In the upper limb, the early spinally mediated excitation (E1) is distributed mainly to distal muscles, without reciprocal organisation, and is increased during power grip. These features and the finding that tactile cutaneous volleys favour the recruitment of high-threshold motor units suggest that reflexes evoked by tactile afferents prevent grasped objects from slipping from the hand. In the lower limb, spinally mediated placing reactions tend to increase the contact with the ground, while transcortically mediated excitatory responses appear in flexor muscles during the swing phase of gait and are involved in lifting the foot over an obstacle.

A major role of cutaneous afferents in motor control is to modulate the transmission in 'proprioceptive' pathways. This role is made possible because of their extensive convergence onto various spinal pathways. For example, the exteroceptive volley evoked when the moving limb meets an obstacle helps curtail a movement through: (i) activation of inhibitory Ib interneurones transmitting the Ib feedback from the contracting muscle, and (ii) inhibition of cervical propriospinal neurones mediating the descending command.

Changes in cutaneous reflexes in patients

Patients with complete spinal transection

When the lesion is chronic, early withdrawal reflexes more or less disappear and are replaced by late withdrawal responses with a stereotyped pattern of flexion. Dishabituation is usual and may lead to flexor spasms.

Other upper motoneurone lesions produce characteristic changes in cutaneous reflexes: (i) replacement of the normal flexion of toe 1 (physiological extension) by dorsiflexion (Babinski sign);

(ii) abolition of normal cutaneous responses, such as the abdominal and cremasteric reflexes.

The RIII reflex produced by sural stimulation in the biceps femoris provides an objective method for monitoring the effects of medication for pain.

Résumé

Cutaneous afferents converge on interneurones intercalated in pathways fed by muscle afferents and descending tracts and on PAD interneurones mediating presynaptic inhibition of muscle afferents. Through this extensive convergence, exteroceptive volleys help an appropriately timed termination of the movement when the moving limb meets the target or an unexpected obstacle. Cutaneous receptors can be activated during movement even without contact with an external object, and thereby modulate the motor output. This role is considered in detail in the other chapters. Cutaneous afferents may also act in isolation and are capable of modulating motor behaviour through spinal, supraspinal and transcortical pathways. This chapter deals with such effects, which include two main types of response: withdrawal reflexes mediated by Aδ afferents and cutaneomuscular responses mediated by non-nociceptive cutaneous afferents.

Background from animal experiments

Private cutaneous pathways

Reflexes elicited through private pathways are difficult to distinguish from FRA (flexion reflex afferent) responses, but may be when cutaneous and FRA volleys evoke different responses in the same motoneurones. This is the case for (i) the toe extensor reflex, and (ii) the stumbling corrective reaction evoked from the dorsum of the foot in flexors during the swing phase and in extensors during the stance phase of locomotion. Withdrawal reflexes evoked by noxious stimuli have for long been equated with the classical flexion reflex. They are, in fact, more refined, with a modular organisation where each muscle has a separate cutaneous receptive field activated from nociceptors and, to a lesser extent, slowly adapting mechanoreceptors.

FRA pathways

Flexion reflex afferents (FRA) include cutaneous, group II and group III muscle afferents and joint afferents. All of these afferents *may* evoke the ipsilateral flexion reflex with contralateral extension (short-latency FRA responses) in the acute spinal animal. They have been grouped together, because: (i) they converge on common interneurones interposed in reflex pathways to motoneurones; (ii) they act together on a variety of ascending tracts; (iii) transmission of their effects is similarly influenced by brainstem lesions; and (iv) they are similarly controlled from descending tracts. There are alternative pathways from these afferents, and the term FRA is therefore a misnomer that may have outlived its usefulness, but it has been ratified by use.

Lundberg (1979) formulated the hypothesis that, during normal movement, pathways mediating FRA reflexes could provide selective reinforcement of the voluntary command from the brain. The hypothesis relied on experimental evidence that: (i) there are alternative FRA pathways to the flexion reflex, (ii) there are inhibitory interactions between alternative FRA pathways, and (iii) muscle contraction produced by stimulation of α efferents activates the FRA system.

With DOPA, long-latency FRA responses replace short-latency FRA reflexes, which are depressed. Short- and long-latency responses have a similar pattern of excitation of flexors from ipsilateral FRAs and of extensors from contralateral FRAs, with inhibition of antagonistic motoneurones, but they are mediated through different pathways, and short-latency FRA pathways can inhibit or delay the transmission in long-latency FRA pathways. There is mutual inhibition between long-latency FRA pathways to flexors and extensors, and this half-centre organisation might be responsible for the alternating activation of flexors and extensors during locomotion.

Methodology

General principles

Some principles apply to all cutaneous reflexes: (i) some reflexes may be documented by recording responses when the subject is relaxed; (ii) otherwise the reflex effects of cutaneous volleys may be tested using the H reflex, the on-going EMG or PSTHs of single motor units; (iii) temporal summation or spatial and temporal summation is generally required to cause the response to appear consistently; (iv) cutaneous reflexes are very sensitive to repetition rate; and (v) spinal responses can be frequently distinguished from transcortical responses on latency grounds.

Stimuli

(i) Electrical stimuli may be applied to cutaneous nerves or delivered directly to the skin. Withdrawal reflexes are elicited by painful stimuli and the threshold for pain is the same as the threshold for the nociceptive reflex. Cutaneomuscular responses from low-threshold mechanoreceptors are produced by stimuli that can evoke tactile sensations.

(ii) Mechanical stimuli may reproduce the stimuli of natural situations. Natural stimulation of cutaneous afferents from the fingers may be produced using a small probe to indent the skin or a controlled puff of air. In routine clinical examination plantar responses are evoked by firm stroking of the lateral plantar surface of the foot, and abdominal reflexes by a rapid stroke with a blunt pin on the abdominal skin.

Responses recorded at rest

(i) The RIII withdrawal response of the short head of the biceps femoris is consistently evoked by a stimulus to the sural nerve producing pain, and there is a correlation between reflex size and the sensation. If the stimulus intensity is sufficiently strong, the RIII reflex may be elicited by a single shock, but lower intensities are sufficient to evoke the nociceptive reflex when a train is delivered. Noxious responses are also often investigated in the tibialis anterior to stimulation of the medial aspect of the sole of the foot at the apex of the plantar arch, or of the medial plantar nerve of the foot. Trains of ten painful stimuli to the fingers will produce reflex responses in most upper limb muscles investigated.

(ii) RII Reflex responses are not easily evoked at rest by stimulation of tactile cutaneous (Aβ) afferents, and temporal summation is always required. The RII response elicited in the short head of the biceps femoris by stimulation of the sural nerve at the ankle is the most consistent cutaneous reflex so produced at rest.

Modulation of motoneurone excitability

(i) Changes produced by cutaneous volleys in the amplitude of the H reflex or tendon jerk allow one to distinguish between volleys without effect on the excitability of motoneurones, those which evoke only subliminal excitation of motoneurones when applied alone, and those which produce inhibition of motoneurones.

(ii) Averaging the rectified on-going EMG provides reasonable temporal resolution of cutaneous-induced responses. The method allows one to record rapidly the full time course of the inhibitory and excitatory effects, and has been used extensively to explore the relatively weak responses to tactile cutaneous inputs.

(iii) Investigations of the cutaneous modulation of motoneurone discharge in PSTHs are very important, because cutaneous afferents have been shown to have different effects on different types of motoneurones (innervating slow- and fast-twitch motor units), and no other technique can reveal this.

Critique of the tests to study cutaneous reflexes

(i) Nature of the stimuli. Mechanical stimuli do not allow accurate measurement of latencies and, for this reason, electrical stimuli, although artificial, are usually preferred. When stimulating a nerve trunk, caution should be observed in interpreting the evoked responses because other afferents are almost certainly activated, even when stimulating a 'pure'

cutaneous nerve (e.g. joint afferents in digital nerves).

(ii) Recording the responses at rest allows only excitatory responses to be disclosed.

(iii) Modulation of the average rectified EMG is suitable for comparing the reflex effects of cutaneous volleys in different motor tasks, but volition may bias the transmission in the reflex pathways.

(iv) Modulation of the monosynaptic reflex at rest is not subject to volitional biases, but cutaneous volleys can produce changes in presynaptic inhibition of Ia terminals mediating the afferent volley of the monosynaptic reflex.

(v) PSTHs of single units are important, but it is difficult to keep the same motor unit recording during a withdrawal reflex.

Withdrawal reflexes

Withdrawal reflexes are the reflexes produced by cutaneous afferents used most in the standard neurological examination. There are two classes of withdrawal reflexes in the lower limbs: early reflexes occurring with a latency less than 120 ms, and long-latency responses. In this chapter, 'withdrawal reflexes' denotes the former when not otherwise stated.

Afferent pathway

Small diameter, slowly conducting (17–28 m s^{-1}) Aδ fibres convey the afferent input for withdrawal reflexes and pain sensation. However, there is some evidence that Aβ fibres can contribute to both the RIII reflex and pain, if they are repetitively stimulated.

Central pathways of early withdrawal responses

Because of the slow conduction velocity of Aδ afferents and the length of the afferent pathways after distal stimulation, the latency of withdrawal responses is often the same as that of transcortical responses mediated by Aβ fibres. The finding that responses of the same latency and pattern may be recorded in patients with complete spinal transection must be interpreted with caution (see below, long-latency withdrawal responses). Superficial abdominal reflexes have been unequivocally demonstrated to be spinal, because their minimal central delay is 3–5 ms. The central delay of the withdrawal reflexes of the lower limb is less well defined. However, after allowance for the peripheral conduction time, the gradual decrease in the latency of the inhibition of knee extensors when the nociceptive stimulus is moved up the limb is best explained by a spinal mechanism. The RIII reflex of the biceps femoris after sural nerve stimulation, the best documented withdrawal response, has a minimal latency of ∼80 ms, again compatible with a polysynaptic spinal pathway. In the upper limb, the latency of the nociceptive silent period in the abductor pollicis brevis is 43 ms, a latency that favours a spinal pathway.

Functional organisation of early withdrawal reflexes

Early withdrawal reflexes are organised on a functional basis designed to produce rapid movement away from the offending object. The 'local sign' is an important feature of withdrawal reflexes everywhere (in the trunk as well as in the limbs), and is a consequence of this protective function.

(i) Trunk skin reflexes are regarded as nociceptive reflexes, even though they may be elicited by stimuli of innocuous quality, such as touch, though this may be because of the convergence of tactile and noxious afferents on common interneurones.

(ii) Plantar responses evoked from the sole of the foot are considered separately because of their clinical importance. Stimulation of the ball of the toe evokes a general flexion reflex of the lower limb, including toe 1 dorsiflexion. A stimulus to the hollow of the foot and the surrounding areas produces the normal plantar reflex, i.e. plantar flexion of the toes (physiological extension) with flexion at the ankle, knee and hip, a response that represents the appropriate withdrawal movement.

(iii) Other withdrawal responses in the lower limb also have a protective function. The flexion movement at joints proximal to the stimulus represents the classical flexion reflex, while extensor muscles are activated by stimuli to the overlying and adjacent skin.

(iv) In the upper limb, the combination of the withdrawal reflex in proximal muscles and the silent period in hand muscles is appropriate for protecting the hand, opening and withdrawing it when there is an offending stimulus to the fingers.

(v) The protective function of withdrawal reflexes is very refined with a modular organisation where each muscle has a separate cutaneous receptive field activated from nociceptors and, to a lesser extent, slowly adapting mechanoreceptors.

Late withdrawal responses

These reflex responses occur at latencies above 120 ms after distal stimulation of the lower limb.

In patients with complete spinal transection, they have a lower threshold than early withdrawal reflexes. Several features of these late reflexes are reminiscent of the late FRA responses disclosed in the acute spinal cat treated with DOPA: (i) their latency increases as the stimulus intensity is increased or the stimulus train prolonged; (ii) they are accompanied by a prolonged presynaptic inhibition of Ia terminals; and (iii) they are inhibited from contralateral FRA.

Late responses observed in normal subjects do not have the characteristics of late FRA reflexes, because their threshold is higher than that for early responses, and their latency decreases when the stimulus intensity is increased. In addition, it has been shown that these late withdrawal responses can adapt to a new situation by a change in sign when appropriate, suggesting that they involve higher centres.

Interactions between different inputs in withdrawal reflex pathways

(i) Repeated painful cutaneous volleys facilitate withdrawal reflexes at short ISIs (below 3 s) and suppress them at long ISIs, the response coming back to its control level by 60 s. This facilitation-suppression is due to a spinal mechanism, possibly post-activation facilitation and depression of transmission at the synapses of the cutaneous afferents with interneurones.

(ii) Tactile cutaneous volleys depress the biceps femoris RIII reflex. The depression of RIII responses by tactile afferents is maximal at ISIs of 100–300 ms and lasts for several hundred milliseconds.

(iii) The existence of descending controls is suggested by: the attenuation of early withdrawal reflexes in patients with chronic spinal cord injury, the finding that they are susceptible to hypnotic suggestion, and the depressive effects of heterotopic noxious stimuli applied to a remote part of the body such as the hand or face.

Changes in withdrawal reflexes during motor tasks

These are poorly documented.

(i) The cutaneous reflexes of the trunk evoked by a given stimulus are not invariant, and may be altered by a change in posture or an appropriate voluntary contraction.

(ii) Standing on one leg results in a significant decrease in the withdrawal reflex of the ipsilateral tibialis anterior, whereas a significant facilitation is observed when the subject is standing on the contralateral leg. The functional significance of this suppression would be to prevent the reflexes from interfering with the supporting action of the lower limb.

(iii) The inhibition of the soleus H reflex produced by noxious stimulation of toe 5 is reduced with respect to rest during tonic voluntary contractions of soleus or tibialis anterior.

Cutaneomuscular reflexes evoked by non-noxious stimuli

The different responses

(i) The RII reflex evoked in the short head of the biceps femoris by low-intensity stimuli to the sural

nerve is the most consistent example of a cutaneomuscular reflex recordable at rest.

(ii) Cutaneomuscular reflexes can be recorded by modulating the on-going EMG activity during a voluntary contraction by tactile cutaneous volleys. In the upper limb, with volleys applied to the fingers, the typical pattern is a triphasic response with a modest early excitation (E1) at a latency of ~30–35 ms, followed by an inhibition (I1) and by a large long-latency excitation (E2). Such responses have been recorded in many distal, hand and forearm, muscles. In the lower limb, cutaneomuscular reflexes have a much less stereotyped pattern. Excitation at spinal latency (E1) is rarely seen (extensor digitorum brevis, peroneus longus), and inhibition appears in both the soleus and tibialis anterior after stimulation of the sural nerve. These early responses are followed by a long-latency excitation in all muscles.

(iii) Monosynaptic reflex modulation: In the lower limb, the dominant effect of sural nerve stimulation at 2–2.5 × PT is facilitation of the monosynaptic reflex occurring at ISIs longer than 50 ms in all tested motor nuclei. In the upper limb, mechanical stimulation of the fingertip produces a biphasic low-threshold modulation of the FCR H reflex, with weak short-latency inhibition, followed some 3–4 ms later by a potent facilitation.

Afferent conduction

Given the low threshold of the RII reflex (5 mA), there is little doubt that the responsible afferents are within the large-myelinated Aβ range (mean conduction velocity of 51 m s^{-1}). Accordingly, stimuli evoking these responses generally require an intensity of 2–2.5 × PT, and produce a non-painful sensation of touch, even when a long train is delivered.

Central pathway of short-latency responses occurring at 'spinal latency'

RII-like reflexes at rest and cutaneomuscular responses occurring after distal stimulation at latencies earlier than 45–50 ms in the upper limb and 70–80 ms in the lower limb are probably spinal. For the modulation of the monosynaptic reflex, allowance for the conduction time of the test reflex discharge indicates a similar spinal origin for effects occurring at ISIs of less than ~30 ms in the upper limb and ~55 ms in the lower limb. Thus, on these latency grounds, transmission through spinal pathways is probable for: (i) the RII reflex of the biceps femoris; (ii) the early cutaneomuscular responses, whether E1 in the upper limb or early inhibition in the tibialis anterior and soleus; (iii) the short latency inhibition and following facilitation of the FCR H reflex after stimulation of the fingertip. Temporal summation is required to cause the RII reflex to appear at rest, and this makes uncertain speculations about the number of interneurones intercalated between the cutaneous terminals and motoneurones. When the cutaneomuscular response can be obtained with a single shock, a more precise estimate of the central delay is possible. This may be as short as 1–2 ms in some cases, implying an oligosynaptic pathway.

'Private' pathway or changes in transmission in another pathway?

(i) The RII reflex recorded at rest is probably mediated through a 'private' pathway.

(ii) Cutaneomuscular reflexes recorded during voluntary contractions could result from the modulation of the transmission in other pathways. Given the delay of transmission through the γ loop, any effect on α motoneurones resulting from a change in the γ drive would only occur at long latencies. Cutaneous facilitation of interneurones mediating Ib inhibition to voluntarily activated motoneurones has been observed only with afferents from the skin field that would have come into contact with an obstacle during contraction of the corresponding muscle, and this is not the case for the lateral side of the foot innervated by the sural nerve during contraction of tibialis anterior or soleus.

(iii) Depression of presynaptic inhibition of Ia terminals mediating the afferent volley of the test reflex can be produced by tactile afferents. This would explain why sural stimulation produces profound suppression of the on-going EMG in tibialis anterior and soleus but not of the soleus H reflex.

Central pathway of long-latency effects

The conclusion that long-latency responses have a supraspinal pathway relies on several arguments.

(i) The pattern of the long-latency facilitation of the monosynaptic reflex suggests mediation through a supraspinal centre with reflex activation of the muscles in a rostrocaudal sequence.

(ii) The latencies of late responses, when compared to the sum of the afferent and efferent conduction times to and from the cortex, are compatible with a transcortical pathway.

(iii) Observations in patients with established neurological lesions have shown that the late E2 cutaneomuscular response requires the integrity of the dorsal columns, the sensorimotor cortex and the corticospinal tract. The finding that unilateral stimulation of the digital nerves produces bilateral I1 and E2 responses in the first dorsal interosseous in patients with X-linked Kallmann's syndrome and mirror movements provides further evidence for a transcortical origin of the I1 and E2 components.

(iv) The development of E2 responses in infants parallels the maturation of the corticospinal tract, and provides further support for the view that long-latency cutaneous reflexes have a transcortical origin.

(v) Definitive evidence for a transcortical pathway has come from experiments using motor cortex stimulation. It has been shown that cutaneous volleys facilitate, at the appropriate latency, the MEP and the peak of cortical excitation in the PSTHs, when the cortical stimulation is magnetic, but not when it is electrical.

Projections of cutaneous afferents to different types of motoneurones

Cutaneous afferents from the index finger can shift the weighting of synaptic input associated with a voluntary contraction to favour the recruitment of the more powerful fast-twitch motor units in the first dorsal interosseous. Similarly, sural nerve stimuli below pain threshold produce inhibition in the PSTHs of early-recruited motoneurones and excitation in the PSTHs of late-recruited motoneurones of tibialis anterior. As a result, unconditioned tibialis anterior H reflexes of small amplitude are inhibited by sural stimulation, whereas those of large amplitude are facilitated. The skewed distribution of cutaneous inputs within the tibialis anterior motoneurone pool compresses the range of functional thresholds in the motoneurone pool and thereby increases the slope of the input-output relationship of the test reflex, i.e. it produces a change in the recruitment gain of the reflex.

Pattern and functional role of early responses

(i) The RII reflex evoked at rest in the short head of the biceps femoris tends to increase the contact with the stimulus, much as in a 'placing reaction'.

(ii) In all tested upper-limb muscles, the early spinally mediated cutaneomuscular response is an excitation (E1). The diffuse pattern of excitation of distal muscles, the finding that it is increased during power grip, and the fact that natural tactile cutaneous volleys favour the recruitment of the more powerful fast-twitch units suggest that the reflex responses evoked by tactile afferents help prevent grasped objects from slipping from the hand.

(iii) In the lower limb, apart from placing reactions which tend to increase the contact with the ground, an excitatory response appears at spinal latency in tibialis anterior when stance is unstable. During the swing phase of gait, excitatory responses are revealed in flexor muscles. They might be involved in lifting the foot over an obstacle. However, there is increasing evidence that they are mainly transcortically mediated.

Studies in patients and clinical implications

Complete spinal transection

During spinal shock, withdrawal reflexes are abolished. Then, during a 'transition phase to spasticity',

early withdrawal responses of the same amplitude as in normal subjects reappear. Finally, some 2–6 months after the initial injury when the lesion is chronic, early responses are suppressed and replaced by long-latency responses. In patients with a chronic spinal cord injury, withdrawal responses have an invariant pattern of flexion, regardless of the stimulus location on the foot or leg.

Upper motoneurone lesions

These produce characteristic changes in cutaneous reflexes:

(i) Abolition of normal cutaneous reflexes, such as the abdominal and cremasteric reflexes.

(ii) Appearance of the Babinski response, i.e. the replacement of the normal plantar flexion of toe 1 by dorsiflexion. With mechanical stimuli, the pathological response involves the recruitment of extensor hallucis longus. The pathophysiology of the Babinski response involves the suppression of the normal segmental reflex plantar flexion and disinhibition of the flexion withdrawal reflex, with expansion of the receptive field to include the skin of the lateral side of the sole, in addition to the ball of toe 1. Accordingly, the upward response of toe 1 will be accompanied by activation of other muscles of the flexor synergy. The absence of an expected Babinski sign may be due to a pressure palsy of the peroneal nerve. There may be temporary inexcitability of the segmental reflex pathway in the 'spinal shock' following an acute transverse lesion of the cord.

(iii) Alterations of lower limb withdrawal reflexes can be summarised as follows: breakdown of the adapted modular organisation of withdrawal reflexes, irradiation into muscles normally not involved, decreased threshold, delay or suppression of early reflex components, and dishabituation of reflex activity.

(iv) Flexor spasms are due to an overly vigorous reflex response of the isolated spinal cord to segmental inputs, and have the same clinical and physiological properties as do evoked flexor reflexes in the same patients.

Grasp reflex

The grasp reflex observed in patients with frontal lobe lesions is due to the summation of two local reflexes: an early cutaneous reflex followed by a stretch reflex of finger flexors, the latter ineffective in the absence of the former. The RII reflex evoked in wrist and elbow flexors by cutaneous afferents from the palmar side of the hand is increased and, unlike the case in normal subjects, is insensitive to habituation.

Patients with Parkinson's disease

Withdrawal reflexes differ from those in normal subjects, because: (i) their threshold is lowered; (ii) the normal reciprocal relationships in antagonistic leg motoneurones are disturbed; (iii) cutaneous silent periods are abnormally brief or virtually absent; and (iv) habituation is less evident than normal. Transcortical inhibitory responses (I1) in intrinsic muscles of the hand are suppressed with respect to normal subjects.

REFERENCES

Abbruzzese, G., Rubino, V. & Schieppati, M. (1996). Task-dependent effects evoked by foot muscle afferents on leg muscle activity in humans. *Electroencephalography and Clinical Neurophysiology*, **101**, 339–48.

Alstermark, B. & Lundberg, A. (1992). The C3–C4 propriospinal system: target-reaching and food-taking. In *Muscle Afferents and Spinal Control of Movement*, ed. L. Jami, E. Pierrot-Deseilligny & D. Zytnicki, pp. 327–54. London: Pergamon Press.

Andersen, O. K., Sonnenborg, F. A. & Arendt-Nielsen, L. (1999). Modular organisation of human leg withdrawal reflexes elicited by electrical stimulation of the foot sole. *Muscle and Nerve*, **22**, 1520–30.

Aniss, A. M., Gandevia, S. C. & Burke, D. (1992). Reflex responses in active muscles elicited by stimulation of low threshold afferents from the human foot. *Journal of Neurophysiology*, **67**, 1375–84.

Babinski, J. (1898). Du phénomène des orteils et sa valeur sémiologique. *Semaine Médicale*, **18**, 321–2.

Baldissera, F., Hultborn, H. & Illert, M. (1981). Integration in spinal neuronal systems. In *Handbook of Physiology*,

section I, *The Nervous System*, vol. II, *Motor Control*, ed. V. B. Brooks, pp. 508–95. Bethesda, MD: American Physiological Society.

Barbeau, H., McCrea, D. A., O'Donovan, M. J., Rossignol, S., Grill, W. M. & Lemay, M. A. (1999). Tapping into spinal circuits to restore motor function. *Brain Research Reviews*, **30**, 27–51.

Bathien, N. & Bourdarias, H. (1972). Lower limb cutaneous reflexes in hemiplegia. *Brain*, **95**, 447–56.

Binder, M. D., Houk, J. C., Nichols, T. R., Rymer, W. Z. & Stuart, D. G. (1982). Properties and segmental actions of mammalian muscle receptors: an update. *Federation Proceedings*, **41**, 2907–18.

Brown, T. G. (1914). On the nature of the fundamental activity of the nervous system: together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *Journal of Physiology (London)*, **48**, 18–46.

Burke, D., Dickson, H. G. & Skuse, N. F. (1991). Task-dependent changes in the responses to low-threshold cutaneous afferent volleys in the human lower limb. *Journal of Physiology (London)*, **432**, 445–58.

Burke, R. E. (1981). Motor units: anatomy, physiology and functional organization. In *Handbook of Physiology*, Section I, *The Nervous System*, vol. II, *Motor Control*, Part 1, ed. V. B. Brooks, pp. 345–422. Bethesda, MD: American Physiological Society.

(1999). The use of state-dependent modulation of spinal reflexes as a tool to investigate the organization of spinal interneurons. *Experimental Brain Research*, **128**, 263–77.

Burke, R. E., Jankowska, E. & Ten Bruggencate, G. (1970). A comparison of peripheral and rubrospinal synaptic input to slow and fast twitch motor units of triceps surae. *Journal of Physiology (London)*, **207**, 709–32.

Bussel, B., Roby-Brami, A., Yakovleff, A. & Bennis, N. (1989). Late flexion reflex in paraplegic patients. Evidence for a spinal stepping generator. *Brain Research Bulletin*, **22**, 53–6.

Caccia, M. R., McComas, A. J., Upton, A. R. M. & Blogg, T. (1973). Cutaneous reflexes in small muscles of the hand. *Journal of Neurology, Neurosurgery and Psychiatry*, **36**, 960–77.

Cambier, J., Dehen, H. & Bathien, N. (1974). Upper limb cutaneous polysynaptic reflexes. *Journal of the Neurological Sciences*, **22**, 39–49.

Carr, L. J., Harrison, L. M., Evans, A. L. & Stephens, J. A. (1993). Patterns of central motor reorganisation in hemiplegic cerebral palsy. *Brain*, **116**, 1223–47.

Cavallari, P. & Lalli, S. (1998). Changes in excitability of the flexor carpi radialis H-reflex following tactile stimulation of the index fingertip. *Experimental Brain Research*, **120**, 345–51.

Chen, C. C., Chen, J. T., Wu, Z. A., Kao, K. P. & Liao, K. K. (1998). Cutaneous reflexes in patients with lacunar infarction. *Journal of Neurological Sciences*, **159**, 28–37.

Chen, R. & Ashby, P. (1993). Reflex responses in upper limb muscles to cutaneous stimuli. *Canadian Journal of the Neurological Sciences*, **20**, 271–8.

Choa, B. H. G. & Stephens, J. A. (1981). Cutaneous reflex responses and central nervous lesions in man. *Electroencephalography and Clinical Neurophysiology*, **52**, S2.

Christensen, L. O., Morita, H., Petersen, N. & Nielsen, J. (1999). Evidence suggesting that a transcortical reflex pathway contributes to cutaneous reflexes in the tibialis anterior during walking in man. *Experimental Brain Research*, **124**, 59–68.

Christensen, L. O., Petersen, N., Andersen, J. B., Sinkjaer, T. & Nielsen, J. (2000). Evidence for transcortical reflex pathways in the lower limb of man. *Progress in Neurobiology*, **62**, 251–72.

Collier, J. (1899). An investigation upon the plantar reflex, with reference to the significance of its variations under pathological conditions, including an enquiry into the aetiology of acquired pes cavus. *Brain*, **22**, 71–99.

Creed, R. S., Denny-Brown, D., Eccles, J. C., Liddell, E. G. T. & Sherrington, C. S. (1932). *Reflex Activity of the Spinal Cord*. London: Oxford University Press.

Datta, A. K. & Stephens, J. A. (1981). The effects of digital nerve stimulation on the firing of motor units in human first dorsal interosseous muscle. *Journal of Physiology (London)*, **318**, 501–10.

Delwaide, P. J. & Crenna, P. (1983). Exteroceptive influences on lower limb motoneurons in man: spinal and supraspinal contributions. *Advances in Neurology*, **39**, 797–807.

(1984). Cutaneous nerve stimulation and motoneuronal excitability. II. Evidence for non-segmental influences. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 190–6.

Delwaide, P. J. & Olivier, E. (1990). Conditioning transcranial cortical stimulation (TCCS) by exteroceptive stimulation in parkinsonian patients. *Advances in Neurology*, **53**, 175–81.

Delwaide, P. J., Schwab, R. S. & Young, R. R. (1974). Polysynaptic spinal reflexes in Parkinson's disease. *Neurology*, **24**, 820–7.

Delwaide, P. J., Crenna, P. & Fleron, M. H. (1981). Cutaneous nerve stimulation and motoneuronal excitability. I. Soleus and tibialis anterior excitability after ipsilateral and contralateral sural nerve stimulation. *Journal of Neurology, Neurosurgery and Psychiatry*, **44**, 699–707.

Deuschl, G., Schenck, E. & Lücking, C. H. (1985). Long latency responses in human thenar muscles mediated by fast conducting muscle and cutaneous afferents. *Neuroscience Letters*, **55**, 361–6.

Deuschl, G., Ludolph, A., Schenk, E. & Lücking, C. H. (1989). The relations between long-latency reflexes in hand muscles, somatosensory evoked potentials and transcranial stimulation of motor tracts. *Electroencephalography and Clinical Neurophysiology*, **74**, 425–30.

Deuschl, G., Michels, R., Berardelli, A., Schenck, E., Inghilleri, M. & Lücking, C. H. (1991). Effects of electric and magnetic transcranial stimulation on long latency reflexes. *Experimental Brain Research*, **83**, 403–10.

Dewald, J. P. A., Beer, R. F., Given, J. D., McGuire, J. R. & Rymer, W. Z. (1999). Reorganization of flexion reflexes in the upper extremity of hemiparetic subjects. *Muscle and Nerve*, **22**, 1209–21.

Dimitrijević, M. R. (1973). Withdrawal reflexes. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 744–50. Basel: Karger.

Dimitrijević, M. R. & Nathan, P. W. (1968). Studies of spasticity in man. 3. Analysis of reflex activity evoked by noxious cutaneous stimulation. *Brain*, **91**, 349–68.

(1971). Studies of spasticity in man. 5. Dishabituation of the flexion reflex in spinal man. *Brain*, **94**, 77–90.

Duysens, J., Trippel, M., Horstmann, G. A. & Dietz, V. (1990). Gating and reversal of reflexes in ankle muscles during human walking. *Experimental Brain Research*, **82**, 403–10.

Eccles, J. C., Kostyuk, P. G. & Schmidt, R. F. (1962). Central pathways responsible for depolarization of primary afferent fibres. *Journal of Physiology (London)*, **161**, 351–8.

Eccles, R. M. & Lundberg, A. (1959). Synaptic actions in motoneurones by afferents which may evoke the flexion reflex. *Archives Italiennes de Biologie*, **97**, 199–221.

Egger, M. D. & Wall, P. D. (1971). The plantar cushion reflex circuit: an oligosynaptic cutaneous reflex. *Journal of Physiology (London)*, **216**, 483–501.

Eklund, G., Hagbarth, K.-E. & Torebjörk, E. (1978). Exteroceptive vibration-induced finger flexion in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **41**, 438–43.

Ellrich, J., Steffens, H. & Schomburg, E. D. (2000). Neither a general flexor nor a withdrawal pattern of nociceptive reflexes evoked from the human foot. *Neuroscience Research*, **37**, 79–82.

Engberg, I. (1964). Reflexes to toe muscles in the cat's hindlimb. In *Progress in Brain Research*, vol. 12, *Physiology of Spinal Neurons*, ed. J. C. Eccles & J. P. Schadé, pp. 274–9. Amsterdam: Elsevier.

Evans, A. L., Harrison, L. M. & Stephens, J. A. (1989). Task-dependent changes in cutaneous reflexes recorded from various muscles controlling finger movement in man. *Journal of Physiology (London)*, **418**, 1–12.

Fisher, M. A., Shahani, B. T. & Young, R. R. (1979). Electrophysiologic analysis of the motor system after stroke: the flexor reflex. *Archives of Physical Medicine and Rehabilitation*, **60**, 7–11.

Floeter, M. K., Gerloff, C., Kouri, J. & Hallett, M. (1998). Cutaneous withdrawal reflexes of the upper extremity. *Muscle and Nerve*, **21**, 591–8.

Forssberg, H., Grillner, S. & Rossignol, S. (1975). Phase dependent reflex reversal during walking in chronic spinal cats. *Brain Research*, **85**, 103–7.

(1977). Phasic control of reflexes from the dorsum of the paw during spinal locomotion. *Brain Research*, **132**, 121–39.

Fuhr, P., Zeffiro, T. & Hallett, M. (1992). Cutaneous reflexes in Parkinson's disease. *Muscle and Nerve*, **15**, 733–9.

Garnett, R. & Stephens, J. A. (1981). Changes in the recruitment threshold of motor units produced by cutaneous stimulation in man. *Journal of Physiology (London)*, **311**, 463–73.

Gassel, M. M. & Ott, K. (1970). Local sign and late effects on motoneuron excitability of cutaneous stimulation in man. *Brain*, **93**, 95–106.

Gibbs, J., Harrison, L. M. & Stephens, J. A. (1995). Cutaneomuscular reflexes recorded from the lower limb in man during different tasks. *Journal of Physiology (London)*, **487**, 237–42.

Grimby, L. (1963). Normal plantar response: integration of flexor and extensor reflex components. *Journal of Neurology, Neurosurgery and Psychiatry*, **26**, 39–50.

Hagbarth, K.-E. (1952). Excitatory and inhibitory skin areas for flexor and extensor motoneurones. *Acta Physiologica Scandinavica*, **26**, 1–58.

(1960). Spinal withdrawal reflexes in the human lower limbs. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 222–7.

Hagbarth, K.-E. & Finer, B. L. (1963). The plasticity of human withdrawal reflexes to noxious skin stimuli in lower limbs. In *Brain Mechanisms. Progress in Brain Research*, vol. 1, ed. G. Moruzzi, A. Fessard & H. H. Jasper, pp. 25–81. Amsterdam: Elsevier.

Hallett, M., Berardelli, A., Delwaide, P. *et al.* (1994). Central EMG and tests of motor control. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology*, **90**, 404–32.

Hammar, I., Slawinska, U. & Jankowska, E. (2002). A comparison of postactivation depression of synaptic actions evoked by different afferents and at different locations in the feline spinal cord. *Experimental Brain Research*, **145**, 126–9.

Harrison, L. M., Norton, J. A. & Stephens, J. A. (2000). Habituation of cutaneomuscular reflexes recorded from the first dorsal interosseus and triceps muscle. *Journal of the Neurological Sciences*, **177**, 32–40.

Hauglustaine, S., Prokop, T., Van Zwieten, K. J. & Duysens, J. (2001). Phase-dependent modulation of cutaneous reflexes of tibialis anterior muscle during hopping. *Brain Research*, **897**, 180–3.

Hiersemenzel, L. P., Curt, A. & Dietz, V. (2000). From spinal shock to spasticity. Neuronal adaptations to a spinal cord injury. *Neurology*, **54**, 1574–82.

Holmqvist, B. & Lundberg, A. (1961). Differential supraspinal control of synaptic actions evoked by volleys in the flexion reflex afferents in alpha motoneurones. *Acta Physiologica Scandinavica*, **54**, suppl. 186, 1–51.

Hongo, T., Jankowska, E. & Lundberg, A. (1966). Convergence of excitatory and inhibitory action on interneurones in the lumbosacral cord. *Experimental Brain Research*, **1**, 338–58.

(1969). The rubrospinal tract. Facilitation of interneuronal transmission of reflex paths to motoneurones. *Experimental Brain Research*, **7**, 365–91.

Hongo, T., Kitazawa, S., Ohki, Y. & Xi, M. C. (1989). Functional identification of last-order interneurones of skin reflex pathways in the cat forelimb segments. *Brain Research*, **505**, 167–70.

Hornby, T. G., Rymer, W. Z., Benz, E. N. & Schmit, B. D. (2003). Windup of flexion reflexes in chronic human spinal cord injury: a marker for neuronal plateau potentials? *Journal of Neurophysiology*, **89**, 416–26.

Hugon, M. (1967). *Réflexes polysynaptiques cutanés et commandes volontaires*. Thèse de Sciences, 232 pp. Paris.

(1973). Exteroceptive reflexes to stimulation of the sural nerve in normal man. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 713–29. Basel: Karger.

Hulliger, M., Nordh, E., Thelin, A. E. & Vallbo, Å. B. (1979). The responses of afferent fibres from the glabrous skin of the hand during voluntary finger movements in man. *Journal of Physiology (London)*, **291**, 233–49.

Hunt, C. C. (1951). The reflex activation of mammalian small nerve fibres. *Journal of Physiology (London)*, **115**, 456–69.

Hunt, C. C. & Perl, E. R. (1960). Spinal reflex mechanisms concerned with skeletal muscle. *Physiological Reviews*, **40**, 538–79.

Issler, H. & Stephens, J. A. (1983). The maturation of cutaneous reflexes studied in the upper limb in man. *Journal of Physiology (London)*, **335**, 643–54.

Jankowska, E., Jukes, M. G. M., Lund, S. & Lundberg, A. (1967a). The effect of DOPA on the spinal cord. 5. Reciprocal organization of pathways transmitting excitatory action to alpha motoneurones of flexors and extensors. *Acta Physiologica Scandinavica*, **70**, 369–88.

(1967b). The effect of DOPA on the spinal cord. 6. Half-centre organization of interneurones transmitting effects from the flexor reflex afferents. *Acta Physiologica Scandinavica*, **70**, 389–402.

Jastrowitz, M. (1875). Beitrag zur Pathologie der Hemiplegien. *Berliner Klinischen Wochenschrift*, **12**, 428–30.

Jenner, H. & Stephens, J. A. (1982). Cutaneous reflex responses and their central nervous pathways studied in man. *Journal of Physiology (London)*, **333**, 405–19.

Johansson, R. S. & Vallbo, Å. B. (1983). Tactile sensory coding in the glabrous skin of the human hand. *Trends in Neurosciences*, **6**, 27–32.

Kanda, K. & Desmedt, J. E. (1983). Cutaneous facilitation of large motor units and motor control in human fingers in precision grip. *Advances in Neurology*, **39**, 253–61.

Kearney, R. E. & Chan, C. W. (1979). Reflex response of human arm muscles to cutaneous stimulation of the foot. *Brain Research*, **170**, 214–17.

Knikou, M. & Conway, B. A. (2001). Modulation of soleus H-reflex following ipsilateral mechanical loading of the sole of the foot in normal and complete spinal cord injured humans. *Neuroscience Letters*, **303**, 107–10.

Kofler, M. (2003). Functional organization of exteroceptive inhibition following nociceptive electrical fingertip stimulation in humans. *Clinical Neurophysiology*, **114**, 973–80.

Kugelberg, E. (1962). Polysynaptic reflexes of clinical importance. *Electroencephalography and Clinical Neurophysiology*, suppl. **22**, 111.

Kugelberg, E. & Hagbarth, K.-E. (1958). Spinal mechanism of the abdominal and erector spinae skin reflexes. *Brain*, **81**, 290–304.

Kugelberg, E., Eklund, K. & Grimby, L. (1960). An electromyographic study of the nociceptive reflexes of the lower limb. Mechanism of the plantar responses. *Brain*, **83**, 394–417.

Lance, J. W. (2002). The Babinski sign. *Journal of Neurology, Neurosurgery and Psychiatry*, **73**, 360–62.

Landau, W. M. & Clare, M. H. (1959). The plantar reflex in man, with special reference to some conditions where the extensor response is unexpectedly absent. *Brain*, **82**, 321–55.

Lundberg, A. (1959). Integrative significance of patterns of connections made by muscle afferents in the spinal cord. In *Symposium of the XXIth International Physiological Congress*, pp. 1–5. Buenos Aires.

(1973). The significance of segmental spinal mechanisms in motor control. In *Symposium 4th International Biophysics Congress, Moscow 1972*, pp. 9–23. Puschino, Moscow.

(1979). Multisensory control of reflex pathways. In *Reflex Control of Posture and Movement, Progress in Brain*

Research, vol. 50, ed. R. Granit & O. Pompeiano, pp. 11–28. Amsterdam: Elsevier.

(1982). Inhibitory control from the brain stem of transmission from primary afferents to motoneurons, primary afferent terminals and ascending pathways. In *Brain Stem Control of Spinal Mechanisms*, ed. B. Sjölund & A. Björklund, pp. 179–224. Amsterdam: Elsevier.

Lundberg, A., Malmgren, K. & Schomburg, E. D. (1987). Reflex pathways from group II muscle afferents. 3. Secondary spindle afferents and the FRA: a new hypothesis. *Experimental Brain Research*, **65**, 294–306.

McNulty, P. A. & Macefield, V. G. (2002). Reflexes in the hand: strong synaptic coupling between single tactile afferents and spinal motoneurones. In *Advances in Experimental Medicine and Biology*, vol. 508, *Sensorimotor Control of Movement and Posture*, ed. S. C. Gandevia, U. Proske & D. G. Stuart, pp. 39–45, New York: Kluwer Academic Plenum Publishers.

Macefield, G., Gandevia, S. C. & Burke, D. (1989). Conduction velocities of muscle and cutaneous afferents in the upper and lower limbs of human subjects. *Brain*, **112**, 1519–32.

Manconi, F. M., Syed, N. A. & Floeter, M. K. (1998). Mechanisms underlying spinal motor neuron excitability during the cutaneous silent period in humans. *Muscle and Nerve*, **21**, 1256–64.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and their Central Action*. 630 pp. London: Arnold.

Mayston, M. J., Harrison, L. M., Quinton, R., Stephens, J. A., Krams, M. & Bouloux, P. M. J. (1997). Mirror movements in X- linked Kallmann's syndrome. 1. A neurophysiological study. *Brain*, **120**, 1199–216.

Meier-Ewert, K., Schmidt, C., Nordmann, G., Hümme, U. & Dahm, J. (1973). Averaged muscle responses to repetitive sensory stimuli. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 767–72. Basel: Karger.

Meinck, H. M., Piesiur-Strehlow, B. & Koehler, W. (1981). Some principles of flexor reflex generation in human leg muscles. *Electroencephalography and Clinical Neurophysiology*, **52**, 140–50.

Meinck, H. M., Benecke, R. & Conrad, B. (1983a). Spasticity and the flexor reflex. In *Clinical Neurophysiology of Spasticity*, ed. P. J. Delwaide & R. R. Young, pp. 39–54. Amsterdam: Elsevier.

Meinck, H. M., Benecke, R., Küster, S. & Conrad, B. (1983b). Cutaneomuscular (flexor) reflex organization in normal man and in patients with motor disorders. In *Motor Control Mechanisms in Health and Disease*, ed. J. E. Desmedt, pp. 787–96. New York: Raven Press.

Meinck, H. M., Küster, S., Benecke, R. & Conrad, B. (1985). The flexor reflex – influence of stimulus parameters on the reflex response. *Electroencephalography and Clinical Neurophysiology*, **61**, 287–98.

Nielsen, J. & Kagamihara, Y. (1993). Differential projection of the sural nerve on early and late recruited human tibialis anterior motor units: change of recruitment gain. *Acta Physiologica Scandinavica*, **147**, 385–401.

Nielsen, J. B. & Sinkjaer, T. (2002). Afferent feedback in the control of human gait. *Journal of Electromyography and Kinesiology*, **12**, 213–17.

Nielsen, J., Petersen, N. & Fedirchuk, B. (1997). Evidence suggesting a transcortical pathway from cutaneous foot afferents to tibialis anterior motoneurones in man. *Journal of Physiology (London)*, **501**, 473–84.

Pedersen, E. (1954). Studies on the central pathway of the flexion reflex in man and animal and changes in the reflex threshold and the circulation after spinal transection. *Acta Psychiatrica Scandinavica*, suppl. **88**, 1–81.

Pierrot-Deseilligny, E., Bussel, B. & Morin, C. (1973a). Supraspinal control of the changes induced in H reflex by cutaneous stimulation, as studied in normal and spastic man. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 550–5. Basel: Karger.

Pierrot-Deseilligny, E., Bussel, B., Sideri, G., Cathala, H. P. & Castaigne, P. (1973b). Effect of voluntary contraction on H-reflex changes induced by cutaneous stimulation in normal man. *Electroencephalography and Clinical Neurophysiology*, **34**, 185–92.

Pijnappels, M., Van Wezel, B. M., Colombo, G., Dietz, V. & Duysens, J. (1998). Cortical facilitation of cutaneous reflexes in leg muscles during human gait. *Brain Research*, **787**, 149–53.

Plaghki, L., Bragard, D., Le Bars, D., Willer, J. C. & Godfraind, J. M. (1998). Facilitation of a nociceptive flexion reflex in man by non noxious radiant heat produced by a laser. *Journal of Neurophysiology*, **79**, 2557–67.

Roby-Brami, A. & Bussel, B. (1989). Long-latency spinal reflex in man after flexor reflex afferent stimulation. *Brain*, **110**, 705–25.

(1990). Effects of flexor reflex afferent stimulation on the soleus H reflex in patients with a complete spinal cord lesion: evidence for presynaptic inhibition of Ia transmission. *Experimental Brain Research*, **81**, 593–601.

(1992). Inhibitory effects on flexor reflexes in patients with a complete spinal cord section. *Experimental Brain Research*, **81**, 201–8.

Roby-Brami, A., Bussel, B., Willer, J. C. & Le Bars, D. (1987). An electrophysiological investigation into the pain-relieving

effects of heterotopic nociceptive stimuli: probable involvement of a supraspinal loop. *Brain*, **110**, 1497–508.

Roby-Brami, A., Ghenassia, J. R. & Bussel, B. (1989). Electrophysiological study of the Babinski sign in paraplegic patients. *Journal of Neurophysiology*, **59**, 1390–7.

Rosenbach, O. (1876). Ein Beitrag zur Symptomatologie cerebraler Hemiplegien. *Archives von Psychiatrist Nervenkranken*, **6**, 845–51.

Rossi, A. & Decchi, B. (1994). Flexibility of lower limb reflex responses to painful cutaneous stimulation in standing humans: evidence of load-dependent modulation. *Journal of Physiology (London)*, **481**, 521–32.

Rowlandson, P. J. & Stephens, J. A. (1985a). Maturation of cutaneous reflex responses recorded in the lower limb in man. *Developmental Medicine and Child Neurology*, **27**, 425–33.

(1985b). Cutaneous reflex responses recorded in children with various neurological disorders. *Developmental Medicine and Child Neurology*, **27**, 434–47.

Sasaki, M., Kitazawa, S., Ohki, Y. & Hongo, T. (1996). Convergence of skin reflex and corticospinal effects in segmental and propriospinal pathways to forelimb motoneurones in the cat. *Experimental Brain Research*, **107**, 422–34.

Schmit, B. D., McKenna-Cole, A. & Rymer, W. Z. (2000). Flexor reflexes in chronic spinal cord injury triggered by imposed ankle rotation. *Muscle and Nerve*, **23**, 793–803.

Schmit, B. D., Hornby, T. G., Tysseling-Mattiace, V. M. & Benz, E. N. (2003). Absence of local sign in withdrawal in chronic human spinal cord injury. *Journal of Neurophysiology*, **90**, 3232–41.

Schomburg, E. D. (1990). Spinal sensorimotor systems and their supraspinal control. *Neuroscience Research*, **7**, 265–340.

Schouenborg, J. (2002). Modular organisation and spinal somatosensory imprinting. *Brain Research Reviews*, **40**, 80–91.

Seki, K., Perlmutter, S. & Fetz, E. E. (2003). Sensory input to primate spinal cord is presynaptically inhibited during voluntary movement. *Nature Neuroscience*, **6**, 1309–16.

Seyffarth, H. & Denny-Brown, D. (1948). The grasp-reflex and the instinctive grasp reaction. *Brain*, **71**, 109–83.

Shahani, B. T. & Young, R. R. (1971). Human flexor reflexes. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 616–27.

(1973). Human flexor spasms. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 734–43. Basel: Karger.

Shahani, B. T., Burrows, P. & Whitty, C. W. (1970). The grasp reflex and perseveration. *Brain*, **73**, 181–92.

Sherrington, C. S. (1906). *The Integrative Action of the Nervous System*. New Haven: Yale University Press.

(1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *Journal of Physiology (London)*, **40**, 28–121.

Shimamura, M., Mori, S. & Yamauchi, T. (1967). Effects of spinobulbo-spinal reflex volleys on extensor motoneurons of hind limb in cats. *Journal of Neurophysiology*, **30**, 319–32.

Sonnenborg, F. A., Andersen, O. K. & Arendt-Nielsen, L. (2000). Modular organization of excitatory and inhibitory reflex receptive fields elicited by electrical stimulation of the foot sole. *Clinical Neurophysiology*, **111**, 2160–9.

Spaich, E. G., Arendt-Nielsen, L. & Andersen, O. K. (2004). Modulation of lower limb withdrawal reflexes during gait: a topographical study. *Journal of Neurophysiology*, **91**, 258–66.

Stephens, J. A., Garnett, R. & Buller, N. P. (1978). Reversal of recruitment order of single motor units produced by cutaneous stimulation during voluntary muscle contraction in man. *Nature*, **272**, 262–4.

Tax, A. A. M., Van Wezel, B. M. H. & Dietz, V. (1995). Bipedal reflex coordination to tactile stimulation during human running. *Journal of Neurophysiology*, **73**, 1947–64.

Turner, L. C., Harrison, L. M. & Stephens, J. A. (2002). Finger movement is associated with attenuated cutaneous reflexes recorded from human first dorsal interosseus muscle. *Journal of Physiology (London)*, **542**, 559–66.

Van Gijn, J. (1996). The Babinski sign: the first hundred years. *Journal of Neurology*, **243**, 675–83.

Van Wezel, B. M. H., Ottenhoff, F. A. & Duysens, J. (1997). Dynamic control of location-specific information in tactile cutaneous reflexes from the foot during human walking. *Journal of Neuroscience*, **17**, 3804–14.

Van Wezel, B. M. H., Van Engelen, B. M. G., Gabreëls, F. J. M., Gabreëls-Festen, A. A. W. M. & Duysens, J. (2000). Aβ fibers mediate cutaneous reflexes during human walking. *Journal of Neurophysiology*, **83**, 2980–6.

Viala, G., Orsal, D. & Buser, P. (1978). Cutaneous fiber groups involved in the inhibition of fictive locomotion in the rabbit. *Experimental Brain Research*, **33**, 257–67.

Walshe, F. M. R. (1914). The physiological significance of the reflex phenomenon in spastic paralysis of lower limbs. *Brain*, **37**, 269–336.

Willer, J. C. (1977). Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain*, **3**, 69–80.

(1983). Nociceptive flexion reflexes as a tool for pain research in man. In *Advances in Neurology*, vol. 39, *Motor Control Mechanisms in Health and Disease*, ed. J. E. Desmedt, pp. 809–28. New York: Raven Press.

Willer, J. C. & Bussel, B. (1980). Evidence for a direct spinal mechanism in morphine-induced inhibition of nociceptive reflexes in humans. *Brain Research*, **187**, 212–15.

Willer, J. C., Boureau, F. & Albe-Fessard, D. (1978). Role of large diameter cutaneous afferents in transmission of nociceptive messages: electrophysiological study in man. *Brain Research*, **152**, 358–64.

Willer, J. C., Roby, A. & Le Bars, D. (1984). Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain*, **107**, 1095–112.

Yang, J. F. & Stein, R. B. (1990). Phase-dependent reflex reversal in human leg muscles during walking. *Journal of Neurophysiology*, **63**, 1109–17.

Young, R. R. (1973). The clinical significance of exteroceptive reflexes. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 697–712. Basel: Karger.

Zehr, E. P. & Stein, R. B. (1999). What function do reflexes have during human locomotion? *Progress in Neurobiology*, **58**, 185–205.

Zehr, E. P., Fujita, K. & Stein, R. B. (1998). Reflexes from the superficial peroneal nerve during walking in stroke subjects. *Journal of Neurophysiology*, **79**, 848–58.

10

Propriospinal relay for descending motor commands

The most important motor function of the spinal cord is to transmit the command for movement from higher centres to spinal motoneurones. In primates, there are monosynaptic cortico-motoneuronal projections, whereas, in the cat, the corticospinal command to forelimb motoneurones is transmitted exclusively through oligosynaptic pathways with intercalated spinal interneurones. Some are located at each segmental level (segmental interneurones). Others are rostral to motoneurones and are referred to as propriospinal neurones in the following (although the term 'propriospinal' has a more general meaning: that of an intrinsic spinal cord neurone, the axon of which terminates in remote spinal cord segments).

The presence of a significant contribution of the cervical propriospinal system to the control of upper limb movement in higher primates has been debated, but there is mounting evidence that, in macaque monkeys (Sasaki *et al.*, 2004) and in humans (Pierrot-Deseilligny, 2002), a substantial part of the cortical command for movement is transmitted to motoneurones through a 'propriospinal' relay located rostral to motoneurones. The existence of a functional propriospinal system in human subjects is of particular interest. Indeed, because of the extensive convergence onto cervical propriospinal neurones of descending and peripheral inputs, the major role of the propriospinal system is probably to enable integration of the descending command *en route* to the motoneurones with the afferent feedback from the moving limb. This provides an example of the integrative action of spinal circuitry, such that the cortical command can be updated at a premotoneuronal level to take into account changes in the internal and external environment.

The cervical propriospinal system

Background from animal experiments

The propriospinal system in the cat

The only premotoneuronal system for which both connections and function are known is the system of C3–C4 propriospinal neurones in the cat, described by Lundberg and his group (for review see Alstermark & Lundberg, 1992; Lundberg, 1999). Connections have been established using classical intracellular recordings from motoneurones and interneurones. Behavioural studies on the effects of selective spinal lesions have elucidated the functional role of the system. Thus, this system can transmit descending commands for target-reaching movements, and the extensive convergence onto C3–C4 propriospinal neurones of descending excitation and inhibition and of peripheral inputs (mainly inhibitory) from the moving limb allows the cortical command to be updated at that premotoneuronal level.

Excitatory projections to and from propriospinal neurones

Multi-excitatory convergence onto propriospinal neurones

Corticospinal volleys evoke oligosynaptic EPSPs in feline forelimb motoneurones through both

propriospinal neurones and segmental interneurones. Propriospinally mediated disynaptic EPSPs disappear after section of the corticospinal tract at C2 but persist after its section at C5. This indicates that propriospinal neurones are located in C3–C4 (Illert, Lundberg & Tanaka, 1977), where they are in the lateral parts of laminae VI and VII. Other descending pathways (rubro-, tecto- and reticulo-spinal) and, to a much lesser extent, peripheral afferents also have monosynaptic excitatory projections onto propriospinal neurones (Illert *et al.*, 1978) (Fig. 10.1).

Projections from propriospinal neurones

Propriospinal axons are located in the ventral part of the lateral funiculus (whereas the corticospinal tract runs in its dorsal part), and project monosynaptically to motoneurones, to interneurones mediating reciprocal Ia inhibition (not shown in Fig. 10.1), or to both. Individual propriospinal neurones may project to motoneurones of various muscles acting at different joints. This creates a hard-wired network in the cervical spinal cord to subserve complex motor synergies in which muscles operating at different joints are co-activated (Alstermark *et al.*, 1990; Chapter 11, pp. 529–30).

Inhibitory mechanisms in the propriospinal system

There is a wealth of inhibitory actions (Fig. 10.1) in the propriospinal system, mediated through inhibitory interneurones also located rostral to motoneurones (Alstermark, Lundberg & Sasaki, 1984a, b, c).

(i) Inhibitory C3–C4 propriospinal neurones (not shown in Fig. 10.1) projecting monosynaptically to motoneurones and feedforward inhibitory interneurones projecting to propriospinal neurones have the same excitatory connections from higher centres as the excitatory propriospinal neurones and are interspersed among the propriospinal neurones in the lateral part of lamina VII. They are presumably used to focus excitation to the muscles required for

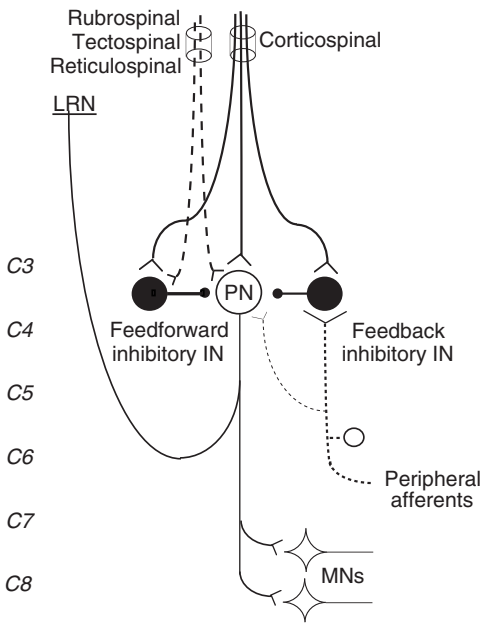


Fig. 10.1. The connections of the C3–C4 propriospinal system in the cat. In this and subsequent figures, segmental cervical levels are indicated on the left in italics, excitatory synapses are represented by Y-shaped bars and inhibitory synapses by small filled circles, excitatory interneurones by open circles and inhibitory interneurones by large filled circles. An individual propriospinal neurone (PN) projects to motoneurones (MNs) innervating different forelimb muscles and receives monosynaptic excitation from corticospinal (thick continuous line) and rubro-, reticulo- and tecto-spinal tracts (thick dashed line) and, to a much lesser extent, from peripheral afferents (thin dotted line). Note that there are no monosynaptic cortico-motoneuronal projections in the cat. Feedback inhibitory interneurones (IN) projecting to PNs receive monosynaptic excitation from peripheral and corticospinal inputs, while feedforward inhibitory INs projecting to PNs receive only monosynaptic excitation from the same descending tracts as PNs. The thick dotted line indicates that the feedback to inhibitory INs is stronger than to PNs. Axons of PNs have ascending collaterals to the lateral reticular nucleus (LRN). Projections of PNs to INs mediating reciprocal Ia inhibition, and inhibitory PNs projecting to MNs and their ascending collaterals to the LRN are not represented. Neither are the ascending collaterals of feedback inhibitory interneurones to the LRN represented. Sketched to illustrate data in Alstermark & Lundberg (1992) and Lundberg (1999).

the particular movement (in a manner analogous to lateral inhibition in sensory pathways).

(ii) Feedback inhibitory interneurones, which project to propriospinal neurones, are excited from peripheral afferents in the moving limb, and are located medially in the laminae V and VI. They are used to regulate the force and speed of the movement and contribute to its termination: whereas transecting the dorsal columns in C2 produces a moderate ataxia easily compensated by visual control, suppressing the afferent input to feedback inhibitory interneurones by transecting them in C5 results in marked hypermetria that cannot be corrected, suggesting that the command centres take feedback inhibition for granted (Alstermark *et al.*, 1986). Feedback inhibitory interneurones are also excited by the corticospinal tract so as to adjust the gain in the feedback inhibitory loop.

Ascending projections

Excitatory propriospinal neurones

These neurones have ascending collaterals to the lateral reticular nucleus (LRN, see Fig. 10.1) (Alstermark *et al.*, 1981a). Antidromic volleys produced by stimulation of the projections in the LRN produce monosynaptic EPSPs in motoneurones, and their size can be used as a measure of the strength of the projection of propriospinal neurones to motoneurones. Via these ascending collaterals, the LRN, which projects to the cerebellum, receives mirror information of the motor command that reaches motoneurones via the propriospinal neurones, i.e. a perfect efference copy (see Lundberg, 1999). This may allow the cerebellum to take corrective measures with a minimal delay, for which purpose it has at its disposal the rubro- and reticulo-spinal tracts which project directly to C3–C4 propriospinal neurones.

Inhibitory propriospinal neurones and feedback inhibitory interneurones

Unlike feedforward inhibitory interneurones, these interneurones also have ascending projections to the LRN, and antidromic volleys produced by stimulation of their projections elicit monosynaptic IPSPs in motoneurones and in propriospinal neurones, respectively (Alstermark, Lundberg & Sasaki, 1984a, b).

Function of the propriospinal system

Behavioural studies on the effects of selective spinal lesions have been performed using a test consisting of reaching to a tube and retrieving food from it. These experiments have shown that the command for target-reaching is mediated by propriospinal neurones, whereas that for object-taking is transmitted by cortico- and rubro-spinal activation of segmental interneurones (Alstermark *et al.*, 1981b). The extensive convergence (descending and peripheral) onto propriospinal neurones suggests that a motor command initiated in higher centres and relayed through motor cortex could be reshaped *en route* to motoneurones by integration in the propriospinal system. This would confer the ability to react to sudden unforeseen changes in the internal or external environment that have occurred during the development of the motor command and its transmission down to the spinal cord level ('updating hypothesis', see Illert *et al.*, 1978).

Conflicting results in the monkey

Scarcity and weakness of propriospinally mediated EPSPs under control conditions

In upper limb motoneurones of the macaque monkey, indirect propriospinally mediated corticospinal EPSPs evoked by strong stimulation of the pyramidal tract are rare and weak, and so too are monosynaptic EPSPs evoked antidromically by stimulation of the projections of propriospinal neurones to the LRN (Maier *et al.*, 1998). Intermediate results between the cat and the macaque monkey were obtained in the squirrel monkey, in which hand dexterity is less advanced than in the macaque monkey. As a result it was argued that there was a positive

correlation between hand dexterity and monosynaptic corticospinal projections across species, and a negative correlation between this function and the strength of the propriospinal system (Lemon, 1999; Nakajima *et al.*, 2000; Kirkwood, Maier & Lemon, 2002).

Disclosure of strong propriospinally mediated EPSPs after reduction of inhibition

Effects after reduction of the inhibition

When the post-synaptic inhibition mediated by feedback and feedforward inhibitory interneurones in propriospinal neurones has been reduced by intravenous strychnine, large corticospinal propriospinally mediated disynaptic EPSPs can be readily demonstrated in most upper limb motoneurones in the macaque monkey (Alstermark *et al.*, 1999). This also applies to monosynaptic EPSPs elicited by stimulation of the LRN (which, under control conditions, are probably partially masked by IPSPs elicited in motoneurones by stimulation of the ascending projections of inhibitory propriospinal neurones). Finally, intracellular recordings from identified C3–C4 propriospinal neurones by Alstermark and Isa have documented their projections directly to upper limb motoneurones and the LRN in the macaque monkey (see Rothwell, 2002).

Selective chronic lesions of the pyramidal tract

Recent experiments performed after selective chronic lesion of the pyramidal tract in C4–C5 further support the view that a functional propriospinal system does exist in higher primates (Sasaki *et al.*, 2004).

(i) Propriospinally mediated disynaptic EPSPs could be induced even without strychnine in half of the forelimb motoneurones, occasionally even by a single stimulus. It was postulated that the strength of the inhibition had decreased so that C3–C4 propriospinal neurones mediating disynaptic EPSPs were more readily activated after a *chronic* corticospinal lesion.

(ii) Despite the lesion interrupting both corticomotoneuronal excitation and excitation *via* segmental interneurones monkeys could grasp a morsel of food using independent finger movements, though there was a deficit in force between the index finger and the thumb.

Conclusions

The species difference might therefore be that in higher primates there is stronger inhibitory control of propriospinal neurones through feedforward and feedback inhibitions, in order to focus the descending command more accurately than in the cat, not that evolution has caused the propriospinal system to disappear (Alstermark *et al.*, 1999; pp. 467–8).

Methodology

Activation of propriospinal neurones may be investigated by assessing (i) the excitation evoked by peripheral volleys in motoneurones, or (ii) the cutaneous suppression of the descending command passing through the propriospinal relay. In both cases, the finding that the more caudal the motoneurone, the longer the central delay of the effect suggests that the relevant neurones are located rostral to the cervical enlargement.

Propriospinally mediated excitation produced by peripheral volleys

Underlying principles

Propriospinal neurones are activated by a volley applied to a peripheral nerve, and the resulting excitation of upper limb motoneurones is assessed as a change in (i) the PSTHs of single motor units, or (ii) compound EMG responses. The characteristics of this excitation of motoneurones are a long central delay, a low threshold, and disappearance when the stimulation is increased, and they allow it to be distinguished from an effect mediated through segmental interneurones.

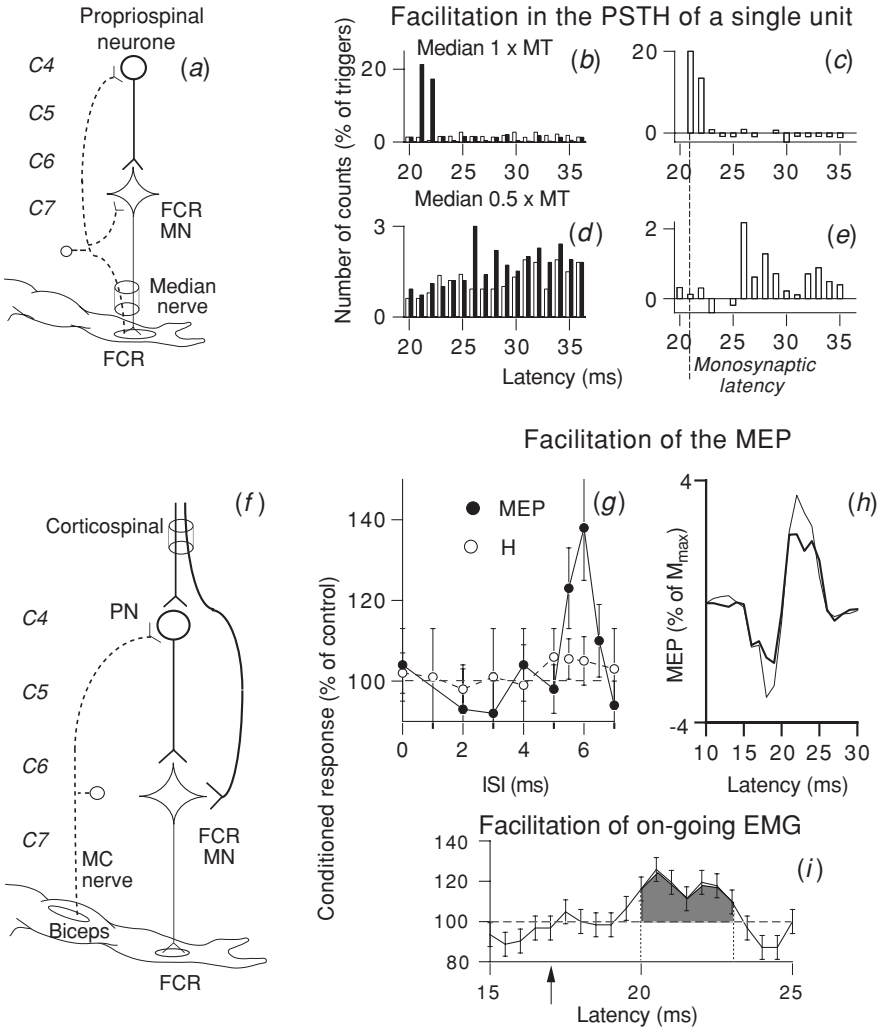


Fig. 10.2. Methods to estimate peripheral propriospinally mediated excitation of cervical motoneurones. (*a*) and (*f*) Sketches of the presumed pathways of peripheral (*a*) and corticospinal (*f*) propriospinally (PN) mediated excitation of a flexor carpi radialis (FCR) motoneurone (MN). (*b*)–(*e*) PSTHs (1 ms bin width) following median nerve stimulation at 1 × MT ((*b*), (*c*)) and 0.5 × MT ((*d*), (*e*)). The firing probability (expressed as a percentage of the number of triggers) of the FCR unit is plotted against the latency after stimulation. (*b*) and (*d*) Histograms with (■) and without (□) stimulation. (*c*) and (*e*) Difference between the histograms with and without stimulation. Note the different scale of the ordinate in (*b*), (*c*) and (*d*), (*e*). Dashed vertical line in (*c*) and (*e*) indicates the monosynaptic latency (21 ms, without allowance for the trigger delay of the unit). (*g*), (*h*) Facilitation of the FCR MEP by a musculocutaneous (MC) volley (0.75 × MT) during a tonic co-contraction of FCR and biceps. (*g*) The area of the MEP (●, TMS intensity 35%) and the FCR H reflex (○) (each adjusted to be ~5% of M_{max} when unconditioned, and expressed as a percentage of the control value) plotted against the interstimulus interval (ISI). 2 ms have been subtracted from the ISI between conditioning and test H reflex volleys so that the appropriate intervals are aligned. Facilitation of the MEP is maximal at the 6-ms interval while there is little change in the reflex. (*h*) Mean control and conditioned (facilitated) FCR MEPs (20 sweeps, thick and thin lines, respectively, expressed as a percentage of M_{max}) at the 5.5 ms ISI. Note that the facilitation spares the initial part of the MEP (see p. 463). (*i*) Facilitation of the on-going rectified voluntary ECR EMG (grey area, conditioned EMG as a percentage of control EMG) by a musculo-cutaneous volley (0.8 × MT) during a co-contraction of ECR and biceps. Facilitation occurs 3 ms after the time of arrival of the conditioning volley at the segmental level of the MNs (arrow). Error bars in (*g*), (*i*), ±1 SEM. Modified from Malmgren and Pierrot-Deseilligny (1987) ((*b*)–(*e*)), Nicolas *et al.* (2001) ((*g*), (*h*)), and Marchand-Pauvert *et al.* (1999) (*i*), with permission.

Non-monosynaptic excitation of single voluntarily activated motor units

Investigations performed on single motor units with the PSTH methodology provide the most reliable results. An example of propriospinally mediated excitation obtained for a FCR motor unit after stimulation of the median nerve is shown in Fig. 10.2(*b*)–(*e*). A homonymous monosynaptic Ia peak was evoked by stimulation at 1 × MT (*b*), (*c*), but reducing the stimulus intensity to 0.5 × MT caused it to disappear, revealing a smaller second peak 5 ms later ((*d*), (*e*)) (Malmgren & Pierrot-Deseilligny, 1987, 1988a). Several characteristics of this late, low-threshold excitation distinguish it from effects mediated through segmental interneurones.

(i) Diffuse pattern of input: in any given unit, excitation may be observed after stimulation of any muscle nerve, including those supplying antagonistic muscles (cf. p. 460).

(ii) Slightly increasing the afferent input causes the excitation to disappear (Malmgren & Pierrot-Deseilligny, 1988b). This is characteristic of the propriospinal system, and occurs because the same afferents activate not only excitatory neurones but also inhibitory interneurones that can suppress the activity of those very same excitatory neurones (Fig. 10.5(*a*), pp. 464–5). This explains the absence of late excitation at 1 × MT in Fig. 10.2 (*b*), (*c*).

(iii) The latency of the late peak is 3–6 ms longer than that of monosynaptic Ia excitation (see Table 10.1; Gracies *et al.*, 1991). Since the threshold for the second peak is lower than that of the monosynaptic Ia peak, the longer latency is unlikely to be due to afferents with a slower conduction velocity, but probably reflects a longer central pathway, presumably due to interposed interneurone(s) (see the wiring diagram in Fig. 10.2(*a*)). However, the low threshold and the abrupt onset (see Fig. 10.2(*e*)) of the second peak of excitation suggest that it is mediated through an oligosynaptic pathway, the long latency then being explained by a long conduction time to and from interneurones located at different spinal segments than motoneurones (Pierrot-Deseilligny, 1996, 2002; p. 459).

Non-monosynaptic excitation in compound EMG responses

A similar non-monosynaptic excitation, with all the characteristics of propriospinally mediated excitation described in PSTH experiments (long central delay, low threshold, disappearance when the stimulation is increased) has been observed when various compound EMG responses are conditioned by stimuli to heteronymous nerves.

(i) Facilitation of the monosynaptic reflex (FCR and ECR H reflexes, biceps and triceps tendon jerks) by low-threshold ulnar or musculo-cutaneous volleys has been observed at the onset of a voluntary contraction involving the 'conditioning' muscle(s). This facilitation is documented on pp. 474–5 and Fig. 10.8(*f*) (Burke *et al.*, 1992a; Mazevet & Pierrot-Deseilligny, 1994).

(ii) During a tonic voluntary co-contraction of ECR and biceps, a musculo-cutaneous volley produces weak facilitation of the on-going ECR EMG (Fig. 10.2(*i*); Marchand-Pauvert *et al.*, 1999a).

(iii) Low-threshold afferent volleys also facilitate MEPs elicited by low TMS intensities during tonic co-contraction of the target muscle and of the muscle innervated by the nerve used for the conditioning stimulus. The finding that there was little change in the H reflex during the tonic contractions indicates that the facilitation took place not at the motoneurone but at some premotoneuronal level (Fig. 10.2(*g*); Nicolas *et al.*, 2001).

Limitations of the tests to study propriospinal excitation of upper limb motoneurones

PSTHs have provided an invaluable tool to describe the connections of the putative propriospinal system in humans. However, because it requires a stable discharge of the investigated unit, the method cannot be used to explore changes occurring (i) when

Table 10.1. Central delay of cervical propriospinal excitation

MN pool	Rotro-caudal location	Central delay
Deltoid	C5 C6	3.50 ± 0.5
Biceps	C5 C6	3.68 ± 0.2
ECR	C6 C7 C8	4.20 ± 0.3
FCR	C6 C7 C8	4.24 ± 0.2
ED	C6 C7 C8	4.24 ± 0.4
Triceps	C7 C8 T1	4.66 ± 0.3
FCU	C7 C8 T1	4.54 ± 0.2
FDS	C7 C8 T1	4.61 ± 0.3

Mean (± SEM) central delay (ms) of propriospinal excitation, calculated as the difference between the latency of non-monosynaptic and monosynaptic Ia excitations, both produced by stimulation of the homonymous nerve, for eight motoneurone pools (MN) listed from top to bottom with respect to their rostro-caudal location in the spinal cord. From Pierrot-Deseilligny (1996), with permission.

moving from rest to activity, (ii) at different stages of a motor task (onset, offset), or (iii) in different tasks. Such investigations require studies of the modulation of compound EMG responses. At rest or during tonic contraction, propriospinally mediated facilitation of the monosynaptic reflex is weak and often absent (see pp. 460–1). The modulation of the on-going ECR EMG has so far only been investigated during a tonic contraction, and is only significant on the dominant side (Marchand-Pauvert *et al.*, 1999a). The facilitation of the MEP must be explored with low TMS intensities, because higher intensities activate feedback inhibition, and the facilitation is then reversed to inhibition (cf. p. 464).

Cutaneous suppression of descending excitation

Underlying principles

Descending excitation passing through the propriospinal relay may be suppressed by a cutaneous volley inhibiting propriospinal neurones. Thus, propriospinal neurones mediating the descending command to ECR motoneurones can be inhibited by a superficial radial volley. Although the relation between the cutaneous suppression of descending excitation and the resulting disfacilitation of motoneurones is complex, this constitutes an easy and convenient method of estimating the extent of the descending command relaying through propriospinal neurones in routine studies (see p. 474).

Cutaneous suppression of the on-going EMG

Given that there is no handedness-related asymmetry in the superficial radial-induced modulation of the on-going EMG of ECR or of the MEP in normal subjects during bilateral contractions (Marchand-Pauvert *et al.*, 1999a), cutaneous suppression of on-going EMG may be investigated during bilateral tonic contraction of the ECR. The ECR contractions are just sufficient to maintain the wrist in neutral position against gravity, and in normal subjects this corresponds to a contraction of ∼6–8% of MVC. Voluntary on-going ECR EMG activity is full-wave rectified, averaged and expressed as a percentage of the unconditioned EMG activity measured in the alternating control trials and then integrated over 40 ms to provide a measure of baseline EMG (see Fig. 10.8(*b*)). Stimuli of 1 ms duration are delivered to the superficial radial nerve through bipolar surface electrodes placed on the skin of the inferior part of the radial edge of the forearm. In normal subjects, this produces radiating paresthesiae on the dorsal side of the hand and the first three fingers. To ensure the symmetry of stimulation when there is a sensory deficit in hemiplegics, stimulus intensity may be graded with respect to the motor response in the thenar muscles due to spread of the stimulus to the median nerve. Single stimuli are adjusted to 2–4 × PT, and this corresponds to ∼0.5–1 × MT. Single stimuli or trains (three shocks at 300 Hz) may be used. Given the afferent and efferent conduction times and a central delay of ∼4 ms for the cutaneous suppression (see pp. 471–3),

the window of analysis should start 26 ms after the single volley (or the last shock of a train) (see Mazevet *et al.*, 2003). In order to avoid late effects due to inhibition exerted at cortical level, the duration of the window of analysis should be limited to 10 ms (see Burke *et al.*, 1994). Because the cutaneous volley has little effect on the ECR H reflex recorded during contraction (Fig. 10.8(*b*)), the inhibition is not exerted directly on motoneurones, but indirectly, through a neuronal relay. Given the central delay of only 4 ms, this relay presumably involves spinal interneurone's, such as the propriospinal neurones which transmit a part of the voluntary drive to the ECR motoneurone pool, i.e. the suppression results from disfacilitation of motoneurones (cf. pp. 471–3). The mean EMG suppression measured over the window of analysis due to a single shock is 14.1% at 4 × PT and 5.5% at 2 × PT (the maximal inhibition is greater, cf. p. 474). When using a train of three shocks at 2 × PT, the inhibition is increased from 5.5 to 14% (Mazevet *et al.*, 2003), due to temporal summation between the three volleys in inhibitory interneurones inhibiting propriospinal neurones (p. 478; Fig. 10.9(*c*)).

Cutaneous suppression of the MEP

The MEP elicited in ECR during tonic wrist extension and adjusted to have a size of 5–10% of the maximal M wave is consistently suppressed by a superficial radial volley (single shock, 4 × PT). In the ECR of normal subjects, the mean suppression is on average 32% at the ISI where it is maximal (Fig. 10.8(*b*); Nicolas *et al.*, 2001).

Limitations of the tests to study suppression of propriospinal excitation

The amount of suppression depends on two factors: (i) the magnitude of the component of the descending command relayed through propriospinal neurones (the greater this component, the more profound can be the cutaneous suppression); and (ii) the excitability of the interneurones mediating feedback inhibition to propriospinal neurones which are facilitated from the corticospinal tract (cf. pp. 464–7). Comparison of the effects evoked by a single shock and by a train may help distinguish between these two possibilities (see p. 478).

Rostral location of the relevant interneurones with respect to motoneurones

Evidence for a rostral location of the relevant interneurones

(i) Table 10.1 shows that the central delay of the peripheral homonymous non-monosynaptic excitation, calculated for single motor units as the difference between the latencies of monosynaptic and non-monosynaptic excitations (see Fig. 10.2(*b*)–(*e*)), is longer the more caudal the motoneurone pool in the spinal cord (Gracies *et al.*, 1991). This finding has been confirmed in a further study in which the afferent volley was applied to the same nerve (median) and the latencies assessed using 0.2 ms bins in biceps, FCR and FDS units (Pauvert, Pierrot-Deseilligny & Rothwell, 1998). For these findings to be explicable by a segmental interneuronal pathway, one would have to postulate more interneurones in the pathway the more caudal the motoneurone pool (or a slower conduction velocity for the axons of interneurones projecting to caudal motoneurones). A more parsimonious explanation is that there is a longer intraspinal pathway for caudal motoneurones, and this implicates premotoneurones located rostral to motoneurones, such as the C3–C4 propriospinal neurones in the cat (cf. p. 453).

(ii) The central delay of the superficial radial-induced suppression of the descending excitation, whether measured as tonic EMG activity or tonic firing in individual units, is also longer the more caudal the motoneurone pool (Burke *et al.*, 1994; Pierrot-Deseilligny, 1996). Here again, this suggests that the excitatory interneurones inhibited by the superficial radial volley, the presumed site of disfacilitation, are located rostral to the motoneurones, as are C3–C4 propriospinal neurones.

The evidence for a propriospinal relay in humans is indirect

However, whatever the input to the system – whether excitatory or inhibitory, peripheral or corticospinal (see below) – the more caudal the motoneurone pool in the spinal cord the longer the central delay of the effect. These data strongly suggest that the relevant interneurones are located rostral to the cervical enlargement. There are a number of other analogies with the feline system of C3–C4 propriospinal neurones (see below the pattern of connections) and, based on the totality of the evidence, the existence of a similar system in humans is highly probable, and further supported by the recent demonstration of a functional propriospinal system in the macaque monkey (see p. 455).

Organisation and pattern of connections

Excitatory inputs to propriospinal neurones

Peripheral excitatory input

Peripheral afferent input

The low threshold of the propriospinally mediated excitation is within the range of group I effects, and there is evidence for a contribution of muscle spindle Ia afferents (Malmgren & Pierrot-Deseilligny, 1988a). There may also be a contribution from cutaneous afferents, though to a lesser extent (Gracies *et al.*, 1991; Burke *et al.*, 1992a).

Why is the threshold so low?

Several reasons account for the finding that the threshold of the late peak in PSTHs is lower than that of the monosynaptic peak (Malmgren & Pierrot-Deseilligny, 1988a):

(i) The particular PSTH technique used tends to raise the threshold for monosynaptic Ia excitation with respect to that of late excitation (stimulation is set with respect to the discharge of the unit, see p. 32). (ii) Heteronymous Ia afferents in the 'conditioning' nerve may have no monosynaptic projection onto the tested motoneurone but may still activate propriospinal neurones. (iii) Afferents other than Ia (in particular, Ib) contribute to the excitation of propriospinal neurones (see pp. 516–17). (iv) There is spatial facilitation in propriospinal neurones between peripheral and descending inputs maintaining the voluntary firing of the motor unit required for the PSTHs (see below).

Widespread sources of input

In a given unit, excitation was observed after stimulation of either the nerve supplying the corresponding muscle or any other muscle nerve, including that supplying antagonistic muscles (e.g. see Fig. 10.3). Peripheral propriospinally mediated excitation has been found in motor units of all upper limb muscles explored, except the intrinsic hand muscles (Pierrot-Deseilligny, 1996).

Weakness of the peripheral excitatory input

In the cat, excitation from the deep radial nerve is found in only 23% of propriospinal neurones (Illert *et al.*, 1978), while deep radial-induced propriospinally mediated excitation has been found in the PSTHs of more than 50% of human upper limb motor units (Gracies *et al.*, 1991). In the human studies, excitation was investigated under conditions that would favour spatial facilitation in propriospinal neurones between the peripheral volley and the descending input maintaining the voluntary firing of the unit for the PSTHs. However, despite this spatial facilitation, the propriospinally mediated excitation is weak, considerably smaller than the monosynaptic Ia excitation (e.g. 3.5 vs. 37% of the number of triggers in the PSTHs of Fig. 10.2, when adding all the counts contributing to each peak). Accordingly, peripheral propriospinally mediated facilitation of the H reflex is weak and often absent at rest or during tonic contractions (e.g. open circles in Fig. 10.2(*g*); Burke

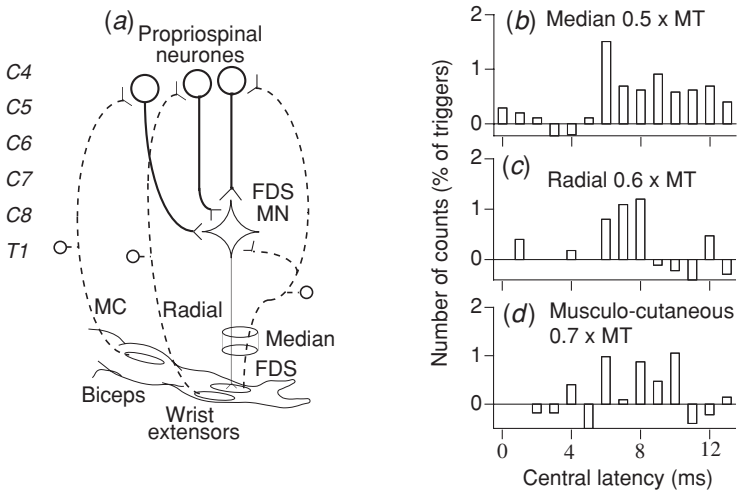


Fig. 10.3. Propriospinally mediated facilitation elicited in the PSTHs of the same FDS unit by stimulation of various nerves. (*a*) Sketch of the presumed pathways. Propriospinally mediated excitation from each muscle is transmitted to a given motoneurone (MN) pool (here flexor digitorum superficialis, FDS) through different subsets of propriospinal neurones (PN) (see pp. 468–9). (*b*)–(*d*) PSTHs (after subtraction of the background firing, 1 ms bin width) with the number of counts (expressed as a percentage of the number of triggers) plotted against the central latency after stimulation. Latencies are measured from the monosynaptic latency following median nerve stimulation at 1 × MT, after allowance for the differences in peripheral afferent conduction times. (*b*) Stimulation of the median nerve (0.5 × MT). (*c*) Stimulation of the radial nerve (0.6 × MT). (*d*) Stimulation of the musculo-cutaneous nerve (MC, 0.7 × MT). In all three cases, excitation occurred at the 6 ms central delay. Modified from Gracies *et al.* (1991), with permission.

et al., 1992a; Mazevet & Pierrot-Deseilligny, 1994). This apparent weakness may reflect intrinsically weak peripheral excitatory connections to propriospinal neurones, as in the cat. However, it might also be the consequence of stronger projections of peripheral afferents to feedback inhibitory interneurones which, when the peripheral volley is big enough, could cause the discharge of feedback inhibitory interneurones to overwhelm the facilitation in propriospinal neurones (see p. 464).

Corticospinal excitation of propriospinal neurones

In order to demonstrate that propriospinal neurones receive corticospinal excitation: (i) evidence has first been sought for convergence of peripheral and corticospinal volleys onto common interneurones, a finding that would imply that part of the corticospinal excitation to motoneurones is mediated through an interneuronal relay; and (ii) it was then shown that transmission through this relay has the same features as propriospinally mediated excitation revealed in the PSTHs of single motor units described above (Pauvert, Pierrot-Deseilligny & Rothwell, 1998; Nicolas *et al.*, 2001).

Extra facilitation on combined stimulation

Evidence for extra facilitation on combined stimulation has been sought by comparing the effects of peripheral and corticospinal volleys when delivered separately and together on the PSTHs of forearm motoneurones. Thus, Fig. 10.4(*b*)–(*e*) shows that a musculo-cutaneous volley, which by itself hardly increased the firing probability of a FDS unit

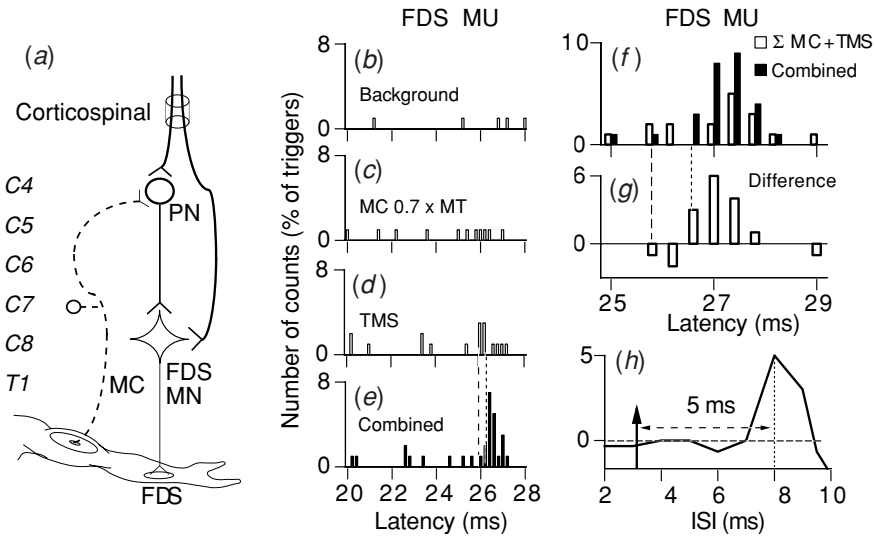


Fig. 10.4. Peripheral facilitation of the corticospinal peak in single units. (*a*) Sketch of the presumed pathways. Musculo-cutaneous (MC) and corticospinal volleys converge on propriospinal neurones (PN) projecting to a flexor digitorum superficialis (FDS) motoneurone (MN). (*b*)–(*g*) PSTHs: the number of counts (as a percentage of the number of triggers) is plotted against the latency after TMS (even in (*c*) when peripheral stimulation is given alone). (*b*)–(*e*) PSTHs for a FDS unit (0.2 ms bin width). (*b*) Background firing. (*c*) Effect of separate MC nerve stimulation (0.7 × MT). (*d*) Effect of separate TMS (26% of the maximal stimulator output). (*e*) Effect of combined stimulation (8 ms ISI). (*f*), (*g*) PSTHs for another FDS motor unit (MU) (0.4 ms bin width). (*f*) The effect on combined stimulation (8 ms ISI, ■) is compared to the sum of the effects of separate stimuli (MC and TMS, □). (*g*) Extra facilitation on combined stimulation, i.e. the difference between filled and open columns in (*f*). Dashed and dotted vertical lines in (*d*), (*e*) and (*f*), (*g*) indicate the onsets of the corticospinal peak and of the extra facilitation on combined stimulation, respectively. (*h*) The extra facilitation on combined stimulation (sum of the columns within the window 26–28 ms in (*g*), same unit as in (*f*), (*g*)) is plotted against the interstimulus interval (ISI). The vertical arrow indicates that the two volleys arrived synchronously at the segmental level of the motoneurone when TMS was elicited 3 ms after the MC volley. Modified from Pauvert, Pierrot-Deseilligny & Rothwell (1998) ((*b*)–(*g*)), and Pierrot-Deseilligny (2002) (*h*), with permission.

facilitated the corticospinal peak when the two stimuli were combined. The same result is illustrated in another way in Fig. 10.4(*f*) which shows for another FDS unit that the facilitation on combined stimulation of the musculo-cutaneous nerve and the motor cortex was larger than the sum of the effects of separate stimuli. The subtraction histogram in Fig. 10.4(*g*) (effect on combined stimulation *minus* the sum of effects of separate stimuli) shows the extra facilitation on combined stimulation over and above that expected from the sum of the two separate responses. A similar statistically significant extra facilitation has been found in almost all motor units tested (48 out of 51, 94%).

Extra facilitation implies convergence onto common interneurones

Since the summation of two excitatory inputs in a motoneurone produces little more than the sum of their effects in the PSTHs, extra facilitation implies spatial facilitation of the two inputs at an interneuronal level (Chapter 1, pp. 46–7). As sketched in Fig. 10.4(*a*), corticospinal and musculo-cutaneous inputs converge onto a population of interneurones which then project onto the motoneurone under test. Because the two conditioning volleys are weak, some inactive interneurones in that population will fail to fire in response to either input alone and will

discharge only if both inputs arrive at the same time. The net result of this is that the response of the interneuronal population to two inputs will be more than the sum of the responses to the two inputs given separately (spatial facilitation). This in turn will be reflected in the motoneurone discharge.

Initial sparing

Convergence of the two volleys onto interneurones is further supported by the absence of extra facilitation in the first bins of the corticospinal peak (see the vertical dashed and dotted lines in Figs. 10.4(*d*), (*e*) and (*f*), (*g*), which indicate the onset of the corticospinal peak and of the extra facilitation, respectively). Such sparing was found with virtually all motor units, with a mean duration of 0.8 ms. This corresponds to the delay required for transmission across one interneurone in human pathways (Pierrot-Deseilligny *et al.*, 1981; Chapter 1, pp. 14–16). This is what would be expected if the two volleys converged onto common interneurones rather than directly onto the motoneurone. Because of the synaptic delay at the interneurone, this input would arrive at the motoneurone after the direct rapidly conducting monosynaptic corticomotoneuronal input. Thus interneuronal facilitation would be unable to affect the onset of the corticospinal response and initial sparing would occur.

Which interneurones?

Figure 10.4(*h*) shows that, for the motor unit illustrated in Fig. 10.4(*f*), (*g*), extra facilitation on combined stimulation occurred at the 8 ms ISI (vertical dotted line), an interval that corresponds to a central delay of 5 ms (since, as indicated by the arrow, the two volleys arrived synchronously at the segmental level of the motoneurone when TMS was elicited 3 ms after the musculo-cutaneous volley; Pauvert, Pierrot-Deseilligny & Rothwell, 1998). It has been shown that the mean ISI at which the extra facilitation first occurs becomes greater the more caudal the motoneurone pool tested in the spinal cord (Nicolas *et al.*, 2001). This indicates that the more caudal the motoneurone pool the longer the central delay of the extra facilitation of the corticospinal peak, as for the peripheral non-monosynaptic excitation. Again, this suggests mediation through propriospinal neurones.

Disappearance of the extra facilitation when the peripheral volley is increased

A further argument favouring the view that extra facilitation of the corticospinal peak takes place in propriospinal neurones is the finding that slightly increasing the musculo-cutaneous volley can cause the extra facilitation to disappear (Nicolas *et al.*, 2001), much as it suppresses the peripheral propriospinally mediated excitation (cf. p. 464).

Corticospinal facilitation of propriospinal neurones at rest

The FCR H reflex was conditioned by a weak (0.6–0.8 × MT) volley to the ulnar or the musculocutaneous nerve, and by TMS (Gracies, Meunier & Pierrot-Deseilligny, 1994). There was extra facilitation of the reflex on combined stimulation over and above that expected from the sum of the effects of the two separate conditioning stimuli. This extra facilitation began ~1 ms later than the onset of the control reflex facilitation. Assuming that the onset of the latter reflects the arrival of the monosynaptic corticospinal volley at the motoneurone pool, the 1-ms delay again suggests a disynaptic pathway for the cortical excitation of motoneurones through propriospinal neurones.

Inhibition of propriospinal neurones via feedback inhibitory interneurones

With the artificially synchronised volleys used in these experiments, excitation is invariably reversed to inhibition when the input (peripheral or corticospinal) is increased.

Peripheral inhibition of propriospinal neurones

'Homonymous' and 'heteronymous' group I inhibition

Increasing slightly the intensity of the peripheral nerve stimulation depresses the propriospinally mediated excitation. Thus, in Fig. 10.5(*b*), (*c*), propriospinally mediated excitation evoked in a FCU motor unit by stimulation of the median nerve at 0.4 × MT completely disappeared when the intensity was increased to 0.7 × MT. This suppression at higher stimulus intensities by the same afferents as those that evoke the excitation is referred to as 'homonymous' in the following. It was consistently observed in all motor units tested (Malmgren & Pierrot-Deseilligny, 1988b), and the mechanism underlying it is discussed below (p. 467). Propriospinally mediated excitation has also been shown to be consistently suppressed when weak volleys in two different nerves (e.g. median and ulnar), which separately produced excitation, were applied together (Malmgren & Pierrot-Deseilligny, 1988b). This is referred to as 'heteronymous' or lateral inhibition in the following.

Cutaneous suppression

Cutaneous afferents also suppress the propriospinally mediated excitation. This cutaneous suppression has a particular pattern (Fig. 10.5(*e*)–(*g*); Nielsen & Pierrot-Deseilligny, 1991), which is considered in detail with its possible functional role on p. 478.

Evidence for disfacilitation

The suppression seen above could reflect inhibition exerted directly onto motoneurones (i.e. eliciting IPSPs in motoneurones) or inhibition of interneurones transmitting excitation to motoneurones (i.e. a disfacilitation). Two arguments favour disfacilitation: (i) the peak of monosynaptic excitation (whether Ia or corticospinal) is less suppressed by a peripheral volley than the propriospinally mediated excitation (Nielsen & Pierrot-Deseilligny, 1991; Mazevet, Pierrot-Deseilligny & Rothwell, 1996), whilst an IPSP at motoneurone level should have reduced the two excitations to the same extent; and (ii) in each motor unit, both excitation and depression elicited by a given mixed nerve volley occurred at the same latency, a timing which, if the inhibition were exerted at the motoneurone level, would require an absolute, and highly improbable, parallel between the excitatory and inhibitory connections of each motoneurone (Malmgren & Pierrot-Deseilligny, 1988b).

Which premotoneurones?

The central delay of the cutaneous suppression is longer the more caudal the motoneurone pool (see p. 459). In addition, in the PSTHs of single units, suppression of the peak of excitation – when the mixed nerve volley is increased – systematically occurs at the same latency as excitation (cf. above), and this is greater the more caudal the motoneurone pool (Table 10.1(*a*)). Again, this favours the view that the inhibition is exerted on neurones located rostral to the motoneurones.

Corticospinal excitation of feedback inhibitory interneurones

Here also, a technique relying on the convergence of peripheral and corticospinal volleys onto propriospinal neurones has been used, and the results obtained with weak and higher TMS intensities have been compared (Nicolas *et al.*, 2001).

Increasing TMS intensity results in a decrease in the peripheral extra facilitation of the corticospinal peak in all motor units tested

Thus, in the FCU unit in Fig. 10.6(*b*)–(*d*), clear musculo-cutaneous-induced extra facilitation of the corticospinal peak with TMS at 26% was reversed to strong inhibition with TMS at 32%. This reversal

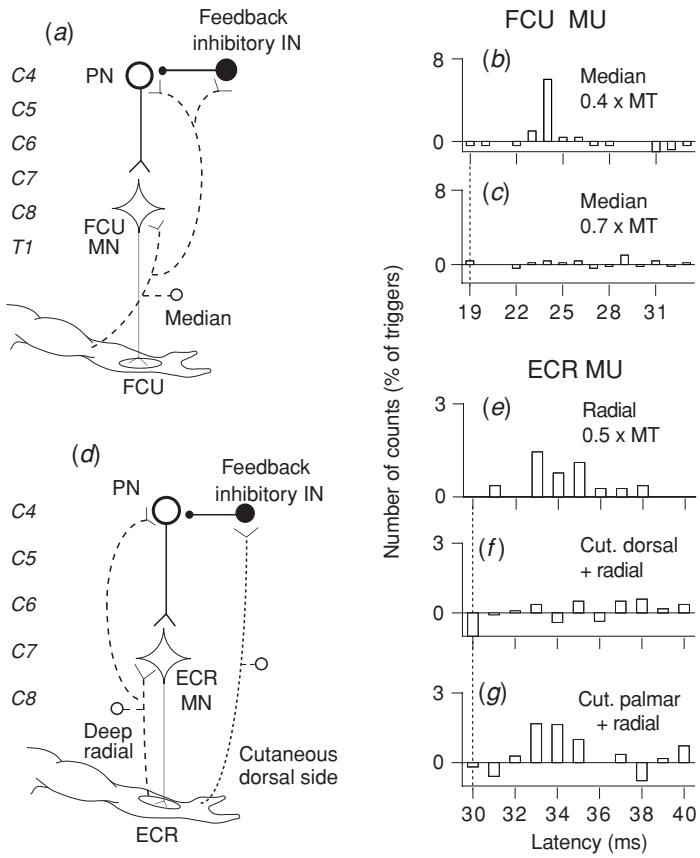


Fig. 10.5. Peripheral inhibition of the peak of propriospinally mediated excitation in single units. (*a*) and (*d*) Sketches of the presumed pathways for the results illustrated in (*b*), (*c*) and (*e*)–(*g*), respectively. Peripheral (group I in (*a*), cutaneous in (*d*)) volleys inhibit propriospinal neurones (PN) projecting to a flexor carpi ulnaris (FCU, (*a*)) and an extensor carpi radialis (ECR, (*d*)) motoneurone (MN) through activation of feedback inhibitory interneurones (IN). (*b*), (*c*), (*e*)–(*g*) PSTHs (after subtraction of the background firing, 1 ms bin width) with abscissa and ordinate as in Fig. 10.2(*e*). The monosynaptic latency (dotted vertical lines) was 19 ms in (*b*), (*c*), and 30 ms in (*e*)–(*g*) (without allowance for the trigger delay of the units). (*b*), (*c*) The peak of propriospinally mediated excitation elicited in a FCU unit by median nerve stimulation at 0.4 × MT ((*b*), 4 ms central latency) disappears when the intensity of stimulation is increased to 0.7 × MT (*c*). (*e*)–(*g*) The significant peak of propriospinally mediated excitation elicited in a ECR unit by deep radial stimulation at 0.5 × MT ((*e*), 3 ms central latency) is inhibited by a cutaneous volley from the dorsal side of the hand ((*f*) 2 × PT, preceding radial stimulation by 10 ms), but not from the palmar side (*g*). Modified from Malmgren & Pierrot-Deseilligny (1988b) ((*b*), (*c*)), and Nielsen & Pierrot-Deseilligny (1991) ((*e*)–(*g*)), with permission.

is well illustrated in the graph in Fig. 10.6(*d*), in which the difference between the effect on combined stimulation and the sum of effects of separate stimuli is plotted against TMS intensity. Inhibition with stronger TMS had the same time course as facilitation with weak TMS, i.e. significant musculocutaneous-induced facilitation of the corticospinal peak with weak TMS and significant inhibition with stronger TMS, both appearing at the 8 ms ISI and disappearing at the 9 ms ISI (Nicolas *et al.*, 2001).

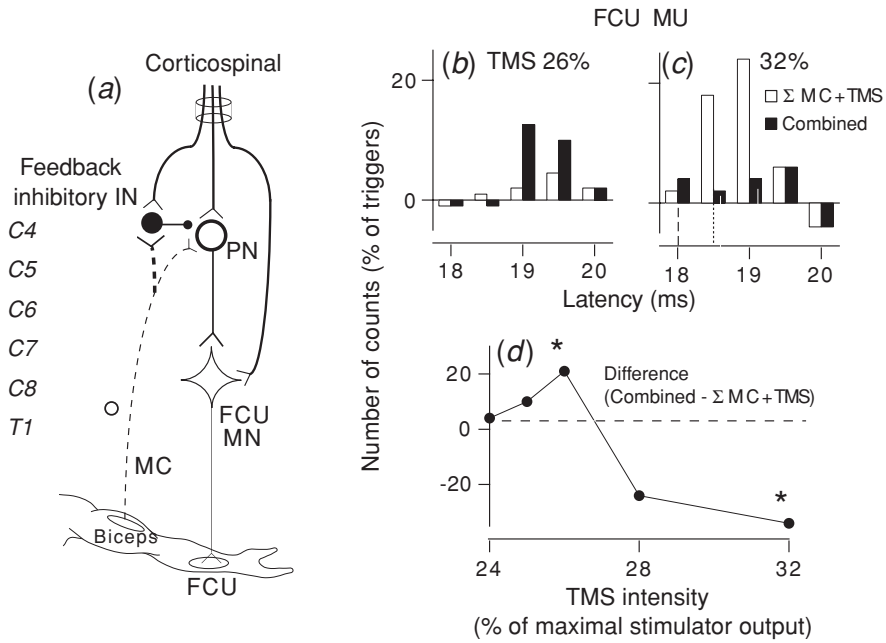


Fig. 10.6. Reversal from facilitation to inhibition when TMS is increased. (*a*) Sketch of the presumed pathways. Musculo-cutaneous (MC) and corticospinal volleys converge on both propriospinal neurones (PN) and feedback inhibitory interneurones (IN). The thick dashed line indicates that the feedback to inhibitory INs is stronger than to PNs. (*b*), (*c*) Effects of varying TMS intensity (26% of the stimulator output in (*b*), 32% in (*c*)) on the PSTHs (after subtraction of the background firing, 0.5 ms bin width) of a flexor carpi ulnaris (FCU) unit while the MC stimulus remained at 0.75 × MT and interstimulus interval (ISI) 8 ms; the effect on combined stimulation (■) is compared to the sum of the effects of separate stimuli (TMS and MC, □) within the window 18–20 ms corresponding to the corticospinal peak. Dashed and dotted vertical lines in (*c*) (placed between the two columns of a pair of open and filled columns with the same latency) indicate the onset of the corticospinal peak and of the inhibition on combined stimulation, respectively. (*d*) Changes in the difference between the effect on combined stimulation and the sum of effects of separate stimuli are plotted against TMS intensity as a percentage of the maximal stimulator output (same MU as in (*b*), (*c*)). The asterisks indicate $P < 0.05$. Modified from Nicolas *et al.* (2001), with permission.

Mechanisms underlying the reversal

The reversal was not due to occlusion in propriospinal neurones of the effects of two excitatory inputs (cortical and peripheral) because the corticospinal peak was reduced below its control level. Neither was it due to corticospinal facilitation of segmental interneurones mediating oligosynaptic musculo-cutaneous-induced inhibition of forearm motoneurones. As mentioned above, the central delay of the inhibition was the same as that of the facilitation (∼5 ms), much longer than that of the musculo-cutaneous-induced non-reciprocal group I inhibition (∼0.8 ms, Chapter 6, p. 253). The peripheral suppression spared the initial bin(s) of the corticospinal peak (see the 18-ms bin in Fig. 10.6(*c*)), while post-synaptic inhibition exerted on motoneurones would affect the entire corticospinal response, including its initial direct monosynaptic component (Mazevet, Pierrot-Deseilligny & Rothwell, 1996; Fig. 10.8(*d*)). Thus the reversal was due to inhibition of premotoneurones transmitting indirect corticospinal excitation (i.e. it was due to disfacilitation).

Which interneurones?

The mean interval between the onset of the monosynaptic corticospinal excitation and the onset of inhibition (i.e. the initial sparing) was 0.7 ms (Nicolas *et al.*, 2001). This suggests that inhibition is exerted at the premotoneuronal level of a disynaptic pathway mediating corticospinal excitation. The findings that suppression of the corticospinal peak consistently occurred at the shortest ISI with extra facilitation and that this was greater the more caudal the motoneurone pool again favour the view that the premotoneurones in question are cervical propriospinal neurones.

Interaction between excitatory and inhibitory inputs

Activation of propriospinal neurones and of inhibitory interneurones

The results described above fit a system of propriospinal neurones receiving monosynaptic excitation from peripheral and corticospinal inputs and disynaptic inhibition from the same sources, as described in the cat (Alstermark, Lundberg & Sasaki, 1984b) and the macaque monkey (see p. 455).

Peripheral stimuli

In PSTH experiments, because of the spatial facilitation between descending and peripheral inputs at the level of propriospinal neurones (see above), and because excitation involves a pathway with one less synapse than inhibition, excitation will dominate at low stimulus intensities. The finding that increasing the peripheral afferent input results in suppression of the propriospinally mediated excitation (Fig. 10.5(*b*),(*c*)) indicates that, when the peripheral volley is big enough, the discharge of feedback inhibitory interneurones becomes sufficient to overwhelm the facilitation in propriospinal neurones, most probably because, as in the propriospinal system of the cat (cf. Alstermark, Lundberg & Sasaki, 1984b), peripheral afferent excitation is much stronger to neurones mediating feedback inhibition than to propriospinal neurones themselves.

Corticospinal stimulation

Convergence of peripheral and corticospinal inputs onto both propriospinal neurones and feedback inhibitory interneurones (sketched in Fig. 10.6(*a*)) explains that slightly increasing the corticospinal input causes the facilitation to be reversed to inhibition. At low TMS intensities, summation of the weak peripheral and weak corticospinal inputs in the inhibitory interneurones would be insufficient to produce large IPSPs in propriospinal neurones. This would allow the facilitatory convergence onto common excitatory propriospinal neurones to be revealed. At higher TMS intensities, the facilitation would be reversed to suppression because the corticospinal facilitation of feedback inhibitory interneurones would then be sufficient to allow the peripheral volley to discharge feedback inhibitory interneurones producing large IPSPs in propriospinal neurones, thereby overwhelming the spatial facilitation of excitatory inputs.

Explanation for the conflicting conclusions by different groups

Activation of inhibitory interneurones

Corticospinal activation of inhibitory interneurones projecting to propriospinal neurones can explain why stimulation of the pyramidal tract by itself in the macaque monkey (see pp.454–5) or of the motor cortex by itself in humans (Maertens de Noordhout *et al.*, 1999) has provided little evidence for disynaptic corticospinal EPSPs in upper limb motoneurones. These inhibitory interneurones include not only feedback inhibitory interneurones, but also feedforward inhibitory interneurones (see Fig. 10.1), though the latter have not been explored specifically in human studies. Transcranial and pyramidal tract stimulation produces unnaturally synchronised volleys, which will evoke gross activation of inhibitory interneurones, capable of preventing a discharge

of propriospinal neurones in response to corticospinal excitation. This would be especially so when tested in motoneurones that are refractory, having discharged in response to a monosynaptic volley (Maertens de Noordhout *et al.*, 1999; Olivier *et al.*, 2001). If there is stronger inhibitory control of transmission through propriospinal neurones in higher primates than in the cat, it is not surprising that propriospinally mediated disynaptic corticospinal EPSPs would be rare and weak in motoneurones of the macaque monkey under control conditions, but readily demonstrable when inhibition has been reduced by intravenous strychnine (which blocks postsynaptic inhibition, see pp. 454–5). The fact that the inhibitory pathway involves one extra synapse would not prevent disynaptic IPSPs from suppressing the monosynaptic discharge of propriospinal neurones: indeed, it was demonstrated that disynaptic reciprocal Ia inhibition can prevent motoneurone discharge in the monosynaptic reflex (Araki, Eccles & Ito, 1960; Chapter 1, pp. 9–10). The activation of feedback inhibitory interneurones by strong ($\geq 1 \times$ MT) peripheral volleys may similarly explain the absence of oligosynaptic median-induced excitation of human FCR motor units reported by Maertens de Noordhout *et al.* (1999), since propriospinal neurones are then consistently inhibited (cf. p. 464).

How to disclose corticospinal propriospinally mediated excitation?

To disclose corticospinal propriospinally mediated excitation of upper limb motoneurones in primates it is necessary that the corticospinal volley activates propriospinal neurones without significantly activating inhibitory interneurones. This is possible under some specific experimental conditions: (i) blockade by strychnine of post-synaptic inhibition in the macaque monkey (p. 455); (ii) reduction of the inhibition in the macaque after a chronic corticospinal lesion (p. 455); (iii) stimulation of specific sites of the motor cortex in the macaque (B. Alstermark & T. Isa, personal communication); (iv) use of spatial facilitation between weak corticospinal and peripheral volleys in humans (pp. 461–3); and (v) natural activation of the corticospinal system during voluntary movements (pp. 471–8).

Natural vs. artificial activation of the propriospinal system

The fact that corticospinal activation of propriospinal neurones and of inhibitory interneurones cannot be dissociated readily when the pyramidal system is stimulated electrically or by TMS does not imply the absence of effective corticospinal excitation of propriospinal neurones during movement. Indeed, as discussed below, there is ample evidence for descending facilitation of propriospinal neurones during voluntary contractions. This suggests the following.

(i) The corticospinal excitation of propriospinal neurones and of inhibitory interneurones projecting to propriospinal neurones can be controlled independently during 'natural' movement. (In this respect, it is of importance that there is evidence for corticospinal excitation of propriospinal neurones and of inhibitory interneurones from different cortical sites in the macaque monkey; B. Alstermark & T. Isa, personal communication.)

(ii) The cortical control of the gain in the feedback inhibitory loop is adjusted so that the 'natural' peripheral input related to voluntary movement can modulate the firing of propriospinal neurones but does not abolish it. In fact, it is shown below that this control varies throughout the course of the movement (p. 478). It is also likely that artificially synchronised volleys are more effective in inhibiting propriospinal neurones than 'natural' peripheral inputs.

Organisation of the cervical propriospinal system

Organisation in subsets with regard to the muscle afferent input

A further contribution of human experiments to the organisation of the propriospinal system is evidence

that propriospinal neurones are organised in subsets specialised with regard to their excitatory muscle afferent input rather than their target motoneurones: (i) peripheral excitation of propriospinal neurones is significantly facilitated at the onset of a voluntary contraction when, and only when, the conditioning stimulus is applied to group I afferents from the contracting muscle, irrespective of the target motoneurone pool (cf. p. 476); and (ii) propriospinally mediated excitation evoked from one muscle is inhibited by cutaneous afferents from the skin field which would encounter the target at the end of movements produced by that muscle, again irrespective of the target motoneurone pool (cf. p. 478).

Convergence

Despite an organisation into separate subsets, there is still some peripheral convergence onto propriospinal neurones: they receive their main input from a given muscle, but also weak excitation from a wide range of muscle and cutaneous peripheral afferents (Burke *et al.*, 1992a). The main *excitatory* convergence onto a given subset of propriospinal neurones is between group I afferents from one muscle and corticospinal projections directed to motoneurones innervating this muscle. On the other hand, there is evidence for convergence of muscle and cutaneous inputs onto common feedback *inhibitory* interneurones (Nicolas *et al.*, 2001).

Divergence

Results dealing with the facilitation of the monosynaptic reflex at the onset of voluntary contraction suggest that, as in the cat, propriospinal neurones might have diverging projections to motoneurones belonging to different pools (detailed on p. 478).

Projections to early and late recruited motoneurones

Most inputs, including cortico-motoneuronal monosynaptic projections associated with voluntary contractions (Bawa & Lemon, 1993), recruit motoneurones in an orderly sequence from small motoneurones innervating slow-twitch motor units to large motoneurones innervating fast-twitch motor units (see Chapter 1). However, in the cat, propriospinally mediated corticospinal EPSPs have an equal distribution to large and small motoneurones (Alstermark & Sasaki, 1986). The distribution of propriospinally mediated excitation to early and late recruited motoneurones has been investigated in humans, during voluntary contraction, using two experimental paradigms (Marchand-Pauvert *et al.*, 2000).

Sensitivity of FCR H reflexes of different size to propriospinally mediated excitation

Propriospinally mediated facilitation of the FCR H reflex evoked by musculo-cutaneous stimulation was tested at the onset of biceps contraction, so that the relevant propriospinal neurones would receive significant descending facilitation (see p. 476). When the size of the H reflex was increased, the amount of propriospinally mediated facilitation increased (Fig. 10.7(*b*)). In contrast, the reflex facilitation by the heteronymous monosynaptic Ia input from intrinsic hand muscles first increased, and then decreased, producing a 'bell-shaped' curve. The latter pattern is characteristic for those inputs which have a more powerful effect on early than on late recruited motoneurones (Crone *et al.*, 1990; Chapter 1, pp. 17–18). Deviations from this pattern, as found for the propriospinally mediated excitation, indicate a more even distribution of the excitation or even a preferential distribution to high-threshold motoneurones.

Distribution in single motor units

The distribution of monosynaptic Ia and propriospinally mediated excitations elicited by stimulation of the homonymous radial nerve has been compared in the PSTHs of single ECR units during tonic ECR voluntary contractions. In this instance, there is spatial facilitation in propriospinal neurones between peripheral and descending inputs

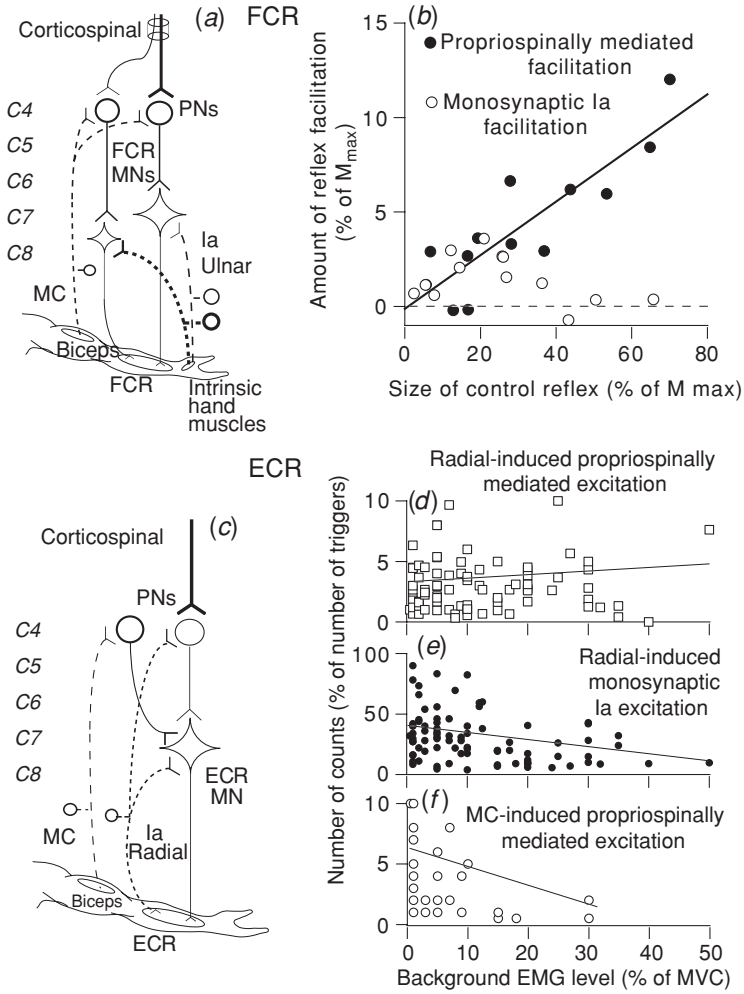


Fig. 10.7. Strength of corticospinal excitation of propriospinal neurones projecting to early and late recruited motoneurones. (*a*), (*c*) Sketch of the presumed pathways to flexor carpi radialis (FCR, (*a*)) and extensor carpi radialis (ECR, (*c*)) motoneurones (MN) (monosynaptic corticospinal projections have been omitted). (*a*) Corticospinal excitation is more potent on propriospinal neurones (PN) projecting to large ('fast') MNs (thick line) than on PNs projecting to small ('slow') MNs (thin line), whereas monosynaptic Ia projections are more potent on small (thick dotted line) than on large (thin dotted line) MNs. (*c*) Different subsets of PNs transmit excitation from ECR and biceps afferents to ECR MNs, and during selective ECR contraction only the subset fed by ECR afferents receives corticospinal excitation. (*b*) The amount of facilitation of the FCR H reflex (conditioned–unconditioned reflex, as a percentage of M_{max}) is plotted against the size of the unconditioned reflex (as a percentage of M_{max}), which recruits small motoneurones before large. Propriospinally mediated excitation elicited by musculo-cutaneous (MC) stimulation (●, 0.75 × MT, 4 ms ISI) and heteronymous monosynaptic Ia excitation elicited by stimulation of the ulnar nerve at the wrist (○, 1 × MT, 5.5 ms ISI), both effects tested at the onset of a selective biceps voluntary contraction. Each symbol is the mean of 20 measurements. (*d*)–(*f*) The size of the peak of non-monosynaptic (*d*) and monosynaptic (*e*) excitations elicited by stimulation of the radial nerve and of non-monosynaptic excitation elicited by MC stimulation (*f*) in the PSTHs for single ECR motor units (MU). Each symbol is the size of the peak in one MU (expressed as a percentage of the number of triggers) plotted against the background EMG activity (as a percentage of the EMG recorded during MVC) at which each MU was recruited (i.e. from slow to fast units). Oblique lines represent the regression line for the excitation. Modified from Marchand-Pauvert *et al.* (2000) ((*b*)–(*e*)), and J. Nielsen & E. Pierrot-Deseilligny (unpublished results) (*f*), with permission.

maintaining the voluntary firing of the motor unit required for the PSTHs. As expected (Chapter 2, pp. 79–81), homonymous monosynaptic Ia excitation was most marked in the lower-threshold units (Fig. 10.7(*e*)). In contrast, homonymous propriospinally mediated excitation was evenly distributed across units (Fig. 10.7(*d*)). However, this was no longer the case when the conditioning stimulus was applied to afferents of a non-contracting muscle (J. Nielsen & E. Pierrot-Deseilligny, unpublished data). Thus, Fig. 10.7(*f*) shows that propriospinally mediated excitation elicited by musculo-cutaneous stimulation is preferentially distributed to ECR units in the low-threshold range during selective ECR contractions, i.e. when propriospinal neurones mediating musculo-cutaneous excitation are not facilitated from descending tracts (see p. 476).

Conclusions

The above results are compatible with the findings in the cat (Alstermark & Sasaki, 1986): the projections of propriospinal neurones themselves, like most inputs to motoneurones, are distributed preferentially to early recruited units, as revealed when the tested propriospinal neurones do not receive descending excitation. However, recruitment of propriospinal neurones by descending inputs favours those projecting to high-threshold motoneurones and, as a result, propriospinal excitation is then preferentially distributed to late-recruited motoneurones (see the sketch in Fig. 10.7(*a*)). This could account for the finding that *at rest* TMS may recruit ECR motoneurones in a sequence different from the orderly recruitment of the H reflex (Nielsen *et al.*, 1999; Chapter 1, p. 45).

Motor tasks and physiological implications

The rationale for an integrative centre near but distinct from the motoneurone lies in the fact that transmission of descending commands can be mixed and modulated without altering the excitability of the motoneurone pool. Intense suppression (or intense activity) of the motoneurone pool could render it transiently less able to respond to further inputs, and there are therefore advantages in having these processes located elsewhere so that only the updated command would impinge on the motoneurone. In human studies, two different experimental paradigms have been employed to elucidate the extent to which the propriospinal system is used in natural movement: (i) cutaneous suppression of the on-going voluntary EMG, and (ii) facilitation of the propriospinally mediated excitation of the H reflex during voluntary contraction.

Evidence for propriospinal transmission of a part of the descending command

Underlying principles

The effects upon the voluntary motoneurone discharge of a peripheral volley known to inhibit propriospinal neurones have been explored (Burke *et al.*, 1994). The rationale behind these experiments was that, if a significant part of the descending command passed through the propriospinal relay, the inhibitory volley would interrupt it and thus suppress the voluntary EMG (see the sketch in Fig. 10.8(*a*)). In these experiments superficial radial volleys were used to inhibit propriospinal neurones projecting to wrist extensors, biceps and triceps motoneurones.

Evidence for disfacilitation

Suppression of the on-going ECR EMG while the H reflex is spared

A single superficial radial volley suppresses the tonic on-going ECR EMG activity, with a central delay of 4 ms (Fig. 10.8(*b*) and its legend). In contrast, the same cutaneous volley has little effect on the ECR H reflex recorded during a similar voluntary contraction, and this indicates that the inhibition is not exerted directly on motoneurones. Instead, it is

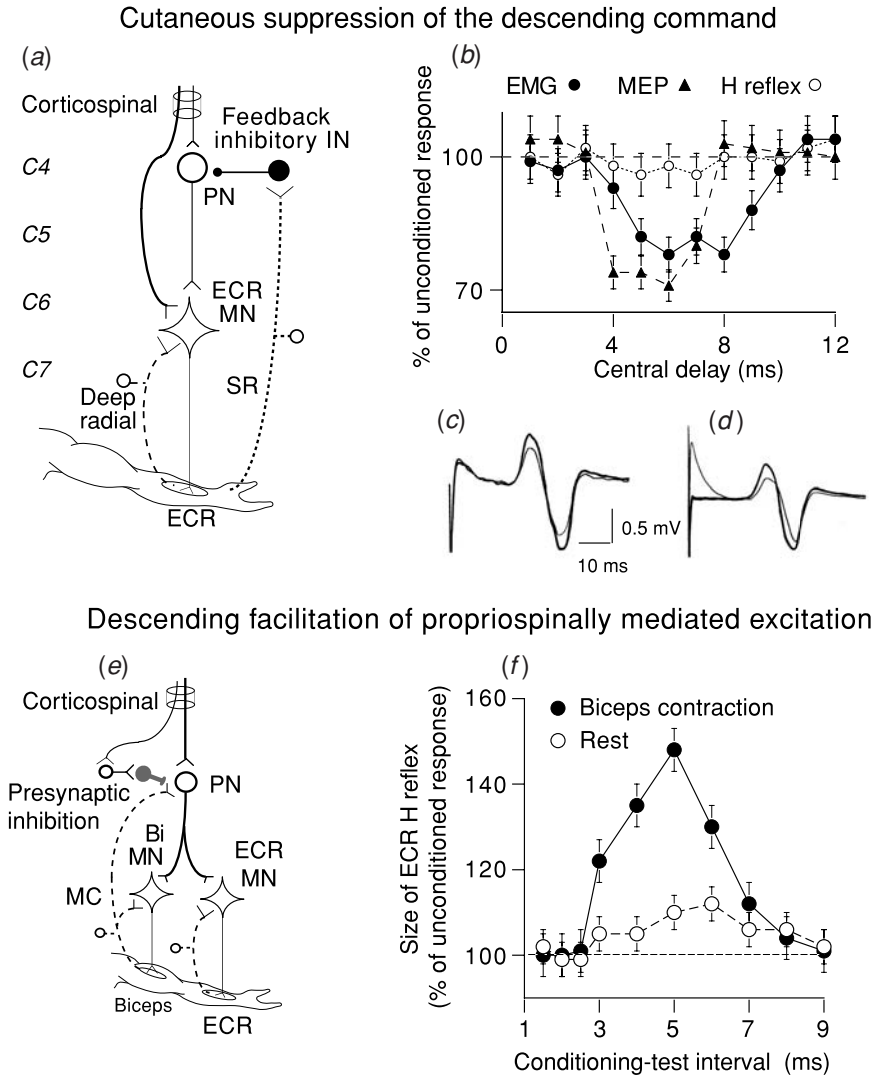


Fig. 10.8. Evidence for transmission of a component of the descending command for movement through the propriospinal relay. (*a*)–(*c*) Cutaneous suppression of the propriospinally mediated descending command for tonic extensor carpi radialis (ECR) voluntary contraction. (*a*) Sketch of the presumed pathways. Cutaneous volleys in the superficial radial nerve (SR) activate feedback inhibitory interneurones (IN) which inhibit propriospinal neurones (PN) projecting to ECR motoneurones (MN). (*b*) Effects of a cutaneous stimulus to the SR (single shock, 3 × PT) on the ongoing EMG activity (average of 300 sweeps, ●), the motor evoked potential (MEP elicited by TMS, ▲) and the H reflex (❍) of the ECR (mean ± SEM of 20 responses). Conditioned responses (as a percentage of unconditioned responses) plotted against the central latency, i.e. zero on the abscissa corresponds to the synchronous arrival of conditioning and test volleys at the segmental level of the MN pool (▲, and ❍), or to the arrival of the cutaneous volley at that level (●, estimated from the latency of the ECR H reflex and the difference in afferent conduction times of the cutaneous and Ia volleys). (*c*), (*d*) Mean MEP responses elicited by TMS in the ECR (20 sweeps, control, thick lines; conditioned, thin lines) are conditioned by SR stimulation ((*c*), 3 × PT, 11 ms ISI) and median nerve stimulation ((*d*), 1 × MT, 3 ms ISI). (*e*), (*f*) Descending facilitation of the propriospinally mediated excitation from the musculo-cutaneous nerve (MC) to ECR. (*e*) Sketch of the presumed pathways (monosynaptic corticospinal projections have been omitted). It is assumed that the same subset of PNs, activated by biceps (Bi) group I afferents, projects to Bi and ECR MNs. Presynaptic inhibition of MC group I afferents synapsing with PNs is represented (see p. 475). (*f*) Changes in the ECR H reflex amplitude after stimulation of the MC nerve (as a percentage of control values) are plotted against the ISI at rest (❍) and at the onset of a selective biceps voluntary contraction (●), the hand being in pronation. Modified from Burke *et al.* (1994) (*b*), Mazevet, Pierrot-Deseilligny & Rothwell (1996) ((*c*), (*d*)), and Mazevet & Pierrot-Deseilligny (1994) (*f*), with permission.

presumably exerted on 'premotoneurones' which transmit a part of the voluntary drive to the ECR motoneurone pool, and the suppression is due to disfacilitation of motoneurones. (Such a disfacilitation bears no relationship to the short latency – 2 ms – cutaneous inhibition of the FCR H reflex evoked from both sides of the fingers, see Chapter 9, pp. 415–18).

Complex effects of disfacilitation

The effects of disfacilitation are complex because a withdrawal of excitation must affect the excitability of the motoneurone pool. Nevertheless, disfacilitation is not the equivalent of inhibition because it is not accompanied by a conductance change, which is the major factor suppressing motoneurone discharge with postsynaptic inhibition (Chapter 1, p. 27). Disfacilitation does reduce the monosynaptic part of the peak of Ia excitation slightly (see p. 464) and accordingly, during contraction, it would prevent the less excitable motoneurones firing in the control reflex from being recruited by the test volley. However, this would be offset (at least in part) by the availability for the H reflex of motoneurones no longer engaged in the contraction, now the most excitable of the subliminal fringe. In other words, disfacilitation will produce a decrease in excitability for each individual motoneurone, but the H reflex would be modified only slightly because the reflex can now access motoneurones no longer active in the contraction, thus compensating for the failure to recruit less excitable motoneurones.

Parallel suppression of the on-going EMG and of the MEP

Disfacilitation at premotoneuronal level is also supported by the finding that the superficial radial volley suppressed the MEP elicited by TMS or electrical stimulation of the motor cortex to a similar extent as the on-going EMG (Fig. 10.8(*b*); Burke *et al.*, 1994; Mazevet, Pierrot-Deseilligny & Rothwell, 1996). The cutaneous suppression largely spared the initial part of the MEP due to the monosynaptic cortico-motoneuronal volley (Fig. 10.8(*c*); Mazevet, Pierrot-Deseilligny & Rothwell, 1996). Again, this initial sparing is consistent with disfacilitation, because inhibition exerted on motoneurones should affect the entire corticospinal response, as occurs with median-induced disynaptic "reciprocal" inhibition of ECR motoneurones (Fig. 10.8(*d*)).

Site of disfacilitation

Cutaneous depression of the corticospinal excitation reaching the motoneurone pool could occur through three mechanisms: depression of motor cortex excitability (Maertens de Noordhout *et al.*, 1992); presynaptic inhibition of the terminals of corticospinal axons with motoneurones; depression of interneurones in the corticospinal pathway. The first alternative can be excluded on latency grounds (Burke *et al.*, 1994). The second alternative is unlikely because the available evidence indicates that corticospinal terminals on motoneurones are not subjected to presynaptic inhibition (Nielsen & Petersen, 1994). This leaves only the third alternative, depression of premotoneurones interposed in the corticospinal pathway. Two arguments favour the view that the relevant premotoneurones are located rostral to motoneurones: (i) the central delay of the suppression of the on-going EMG is longer the more caudal the motoneurone pool (see p. 459); and (ii) the central latency of the cutaneous suppression of the MEP is compatible with inhibition of premotoneurones located 1–2 ms rostral to the motoneurones (Mazevet, Pierrot-Deseilligny & Rothwell, 1996).

Cutaneous suppression of the corticospinal command to various motor nuclei

Superficial radial stimulation suppresses the voluntary EMG recorded during tonic and phasic contractions of wrist extensors (Pierrot-Deseilligny & Mazevet, 1993; Burke *et al.*, 1994). Suppression of the on-going voluntary EMG of biceps and triceps by the same cutaneous volley has also been observed during tonic and phasic contractions of these muscles. Here also parallel depression of the MEP with the same central delay as that of the on-going EMG but

the absence of parallel modification of the tendon jerk during contraction are in favour of disfacilitation interrupting the descending excitation at a premotoneuronal level (cf. Pierrot-Deseilligny, 1996).

Quantification of transmission of the descending command via the propriospinal relay

Amount of suppression

Cutaneous suppression of the ECR MEP is often profound: it is maximal at the 8–9 ms ISIs when using TMS (Marchand-Pauvert *et al.*, 1999a), and the mean suppression is 32% (Nicolas *et al.*, 2001). The amount of suppression of the on-going tonic EMG activity (difference between conditioned and control EMG, expressed as a percentage of control EMG), at the latency where it is maximum, is on average 38% in the ECR (Burke *et al.*, 1994) and can reach up to 70% in the triceps brachii (Fig. 10.9(*b*); Pierrot-Deseilligny, Mazevet & Meunier, 1995). The *maximal* suppression is, not surprisingly, greater than the *mean* suppression over 10 ms given above (p. 459).

Limitations

The greater the component of the descending command passing through the propriospinal relay, the more profound will be the cutaneous disfacilitation. However, this does not imply that the percentage of EMG suppression reflects the percentage of the voluntary command transmitted to motoneurones through the propriospinal relay. The corticospinal response is produced by spatial summation at the motoneurone pool of the propriospinally mediated and monosynaptic corticospinal EPSPs, and removal of either could have a large effect. Conversely, the amount of cutaneous inhibition also depends on the cortical drive on feedback inhibitory interneurones. If this cortical drive is weak (e.g. at the onset of movement, see p. 478), a single cutaneous volley may not recruit all feedback inhibitory interneurones. The resulting inhibition would silence only some propriospinal neurones, and the component of the descending command relayed by the propriospinal relay, as assessed by this method, would be underestimated.

Conclusions

The relationship between the cutaneous suppression of descending excitation at the propriospinal level and the resulting disfacilitation of motoneurones is complex, and the percentage of the corticospinal drive that is relayed through this indirect system cannot be measured in isolation. However, it is safe to conclude that this oligosynaptic component makes a substantial contribution to the contraction.

Propriospinally mediated facilitation of motoneurones during voluntary contraction

Reflex facilitation at the onset of voluntary contraction

Changes in transmission across propriospinal neurones have been examined during voluntary contractions. Monosynaptic reflex testing has been used to compare these data with data at rest. The test reflex was the H reflex for FCR and ECR, or the tendon jerk for biceps and triceps. Conditioning volleys were applied to group I afferents in the ulnar, musculocutaneous or triceps nerves. The resulting group I facilitation of the reflex had all the characteristics of a propriospinally mediated effect (long central delay, low threshold, and disappearance when the stimulation was increased, see p. 457). The central finding of these studies, illustrated in Fig. 10.8(*f*) for the musculo-cutaneous facilitation of the ECR H reflex, was that a small or absent effect at rest became much larger at the onset of a selective voluntary contraction of the muscle innervated by the nerve stimulated to

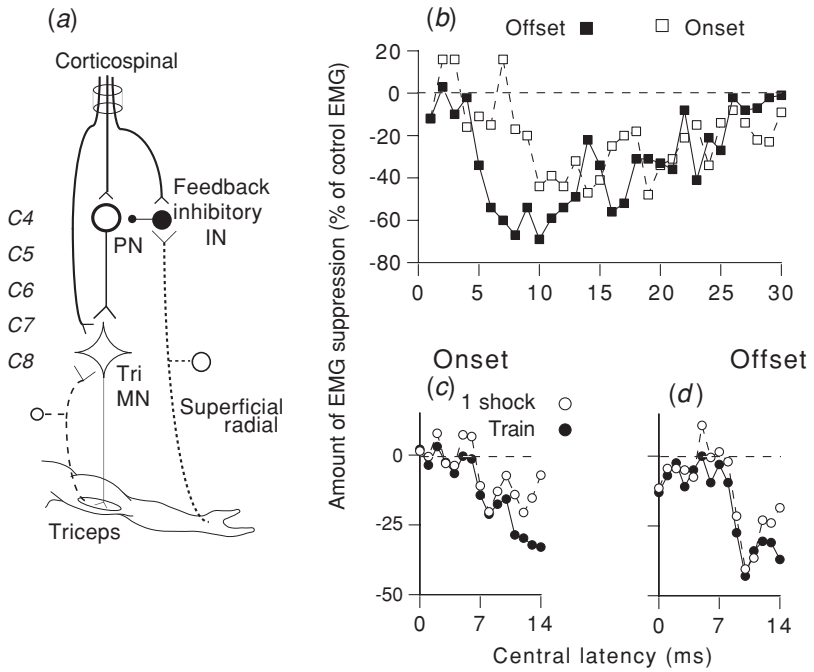


Fig. 10.9. Cutaneous inhibition of the on-going EMG activity of triceps brachii at the onset and the offset of movement. (*a*) Sketch of the presumed pathways, with the corticospinal excitation of feedback inhibitory interneurones (IN) inhibiting propriospinal neurones (PN) projecting to triceps brachii (Tri) motoneurones (MN). (*b*) The amount of suppression of the ongoing triceps brachii EMG (conditioned *minus* control EMG, as a percentage of control EMG) elicited by a single superficial radial volley (3 × PT) (average of 300 sweeps) at the onset (first 100 ms, □) and the offset (last 100 ms, ■) of a co-ordinated reaching movement lasting for ~1 s plotted against the central latency, i.e. zero on the abscissa corresponds to the arrival of the cutaneous volley at the segmental level of the MN pool. Care was taken to ensure that the background EMG level was similar in the two situations. (*c*), (*d*) The initial cutaneous suppression evoked by a single stimulus (○) and a train (3 shocks at 300 Hz, ●) to the superficial radial nerve (3 × PT) at the onset (*c*) and the offset (*d*) of the movement (same abscissa and ordinate as in (*b*)). Modified from Pierrot-Deseilligny, Mazevet & Meunier (1995) (*b*) and Pierrot-Deseilligny (1996) ((*c*), (*d*)), with permission.

produce the conditioning volley (Burke *et al.*, 1992a; Mazevet & Pierrot-Deseilligny, 1994).

Evidence for descending facilitation of propriospinal neurones

The increased reflex facilitation observed at the onset of contraction was shown not to be due to decreased presynaptic inhibition of group I afferents synapsing with propriospinal neurones (if anything this was increased, Burke *et al.*, 1992b). The increased facilitation of transmission in the propriospinal system during voluntary contractions presumably therefore results from increased excitability of propriospinal neurones. In these experiments the conditioning–test stimulus pair was triggered by the first voluntary EMG potential of the contraction, i.e. in advance of the spindle, Ib and cutaneous afferent discharges evoked by the voluntary movement (see pp. 133, 168, 388). Under these circumstances the increased reflex facilitation observed at the onset of voluntary movement is likely to reflect descending facilitation of transmission in propriospinal pathways.

Pattern of descending excitation at the onset of voluntary contraction

Focused descending excitation

Descending facilitation at the onset of voluntary movement was consistently found when, and only when, the conditioning stimulation eliciting propriospinal excitation was applied to group I afferents from the contracting muscle (Burke *et al.*, 1992a; Mazevet & Pierrot-Deseilligny, 1994). Thus, the musculo-cutaneous-induced facilitation of the ECR H reflex is not modified during selective contraction of any muscle (including ECR itself) other than biceps, and facilitation of the ECR and FCR H reflexes by stimulation of the triceps brachii nerve is increased only at the onset of a triceps contraction. This indicates that descending excitation associated with a voluntary contraction is focused on propriospinal neurones which receive the afferent feedback from the contracting muscle. This supports the view that propriospinal neurones are organised in subsets with regard to their muscle afferent inputs.

Further insights on the organisation of the propriospinal system

Divergent projections of propriospinal neurones (through branching of their axons) might explain why the propriospinally mediated excitation of forearm motoneurones is facilitated at the onset of a selective contraction of biceps (Fig. 10.8(*f*)), although forearm muscles are not involved in the voluntary contraction. As sketched in Fig. 10.8(*e*), during biceps contractions, propriospinal neurones fed by biceps afferents mediate part of the natural descending excitation to biceps motoneurones, in parallel with the monosynaptic corticomotoneuronal pathway (not illustrated in the sketch in Fig. 10.8(*e*)). If, as in the cat (Alstermark *et al.*, 1990), propriospinal neurones have divergent projections to different motoneurone pools operating at different joints, projections of propriospinal neurones fed by biceps afferents to wrist muscle motoneurones would be an elegant way of ensuring that elbow movements are accompanied by contractions required to maintain the position of the wrist against gravity during such movements. In this connection, it is of interest that during a contraction involving selectively elbow muscles, propriospinally mediated descending excitation is distributed preferentially to motoneurones of the wrist muscles which counteract gravity (wrist extensors when the hand is in pronation, wrist flexors in supination), presumably so that the hand would be in an optimal position for grasping (Mazevet & Pierrot-Deseilligny, 1994).

Factors limiting the increase in reflex facilitation during contractions

The excitation of propriospinal neurones, as assessed by the effects of a conditioning peripheral volley on the H reflex, is underestimated. Several factors contribute to this limitation: (i) occlusion in the excitatory pathway between descending inputs, the peripheral volley, and (during tonic contraction) background peripheral afferent activity; (ii) the fact that peripheral conditioning volleys can produce both facilitation and inhibition in propriospinal neurones, and that inhibition is increased during contraction (Malmgren & Pierrot-Deseilligny, 1988b); and (iii) the gating by increased presynaptic inhibition during contraction of the group I afferent volleys synapsing with propriospinal neurones, which could prevent the true extent of the increased excitation of propriospinal neurones from being revealed (Burke *et al.*, 1992b). This explains why the increase in propriospinally mediated facilitation of the monosynaptic reflex is weak and often absent during tonic contractions (Burke *et al.*, 1992a).

Functional implications: role of the propriospinal relay in normal motor control

Handedness-related asymmetry of propriospinal excitation during simple tasks

In a simple task, such as a tonic ECR contraction, the contribution to motoneurone excitation of the

propriospinally mediated afferent discharge from the contracting muscle is significantly greater on the preferred side than on the non-preferred side (Marchand-Pauvert *et al.*, 1999a). This peripheral 'take-over' would have the advantage of leaving more cortical neurones to accomplish the rapid, finely skilled movements in which the motor cortex is particularly implicated (Cheney & Fetz 1980; Muir & Lemon, 1983) and that characterise handedness.

Integration of peripheral and descending inputs at propriospinal level

The major role of the propriospinal system is to allow integration in propriospinal neurones of the descending command and the afferent feedback from the moving limb. This would (i) provide a safety factor to the command for the contraction, and (ii) allow the descending command to be updated *en route* to motoneurones according to the requirements of the internal and external environment.

Facilitation of the descending command by the peripheral input

Because the peripheral propriospinally mediated excitation is relatively weak (pp. 460–1), it is unlikely that the excitatory peripheral input to propriospinal neurones functions to provide reflex support in the absence of other significant drives. However, when reinforcing the corticospinal drive (cf. pp. 461–3), it might bring a safety factor to the firing of propriospinal neurones. This would fit with the finding that descending excitation is focused on the subset of propriospinal neurones receiving the afferent feedback from the contracting muscle (see above).

Servo-assistance and diffuse distribution

When higher centres activate both α and γ motoneurones (α-γ co-activation) and propriospinal neurones, the Ia discharge from the contracting muscle may provide servo-assistance to motoneurones at the propriospinal level: misalignment between intended and actual muscle length would then decrease or increase the firing of propriospinal neurones transmitting the descending command to motoneurones. It would then be appropriate that the descending excitation is focused on propriospinal neurones that receive the afferent feedback from the contracting muscle. Of course, there would also be servo-assistance to motoneurones through monosynaptic Ia pathways, but that support is restricted to homonymous motoneurones and to the limited number of upper limb motoneurone pools with heteronymous monosynaptic Ia projections. There are no such projections from proximal to distal muscles (see Chapter 2, p. 84). In contrast, servo-assistance through propriospinal neurones, with their divergent projections onto many motor nuclei, might be of value for contractions in complex movements (such as reaching) involving several muscles operating at different joints.

Inhibition by muscle group I afferents

Group I inhibitory projections to propriospinal neurones can completely suppress the excitation elicited by corticospinal or peripheral inputs. This could be important for two reasons: (i) adjustment of the force and speed of the movement through the potent cortical control of the gain in the feedback inhibitory loop of 'homonymous' inhibition; and (ii) lateral inhibition ('heteronymous' inhibition, cf. p. 464) preventing the activation of propriospinal neurones not required for the movement, through selection by the corticospinal tract of the relevant inhibitory interneurones (in a manner analogous to lateral inhibition in sensory pathways). In this latter role, the group I feedback would operate in collaboration with feedforward inhibitory interneurones.

Distribution to different types of motoneurones

The even distribution of propriospinally mediated descending excitation to early- and late-recruited motoneurones might be of importance in movements where it is necessary to activate a wide range of motoneurones more or less simultaneously (cf. p. 471).

Conclusions

Because of the presumably prewired connections of each subset of propriospinal neurones with the different motoneurones involved in a multi-joint movement, integration at a premotoneuronal level would allow the command to all these motoneurones to be simultaneously and 'economically' modulated by the same peripheral volleys.

Cutaneous suppression of the descending command

Cutaneous inhibition of propriospinal neurones serves as a good example of the integration of peripheral and descending inputs at the premotoneuronal level.

Pattern of cutaneous suppression

The cutaneous inhibition of propriospinal neurones has a very specific pattern: e.g. propriospinal neurones excited by muscle afferents from wrist extensors are inhibited by cutaneous afferents from the dorsal side of the hand and not by those from the palmar side (Fig. 10.5(*e*)–(*g*)), and vice versa for propriospinal neurones excited by muscle afferents from wrist flexors. Thus, each subset of propriospinal neurones, activated by afferents from a given muscle, receives inhibition from the skin field which would contact the target at the end of the movement produced by that muscle: the dorsal side in case of wrist extension, and palmar side in case of wrist flexion. Propriospinal neurones excited by biceps afferents are inhibited by cutaneous afferents from both sides, presumably because a movement of elbow flexion can approach a target from either direction, depending on whether the hand is in pronation or in supination (Nielsen & Pierrot-Deseilligny, 1991). This suggests that cutaneous inhibition of propriospinal neurones may be used to help terminate a movement: the exteroceptive volley evoked by contact with the target (or with an unexpected obstacle) would inhibit the descending command passing through propriospinal neurones (see the sketch in Fig. 10.8(*a*)). As stated by Alstermark, Lundberg & Sasaki (1984b), 'it would be a reasonable strategy to delegate part of the termination of the movement to spinal cord mechanisms, as termination must be one of the most difficult parameters of a movement for the brain to calculate'. Whether difficult or not, higher centres would be free to focus more on what is done with the target object than with how the activity of multiple muscles is governed.

Corticospinal control of cutaneous suppression

If the above hypothesis is correct, one might expect the cortical facilitation of these inhibitory interneurones to be stronger at the end of the movement. The inhibition of propriospinal neurones projecting to triceps brachii motoneurones by superficial radial volleys was therefore compared within the first and last 100 ms of a visually guided tracking elbow extension lasting for ~1 s (Pierrot-Deseilligny, Mazevet & Meunier, 1995). The depression of the ongoing EMG activity of the triceps brachii was significantly larger and more abrupt at the offset than at the onset of the movement (Fig. 10.9(*b*)). Greater suppression at the offset of movement may result from an increase in that part of the descending command passing through the propriospinal relay, or in an increase in the corticospinal drive of feedback inhibitory interneurones. Comparison of the initial suppression evoked by a single volley and by a train (three shocks) was used to help distinguish between these two possibilities. At the onset of the movement (Fig. 10.9(*c*)), the train produced stronger suppression than the single shock, reflecting the temporal summation between the three volleys of the train in inhibitory interneurones. In contrast, at the offset (Fig. 10.9(*d*)), the inhibition elicited by the single shock was strong and was little different when using the train. A plausible explanation would be an increasing descending excitatory drive on inhibitory interneurones: the greater the descending drive the lesser the reliance on temporal summation to activate the population of inhibitory interneurones.

In which movements is the propriospinal system involved?

For technical reasons, such as the need to maintain stable stimulating conditions during the course of the movement, changes in the propriospinal system have been investigated only during isometric contractions, and further studies of different tasks (postural, reaching, manipulation) need to be devised to define the exact functional role of the system in human subjects. The recent hypothesis of Dietz (2002) that propriospinal neurones in humans would be used mainly for the co-ordination of upper and lower limbs during locomotor tasks, while they would be inhibited during skilled movements (through corticospinal activation of feedforward and feedback inhibitory interneurones), appears unlikely, given available data for the cat. The propriospinal system has been shown to mediate the descending command for visually guided target-reaching movements (Alstermark *et al.*, 1981b) but not to be involved in locomotion (Alstermark & Kümmel, 1990). In primates, one functional consequence of the development of feedforward and feedback inhibitions could be to sharpen the focus in this intrinsically diffuse system, and further studies might reveal whether the presumed propriospinal system is used for a more expanded repertoire of upper limb tasks than in the cat (Burke, 2001). In this respect, recent behavioural experiments in the macaque monkey showing that propriospinal neurones can mediate the command for independent finger movements are of particular interest (Sasaki *et al.*, 2004; p. 455). Leaving aside motoneurones innervating the intrinsic muscles of the hand, for which there is no evidence for propriospinal projections in humans, monosynaptic corticomotoneuronal connections, though important, might contribute only a fraction of the descending drive producing a movement, perhaps only the final adjustment of the movement (Lundberg, 1992). In more proximal muscles, the even distribution of propriospinally mediated corticospinal excitation to early- and late-recruited motoneurones might be important in rapid movements. Lastly, if human propriospinal neurones have ascending projections as in the cat, the possible efference copy provided through these projections might be important in motor learning (see Chapter 11, p. 531).

Studies in patients and clinical implications

Patient with a discrete lesion of the spinal cord at the junction C6–C7 spinal level

A fortuitous opportunity arose to study a patient who suffered transient tetraplegia due to a fracture/dislocation of the C5–C6 vertebrae, and had recovered remarkably after 1 year. The patient was tested 12 years after the injury (Marchand-Pauvert *et al.*, 2001). She had a residual partial Brown–Séquard syndrome with, on the left side, moderate upper motor neurone signs below C7 (sparing the triceps brachii). MRI of the spinal cord showed a lesion at the junction between the C6 and C7 spinal segments (Fig. 10.10(*a*)–(*d*)), confined largely to the left part of the spinal cord (white area in Fig. 10.10(*c*)).

Modulation of the MEP in biceps and triceps brachii

Modulation by ulnar stimulation was investigated on both sides. There was symmetrical ulnar facilitation of the MEP in biceps at the 4.5 ms ISI (Fig. 10.10(*f*)–(*h*)), whereas, in triceps, the ulnar facilitation of the MEP at the 7–8-ms ISIs on the unaffected side was replaced on the affected side by a tendency to inhibition (Fig. 10.10(*i*)–(*k*)). Similarly, there was significant superficial radial suppression of the MEP in biceps on both sides while, in triceps, there was significant suppression on the unaffected side, but not on the affected side. Since control MEPs in triceps (below the lesion) had the same latency and area on both sides (Fig. 10.10(*i*), (*j*)), partial interruption of corticospinal projections to triceps motoneurones (monosynaptic and/or through segmental interneurones) is unlikely to be responsible for the

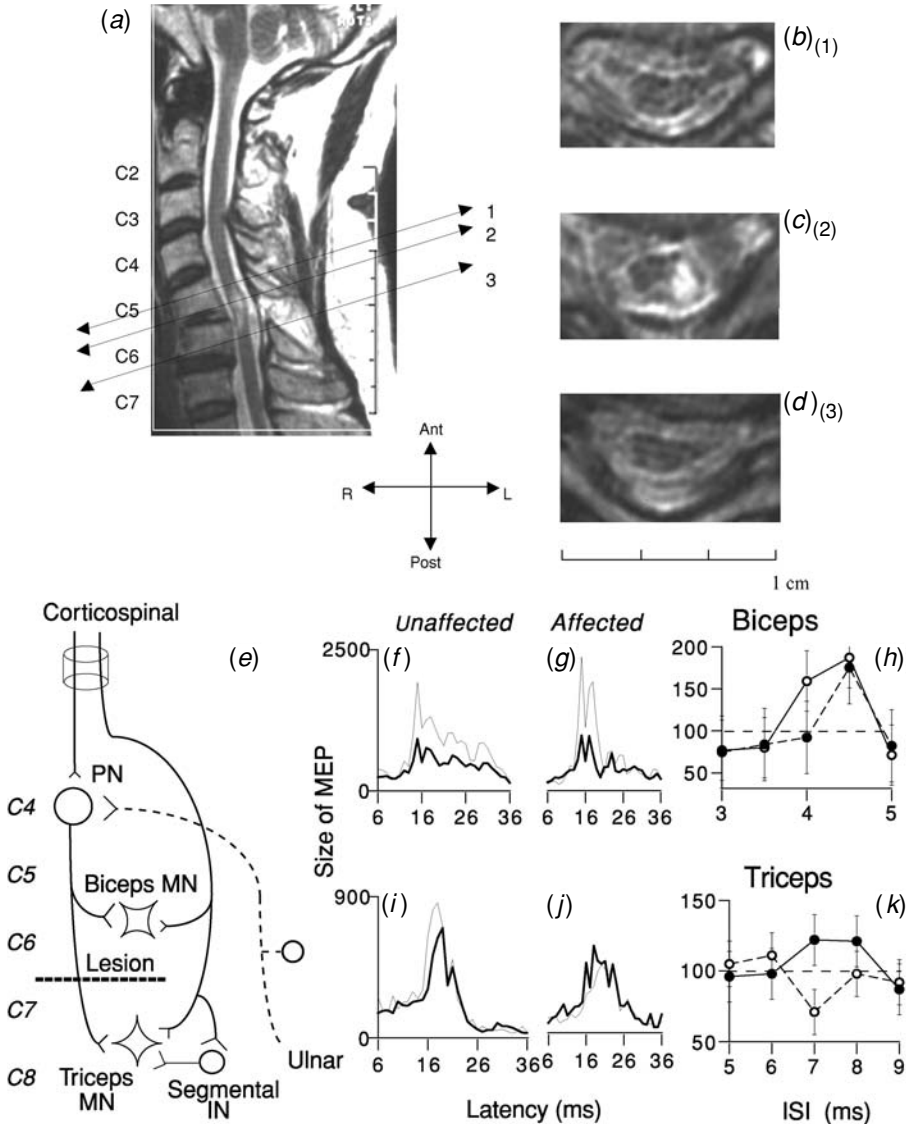


Fig. 10.10. Modulation of the MEP in biceps and triceps brachii by ulnar volleys in a patient with a spinal lesion at the C6–C7 junction. (*a*)–(*d*) Magnetic resonance imaging. (*a*) Sagittal view of the cervical cord, double-headed arrow oblique lines (1–3) indicating the level of the axial views shown in (*b*)–(*d*). (*b*)–(*d*) Axial views of the spinal cord at the upper part of C5 vertebra (*b*), the junction between C5 and C6 vertebrae (*c*), junction between C6 and C7 spinal segments, with the lesion indicated by the white area, and the lower part of C6 vertebra (*d*). (*e*) Sketch of the presumed pathways with biceps and triceps brachii motoneurones (MN), excitatory ulnar projections (entering the spinal cord below the lesion) to propriospinal neurones (PN), and corticospinal monosynaptic projections to MNs and segmental interneurones (IN). The lesion (thick horizontal dotted line) is presumed to interrupt axons of PNs and largely to spare the corticospinal projections to MNs and segmental INs. (*f*)–(*k*) Modulation by ulnar volleys (0.75 × MT) of the MEP in biceps (*f*)–(*h*) and triceps (*i*)–(*k*) during co-contraction of the FCU and of the target muscle. Samples of averaged (20 sweeps) rectified control (thick lines) and conditioned (thin lines) MEPs (expressed as a percentage of the background EMG) are illustrated for the biceps at the 4.5 ms ISI (*f*), (*g*) and for the triceps at the 7.5 ms ISI (*i*), (*j*) on the unaffected side (*f*), (*i*) and the affected side (*g*), (*j*). Control MEPs in triceps (below the lesion) had the same latency (~13 ms) and similar area on both sides, consistent with the relative sparing of the corticospinal projections to low-cervical MNs and segmental INs. (*h*), (*k*) The size of the MEP conditioned by ulnar stimulation in biceps (*h*) and triceps (*k*) plotted against the interstimulus interval (ISI) and compared on the unaffected (●) and affected side (○). Each point is the mean of 20 measurements (±1 SEM). Modified from Marchand-Pauvert *et al.* (2001), with permission.

complete disappearance of the ulnar-induced facilitation of the triceps MEP. Since ulnar volleys would enter the spinal cord below the lesion (at C8–T1), it is unlikely that the lesion selectively interrupted the part of the volley directed to triceps motoneurones (also below the lesion) while sparing an ascending branch towards biceps motoneurones. The simplest explanation would therefore be that, on the affected side, the lesion at the junction between the C6 and C7 spinal segments interrupted the descending axons of rostrally located propriospinal neurones projecting to triceps motoneurones located below the lesion, but spared those projecting to the more rostral biceps motoneurones. Thus, on the affected side, ulnar facilitation and cutaneous inhibition of propriospinal neurones was no longer able to modify the MEP of triceps motoneurones.

Recovery

It is likely that, in this patient, as in the cat after selective section of propriospinal axons, the command normally relayed through propriospinal neurones was subsumed by spared corticospinal projections via segmental interneurones. This would explain why, despite the interruption of propriospinal axons, control MEPs were reasonably symmetrical in triceps, and the motor impairment was mild in this muscle.

Stroke patients

The severe hemiparesis that can accompany a stroke generally recovers partially. So far, discussions concerning changes in neural organisation underlying 'spontaneous' or 'rehabilitation-induced' recovery have mainly focused on hemispheric mechanisms, and plastic changes in the damaged contralateral hemisphere seem to be best suited for producing recovery from stroke (see Hallett, 2001). However, in patients with poor recovery, restricted to proximal muscles, it has been suggested that the residual motor capacity could also involve projections from the ipsilateral intact hemisphere, via bilateral cortico-reticulospinal connections (Benecke, Meyer & Freund, 1991). The take-over by one system of a function lost by another would be more likely if the output from these two systems converged onto common neurones projecting onto motoneurones. In this respect, C3–C4 propriospinal neurones receive extensive excitatory input from several descending tracts and primary afferents, and are well placed to play a role in the process of recovery from hemiplegia.

Asymmetry in the superficial radial-induced suppression of the on-going EMG

Superficial radial-induced suppression of the on-going EMG of ECR has been compared on the two sides of stroke patients and healthy subjects (Mazevet *et al.*, 2003).

Method

The symmetry of the voluntary contraction was achieved by matching the level of integrated rectified EMG activity in contractions of ~6–8% of MVC on the unaffected side. However, an identical level of absolute EMG activity corresponds to a different percentage of maximal effort on the affected and unaffected side, and it is therefore relevant that, in normal subjects, the amount of suppression of on-going EMG is identical for tonic contractions between 5 and 80% of MVC. The intensity of the conditioning stimulus was graded using the motor response in thenar muscles due to a spread of stimulation to the median nerve. Because the suppression elicited by a single volley at 0.95 × MT was symmetrical on the affected and unaffected side, the effects of a train of three shocks at 300 Hz were investigated using an intensity of 0.5 × MT.

Asymmetrical EMG suppression

The central finding of the study was the asymmetry of the suppression elicited by a train. Figure 10.11(*b*), (*c*) shows that the amount of suppression of the on-going EMG produced by the train was symmetrical in

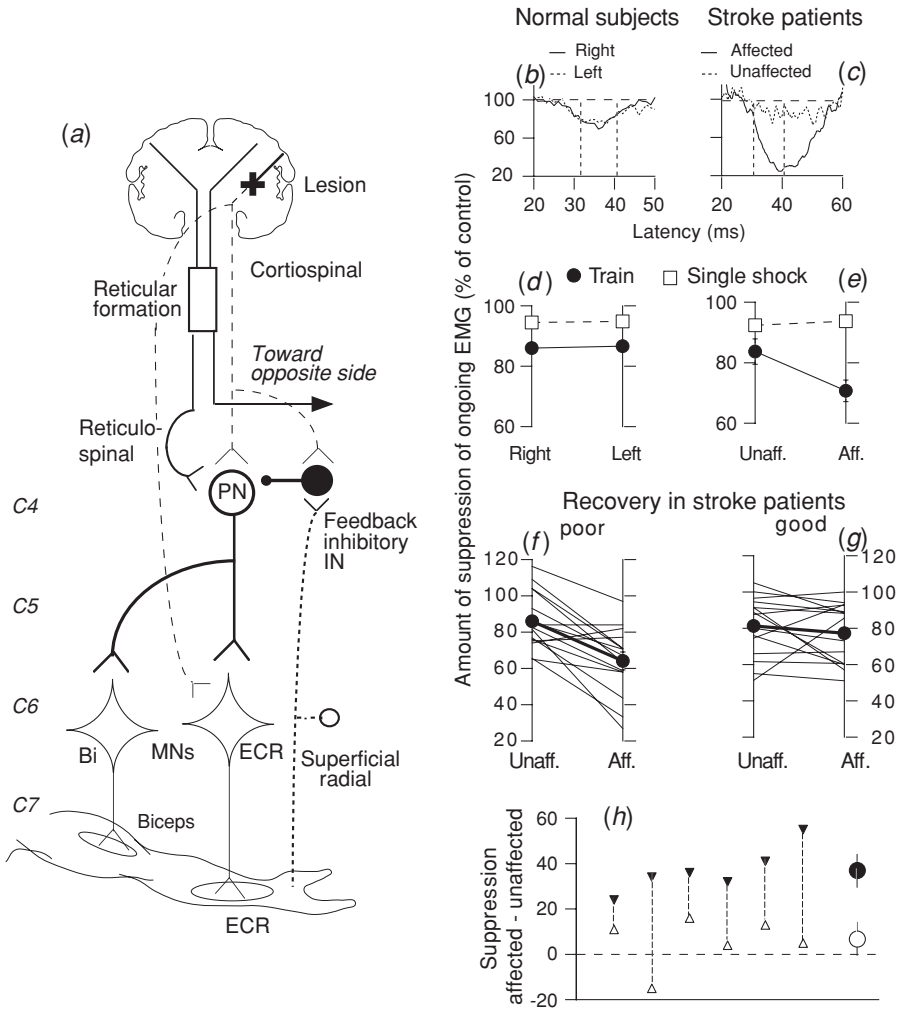


Fig. 10.11. Asymmetry of the superficial radial suppression of the ongoing EMG of ECR in stroke patients. (*a*) Sketch of the presumed pathways. The same subset of propriospinal neurones (PN) project to extensor carpi radialis (ECR) and biceps (Bi) motoneurones (MNs). There is transiently increased efficacy of descending (possibly reticulospinal) projections to PNs (see pp. 483–4). The lesion (✚) has interrupted corticospinal projections to PNs and feedback inhibitory interneurones (IN). (*b*)–(*h*) Effects of a cutaneous train (three shocks at 300 Hz, each shock at 0.5 × MT) to the superficial radial nerve on the on-going ECR EMG (expressed as a percentage of control EMG). (*b*), (*c*) The time course of the cutaneous suppression is compared on the right and left sides of one normal subject (*b*) and the affected and unaffected side of one stroke patient ((*c*), continuous and dotted lines, respectively). Vertical dashed lines indicate the window of analysis (32–41 ms). (*d*), (*e*) Mean values of the suppression observed on the two sides of normal subjects ((*d*), $n = 34$) and of stroke patients ((*e*), $n = 30$) after a single volley (□) or a train (●). (*f*), (*g*) Suppression by a train observed on the two sides (unaffected: Unaff; affected: Aff.) of patients with poor (*f*) and good (*g*) recovery (see p. 484). Each thin line represents one patient and the thick lines (and ●) the mean values. (*h*) In 6 patients, who were studied twice, the difference between the amount of suppression by a train on the affected and unaffected side (i.e. the asymmetry, expressed as a percentage of control EMG) is compared when they had recovered just enough to be tested (filled symbols) and when their strength was almost normal later on (open symbols). Large circles, mean values for these 6 subjects ±1 SEM. Modified from Mazevet *et al.* (2003), with permission.

one normal subject (*b*), but much more profound on the affected side than on the unaffected side of one patient with, as yet, poor recovery (*c*). These results are representative of those in the control and patient groups; the mean values of EMG suppression elicited by the train were not different for the right and left sides of healthy controls and the unaffected side of the patients. However, there was significantly greater EMG suppression on the affected side of patients (Fig. 10.11 (*d*), (*e*)). The asymmetry seen with the train in stroke patients contrasts with the symmetry of the weak suppression elicited by single volleys (0.5 × MT), which produced the same magnitude of suppression in the two groups.

Evidence for disfacilitation

In three patients, it was possible to compare the modulation of the on-going EMG, the MEP and the H reflex at the time of their first test, when the asymmetry of the EMG suppression was prominent. On the unaffected side, the cutaneous volleys produced, as in normal subjects, a suppression of the EMG and of the MEP, with little change in the H reflex. On the affected side, the on-going EMG and the MEP were suppressed more than the H reflex. The asymmetry of the two former responses was significantly greater than the asymmetry of the H reflex, and this argues in favour of disfacilitation in stroke patients, much as in control subjects (see pp. 471–3).

Increased excitation of propriospinal neurones and recovery from hemiplegia

Evidence for a greater component of the descending command relayed through the propriospinal system

Greater suppression of the on-going EMG by cutaneous volleys in patients with poor recovery may result from more of the descending command passing through the propriospinal relay or from an increase in the excitatory corticospinal drive to feedback inhibitory interneurones. However, the finding that the cutaneous inhibition was symmetrical, and of the same magnitude as in normal subjects, when using a single shock (Fig. 10.11(*d*), (*e*)) provides evidence against increased corticospinal activation of inhibitory interneurones (a possibility that would be unlikely, given the corticospinal lesion). In fact, the corticospinal lesion is more likely to have caused decreased corticospinal drive on feedback inhibitory interneurones. The greater suppression observed on the affected side with the train could thus be the net result of two opposing effects: decreased corticospinal drive on inhibitory interneurones, and a greater component of the descending command relayed through the propriospinal system.

MEP during ramp contractions

Support for a greater component of the descending command relayed through the propriospinal system is provided by the asymmetry found in stroke patients between the musculo-cutaneous facilitation of the MEP evoked in the FCR by TMS at the onset of a ramp task involving co-contraction of FCR and biceps: the facilitation was significantly larger on the affected side (Stinear & Byblow, 2004). There is therefore evidence from another laboratory, using a different technique, for increased excitation of propriospinal neurones during voluntary contraction in stroke patients.

Possible mechanisms underlying increased excitation of the propriospinal neurones during voluntary contraction

Increased excitation could result from unmasking and/or reorganisation of projections from the ipsilateral undamaged hemisphere. It has been suggested that the residual motor capacity in patients with poor recovery could involve such projections. Data obtained with TMS of the ipsilateral undamaged hemisphere in patients with poor recovery from stroke are consistent with this view. Indeed, MEPs are more likely to be elicited by stimulation of the undamaged hemisphere in the ipsilateral affected arm and have a lower threshold than in normal subjects (Benecke, Meyer & Freund, 1991; Turton *et al.*,

1996). A good candidate could be the connections from the ipsilateral premotor cortex to the reticular formation, which, in turn, gives rise to bilateral reticulospinal projections (Benecke, Meyer & Freund, 1991; see the sketch in Fig. 10.11(*a*). If data in the cat (cf. Lundberg, 1999) apply to humans, there would be potent reticulospinal projections onto propriospinal neurones in humans, and these could account for the residual motor capacity of patients with poor recovery.

Synkinetic movements

The possibility that a greater part of the descending command for movement is relayed through the propriospinal system in patients with poor recovery is supported by the fact that such patients have involuntary synkinetic movements. Propriospinal neurones have divergent projections onto motoneurones of muscles operating at different joints in the cat (Alstermark *et al.*, 1990), and there is indirect evidence for similar divergent projections of propriospinal neurones in humans (see p. 476). If a greater part of the descending command were mediated through this system, isolated movements would be difficult, especially if the absence of corticospinal drive to inhibitory interneurones prevented the lateral inhibition necessary to sharpen the focus in this intrinsically diffuse system. Thus, only stereotyped synkinetic movements would be performed, much as is often the case in patients with poor motor recovery (cf. Chapter 12, p. 579).

Changes throughout motor recovery

Asymmetry between the cutaneous suppression of the on-going EMG on the affected and unaffected sides was observed in patients with poor recovery of wrist extension, but not in those with good recovery at the time of their first test (Fig. 10.11(*f*), (*g*)). Moreover, Fig. 10.11(*h*) shows that in those patients who were tested twice, the initial asymmetry tended to decrease with further recovery. This finding suggests that the take-over of the transmission of the descending command by propriospinal neurones could be merely a transient compensatory response following the interruption of the contralateral corticospinal pathway by the lesion. With good recovery, plastic changes occur in the contralateral damaged hemisphere, with extension and relocation of the upper limb area (see Hallett, 2001).

Conclusions

There is evidence for more of the descending command passing through the propriospinal relay in patients with poor recovery from stroke. The findings are consistent with transiently greater dependence on descending (possibly reticulospinal) projections onto propriospinal neurones, due to synaptic reinforcement or unmasking and/or reorganisation of the projections to them. The greater reliance on the propriospinal system for the movement repertoire of the upper limb would be accompanied by synkinetic movements.

Patients with Parkinson's disease

The same experimental protocol as in stroke patients (cutaneous suppression of the on-going ECR EMG activity elicited by a train of three shocks to the superficial radial nerve) has been used in patients with Parkinson's disease (Pol *et al.*, 1998).

Greater cutaneous suppression of the on-going EMG

Early in the illness, the cutaneous suppression produced by brief trains of stimuli was significantly increased (with respect to normal subjects) on both sides, despite marked asymmetry in the clinical features. The EMG suppression was similar to that of normal subjects when the duration of the disease was more than 3 years. No correlation was found between the amount of EMG suppression and parkinsonian symptoms, before or after levodopa treatment.

Increased excitation of propriospinal neurones

The increased cutaneous afferent suppression of on-going EMG elicited by a train of three shocks was not paralleled by an increase in the suppression elicited by a single shock. Thus, here again, this suggests that the increased cutaneous suppression was due not to increased cortical drive on feedback inhibitory interneurones, but rather to increased excitation of propriospinal neurones transmitting a component of the descending command (cf. p. 483). This increased excitation of propriospinal neurones was not directly related to the motor disability, since the increased EMG suppression: (i) was not correlated with the severity of symptoms; (ii) was symmetrical whereas the symptoms were clearly asymmetrical; (iii) returned to control level in the more severe patients; and (iv) was not modified by levodopa treatment, which improved the patients' clinical status.

Conclusions

Increased transmission of the descending command through propriospinal neurones might reflect a compensatory mechanism intended to modify the defective command, e.g. the strong inhibitory input from muscle and cutaneous afferents to propriospinal neurones could be an adaptation designed to smooth movement execution and/or to overcome the difficulty of these patients in relaxing. The finding that this presumed mechanism no longer operated on the more affected side of the more advanced patients suggests that the compensatory process arose in and/or was relayed through basal ganglia, such that it could no longer manifest itself when dopaminergic denervation increased.

Conclusions

There is growing evidence that a functional cervical propriospinal system transmitting a significant part of the descending command for upper limb motoneurones does exist in higher primates.

Role of propriospinal transmission of a part of the descending command

The major role of the cervical propriospinal system is to allow integration of the descending motor command *en route* to the motoneurones with afferent feedback from the moving limb at a premotoneuronal level. The descending command for movement is focused on propriospinal neurones that receive excitatory afferent feedback from the contracting muscle, and peripheral excitatory inputs may thereby provide a safety factor for propriospinal neurones which are already depolarised by on-going descending activity. Muscle inhibitory projections may have two roles: (i) adjustment of the force of the movement; and (ii) lateral inhibition, preventing activation of propriospinal neurones not required for the movement. Inhibition of propriospnal neurones by exteroceptive volleys evoked by contact with the target would suppress the descending drive passing through propriospinal neurones, and could contribute to the appropriately-timed termination of the movement. Because of the presumably prewired connections of each subset of propriospinal neurones with the different motoneurones involved in a multi-joint movement, integration at a premotoneuronal level allows the command to all these motoneurones to be simultaneously and 'economically' modulated by the same peripheral volleys. Finally, the even distribution of propriospinally mediated descending excitation to early- and late-recruited motoneurones might be of importance in rapid movements.

Changes in propriospinal transmission of the command in patients

Stroke patients

In the initial stages of recovery from hemiplegia, a greater part of the descending command for movement is mediated through propriospinal neurones, because of synaptic reinforcement or unmasking and/or reorganisation of the descending (probably reticulospinal) projections to them. With recovery,

less of the descending command need be mediated through propriospinal neurones, and their excitability returns to its control level.

Parkinson's disease

In the early stages of the illness (first 3 years), propriospinal transmission of the descending command is significantly increased on both sides, even in patients who are markedly asymmetrical clinically. This could represent a compensatory mechanism, designed to use the strong peripheral inhibitory input to propriospinal neurones to help patients in relaxing.

Résumé

Background from animal experiments

The propriospinal system in the cat

The descending command for target reaching can be mediated through a system of C3–C4 propriospinal neurones which transmit disynaptic excitation to forelimb motoneurones from the descending tracts. Propriospinal neurones also receive feedforward inhibition from descending sources and feedback (mainly inhibitory) from cutaneous and muscle afferents in the moving limb. The extensive convergence of descending excitation, feedforward inhibition and feedback inhibition on C3–C4 propriospinal neurones allows the descending command to be updated at a premotoneuronal level.

Conflicting results in the monkey

Under control conditions, indirect propriospinally mediated cortical EPSPs are rare and weak in upper limb motoneurones of the macaque monkey. However, after intra-venous injections of strychnine to reduce postsynaptic inhibition, corticospinal volleys readily produce propriospinally mediated disynaptic EPSPs in most motoneurones. In addition, despite the interruption of both corticomotoneuronal excitation and excitation via segmental interneurones, monkeys can make sufficiently independent finger movements to grasp a morsel of food using the command transmitted by the propriospinal system. This suggests that the major species difference might be stronger inhibitory control of the C3–C4 propriospinal neurones in the macaque monkey than in the cat.

Methodology

Propriospinally mediated excitation induced by peripheral volleys

Propriospinal neurones are activated by a volley applied to a peripheral nerve, and the resulting excitation of upper-limb motoneurones is assessed as a change in the PSTHs for single motor units, or a change in compound EMG responses. Stimulation of a mixed nerve at $\sim$0.5–0.6 $\times$ MT evokes in the PSTHs for upper limb motor units an excitation occurring with a central delay that is 3–6 ms longer than that of the monosynaptic Ia excitation. In addition to the long central delay, this low-threshold non-monosynaptic excitation differs from an effect mediated through segmental interneurones by its diffuse distribution and its disappearance when the stimulus intensity is slightly increased. The central delay of the peripheral non-monosynaptic excitation in single motor units is longer for more caudal motoneurone pools in the spinal cord. The most parsimonious explanation is that there is a longer intraspinal pathway for caudal motoneurones, and this implicates premotoneurones located rostral to motoneurones, such as the C3–C4 propriospinal neurones of the cat. A similar non-monosynaptic excitation, with the same characteristics, has been observed when various compound EMG responses (H reflex, on-going voluntary EMG activity, MEP) are conditioned by stimuli to heteronymous nerves.

Limitations

With PSTHs, it is difficult to explore changes occurring when going from rest to activity, at different stages of a motor task, or those characterising different tasks. The facilitation of the H reflex at rest is weak and most often absent. That of the on-going

EMG is also weak, and the facilitation of the MEP must be explored using low TMS intensities.

Cutaneous suppression of descending excitation

Propriospinal neurones mediating the descending command to motoneurones may be inhibited by a cutaneous volley, and this produces a disfacilitation of the motoneurones. Cutaneous suppression can be investigated during tonic contractions of ECR, just sufficient to maintain the wrist in neutral position against gravity. The on-going voluntary EMG activity of ECR is full-wave rectified and averaged against the conditioning stimuli. The superficial radial nerve is stimulated at the wrist. To ensure the symmetry of the stimulation when there is a sensory deficit in hemiplegics, the intensity of the conditioning stimulation is graded against the threshold for the motor response in thenar muscles due to spread of stimulation to the median nerve. Single stimuli and trains (three shocks at 300 Hz) are given at 2–4 × PT (or ~0.5–1 × MT, respectively). The window of analysis (after the single volley or the last shock of the train) starts ~8 ms after the latency of the ECR H reflex, and lasts for 10 ms.

Limitations

The amount of suppression depends on two factors: (i) the magnitude of the component of the descending command relayed through propriospinal neurones; and (ii) the excitability of the interneurones mediating feedback inhibition to propriospinal neurones. Comparison of the effects evoked by a single shock and by a train of three shocks at 300 Hz may help distinguish between these two possibilities.

Critique

The evidence for a cervical propriospinal relay in humans is indirect. However, the finding that the more caudal the motoneurone pool in the spinal cord the longer the central delay of the effect, whatever it is (excitatory or inhibitory, peripheral or corticospinal), strongly suggests that the relevant interneurones are located rostral to the cervical enlargement. In addition, there are many other analogies with the feline system of C3–C4 propriospinal neurones.

Organisation and pattern of connections

Excitatory inputs to propriospinal neurones

The main peripheral excitatory input is from group I muscle afferents

The excitation has a diffuse distribution (stimulation of a given nerve elicits the excitation in motoneurones of virtually all upper limb muscles, including the antagonists), but is weak. There are no propriospinal projections to motoneurones of intrinsic hand muscles.

Corticospinal excitation of propriospinal neurones

In the PSTHs of single units, the facilitation evoked by weak peripheral and corticospinal stimuli together is significantly greater than the sum of the effects of separate stimuli. This spatial facilitation implies convergence of the two inputs onto common interneurones. The involvement of an interneurone in the transmission of a part of the descending command is supported by the finding that the initial part of the peak of corticospinal excitation is not facilitated – an effect exerted on motoneurones should affect the entire corticospinal response, including the initial part due to the monosynaptic cortico-motoneuronal projection. The more caudal the motoneurone pool in the spinal cord the longer is the central delay of the extra facilitation of the corticospinal peak. Again, this implicates propriospinal neurones.

Inhibition of propriospinal neurones via feedback inhibitory interneurones

Peripheral inhibition of propriospinal neurones

Propriospinally mediated excitation is suppressed when the strength of the peripheral stimulation

is increased ('homonymous' depression), or when weak stimuli to two different nerves, which separately elicit excitation, are given together ('heteronymous' or 'lateral' inhibition). Cutaneous afferents also suppress the propriospinally mediated excitation. There is evidence that the peripheral suppression is due to inhibition of interneurones transmitting excitation to motoneurones (i.e. that the suppression is a disfacilitation of motoneurones, not a direct inhibition of them). The central delay of the peripheral suppression of the non-monosynaptic excitation increases with the rostro-caudal location of the motoneurone pool and, again, this favours the view that the inhibition is exerted on neurones located rostral to the motoneurones.

Cortical excitation of feedback inhibitory interneurones

Increasing TMS intensity results in a decrease in the peripheral facilitation of the corticospinal peak, and the depression with stronger TMS has the same time course as facilitation with weak TMS. There is evidence that the reversal from facilitation to inhibition is not due to occlusion in excitatory pathways or to corticospinal facilitation of segmental interneurones, but to activation of inhibitory interneurones projecting to propriospinal neurones.

Interaction between excitatory and inhibitory inputs

The results described above fit a system of propriospinal neurones receiving monosynaptic excitation from peripheral and corticospinal inputs and disynaptic inhibition via feedback inhibitory interneurones from the same sources (as described in the cat and the macaque monkey). With weak TMS intensities, inhibitory interneurones would be only marginally activated, and excitation of propriospinal neurones could manifest itself, while with stronger TMS intensities, the activation of inhibitory interneurones would prevent propriospinal neurones from firing. Corticospinal activation of inhibitory interneurones projecting to propriospinal neurones can explain why in higher primates stimulation of the pyramidal system by itself has provided little evidence for propriospinally mediated corticospinal EPSPs in upper limb motoneurones. Indeed, stimulation of the pyramidal system produces unnaturally synchronised volleys, which will evoke gross activation of inhibitory interneurones, capable of preventing a discharge of propriospinal neurones in response to corticospinal excitation. Given a stronger inhibitory control of transmission through propriospinal neurones than in the cat, disclosure of propriospinally mediated corticospinal excitation requires: (i) reduction of post-synaptic inhibition by strychnine or chronic corticospinal lesions (as in macaque experiments), (ii) the use of spatial facilitation between two weak volleys (human experiments), or (iii) activation of the system in natural movements.

Organisation of the cervical propriospinal system

The pattern of peripheral excitation of propriospinal neurones at the onset of a selective voluntary contraction and that of the cutaneous suppression indicate that propriospinal neurones are organised in subsets specialised with regard to their excitatory muscle afferent input rather than their target motoneurones. Results obtained at the onset of movement suggest that, as in the cat, propriospinal neurones have divergent projections to motoneurones belonging to different pools. During voluntary contractions, propriospinally mediated descending excitation is evenly distributed to motoneurones supplying slow- and fast-twitch motor units in the contracting muscle.

Motor tasks and physiological implications

Evidence for propriospinal transmission of a part of the descending command

During tonic ECR contractions, a superficial radial volley suppresses the on-going EMG and the MEP, but has little effect on the H reflex. This indicates that the suppression is due not to inhibition exerted

directly on motoneurones but, instead, to the activation of feedback inhibitory interneurones, which in turn inhibit propriospinal neurones mediating part of the natural descending command. This view is supported by the finding that the MEP suppression does not involve the initial part of the MEP due to the monosynaptic cortico-motoneuronal volley. A similar suppression of the on-going EMG and of the MEP without parallel changes in the monosynaptic reflex has been observed for biceps and triceps, and the more caudal the motoneurone pool, the longer the central delay of the disfacilitation. These results further support the view that a part of the descending command for normal movement is mediated through the propriospinal relay. The larger the propriospinally mediated component of the descending command, the more profound can be the peripheral disfacilitation. The percentage of the motor command transmitted through the propriospinal system is not known and cannot be equated with the percentage of EMG suppression. Nevertheless the contribution of this oligosynaptic component is critical for the contraction of many upper-limb muscles.

Propriospinally mediated facilitation of motoneurones during voluntary contraction

A heteronymous group I volley produces a propriospinally mediated facilitation of the FCR and ECR H reflexes. This effect may be small or absent at rest, but becomes much larger at the onset of a voluntary contraction when, and only when, the conditioning stimulation eliciting propriospinal excitation is applied to group I afferents from the contracting muscle. Descending facilitation is focused on propriospinal neurones which receive the afferent feedback from the contracting muscle. Divergent projections of propriospinal neurones (through branching of their axons) might explain why the propriospinally mediated excitation to forearm motoneurones is facilitated during a selective contraction of elbow muscle(s), even though forearm muscles are not involved in the contraction. This would help ensure that elbow movements are accompanied by appropriate wrist muscle contractions to maintain the hand in an optimal position for grasping.

Functional implications

The major role of the propriospinal system is to allow integration at the level of propriospinal neurones of the descending command with afferent feedback from the moving limb at the propriospinal level. Because of the prewired connections of each subset of propriospinal neurones with the different motoneurone pools involved in a multi-joint movement, integration at a premotoneuronal level would allow the command to these motoneurones to be modulated simultaneously and 'economically' by the same excitatory and inhibitory peripheral volleys. In addition, the even distribution of propriospinally mediated descending excitation to early- and late-recruited motoneurones could be of importance in movements when it is necessary to activate a wide range of motoneurones more or less simultaneously. Cutaneous suppression of the descending command provides a good example of the integration of peripheral and descending inputs at the premotoneuronal level. The cutaneous inhibition of propriospinal neurones has a specific pattern, since each subset receives inhibition from the skin field that would contact the target at the end of the movement produced by the relevant muscle. The resulting inhibition of propriospinal neurones by the exteroceptive volley would help suppress the descending command passing through the propriospinal relay, thus contributing to an appropriately timed termination of the movement. This view is supported by the finding that feedback inhibitory interneurones mediating the cutaneous inhibition of propriospinal neurones receive a stronger descending drive at the offset than at the onset of a visually guided movement.

Studies in patients and clinical implications

Lesion of the spinal cord at the junction C6–C7 spinal level

Comprehensive studies have been undertaken on a patient who had a partial Brown–Séquard syndrome with, on the left side, moderate upper motor

neurone signs below C7, sparing triceps, due to a discrete lesion at the junction between the C6 and C7 spinal segments, largely confined to the left part of the spinal cord. Ulnar volleys produced symmetrical facilitation of the MEP in biceps whereas, in triceps, the facilitation was seen only on the unaffected side. This was interpreted as resulting from the interruption, on the affected side, of the descending axons of rostrally-located propriospinal neurones projecting to triceps motoneurones located below the lesion. As a result, on that side, ulnar-induced facilitation of propriospinal neurones could no longer facilitate the MEP of triceps motoneurones.

Stroke patients

Single cutaneous volleys to the superficial radial nerve suppressed the EMG produced by a tonic ECR contraction symmetrically and to the same degree in patients and controls. In contrast, the amount of on-going ECR suppression produced by a train of three shocks at 300 Hz was significantly greater on the affected side of stroke patients with poor recovery of wrist extension than on their unaffected side or in healthy controls. Significant asymmetry between the cutaneous suppression of the on-going EMG on the affected and unaffected sides was observed only in patients with poor recovery of wrist extension. Moreover, in those patients who were tested twice, the initial asymmetry tended to decrease with recovery. This suggests that, when patients have not yet recovered, a greater component of the descending command is mediated through the propriospinal relay. The findings are consistent with transiently increased efficacy of descending (possibly reticulospinal) projections to propriospinal neurones, due to synaptic reinforcement or unmasking and/or reorganisation of the projections to them. The greater reliance on the propriospinal system for the movement repertoire of the upper limb would be accompanied by synkinetic movements.

Patients with Parkinson's disease

Within the first 3 years of the illness, the suppression of the ECR EMG by trains to the superficial radial nerve was significantly greater than in normal subjects on both sides, even in patients who were clinically asymmetrical. Here also, the greater EMG suppression was probably due to increased transmission of the descending command through propriospinal neurones, but there was no correlation with motor disability. The greater transmission may have been a compensatory mechanism intended to help smooth movement execution and/or to overcome the difficulty of these patients in relaxing.

The lumbar propriospinal system

There is a system of short-axoned lumbar propriospinal neurones, which transmit part of the descending command to lower-limb motoneurones. There are similarities with the cervical system, but also important differences, possibly related to the different motor repertoires of the upper and lower limbs, and these justify separate descriptions of the cervical and lumbar systems. In the following the emphasis is put on these differences. In addition, in cats and humans, a detailed comparison of the system of short-axoned propriospinal neurones at cervical and lumbar levels is made somewhat uncertain because, so far, lumbar propriospinal pathways have been investigated less extensively than the cervical propriospinal system.

Background from animal experiments

Initial studies

The analysis of propriospinal systems that transmit descending motor information to motoneurones began with the finding that activity in bulbospinal pathways activates short-axoned neurones that are in the upper lumbar segments, excite hindlimb motoneurones monosynaptically, and receive convergence from corticospinal fibres (Lloyd, 1941a, b). Two different systems of short-axoned lumbar

propriospinal systems (dorsolateral and ventromedial) have been studied by Russian scientists in Kiev (cf. Kostyuk, 1967) and Leningrad (cf. Shapovalov, 1975). However, (i) the electrophysiological analyses were less sophisticated than in the cervical system, (ii) behavioural investigations have not been performed to address their function, and (iii), the original publications did not appear in the English literature. Perhaps therefore, attention has been more focused on the cervical system. The following description of the lumbar propriospinal systems in the cat is largely based on a comprehensive review by Schomburg (1990), where references to original Russian papers can be found.

Dorsolateral propriospinal neurones

These neurones are located in L3–L5 in the lateral part of laminae IV–VII, and their axons run in the dorsal and intermediate portions of the lateral funiculus. Because their projections are mainly excitatory to motoneurones supplying distal muscles, and their predominant input is derived from the corticospinal and rubrospinal tracts, they have been postulated to transmit the descending command to motoneurones innervating distal hindlimb muscles. After corticospinal excitation these propriospinal neurones show a long period of depressed excitability, a phenomenon that is probably due largely to inhibitory interconnections between propriospinal neurones. It would be inappropriate to compare this system with the C3–C4 propriospinal system because the lumbar dorsolateral propriospinal system receives no input from peripheral afferents.

Ventromedial lumbar short-axoned propriospinal neurones

These neurones are located in L2–L4 in the ventromedial part of lamina VII, in lamina VIII and partly even in lamina IX, and their axons run in the ventral funiculus. The target motoneurones are mainly those of proximal muscles. They receive a strong peripheral input from peripheral afferents, and it is likely that this system includes the mid-lumbar ventromedial L3–L5 interneurones coactivated by group I and II afferents (see Jankowska, 1992; Chapter 7, p. 289). They receive strong excitation from vestibulospinal and reticulospinal tracts. Monosynaptic corticospinal excitation is weak in the cat, but present consistently in the monkey (Kozhanov & Shapovalov, 1977). In the cat, separate subpopulations of neurones appear to be excited by the corticospinal and rubrospinal tracts on the one hand and by the vestibulospinal and reticulospinal tracts on the other hand (Davies & Edgley, 1994).

Methodology

Underlying principle

As in the cervical propriospinal system, lumbar propriospinal neurones are activated by group I volleys, and the resulting excitation of motoneurones may be assessed as a change in the PSTHs for single motor units or in compound EMG responses. The finding that the more caudal the motoneurone, the longer the central delay of any reflex effect again suggests that the relevant neurones are located rostral to the motoneurone pool. The excitation of quadriceps motoneurones by group I afferents in the common peroneal nerve has been employed in most routine studies.

Non-monosynaptic excitation of voluntarily activated single motor units

Stimulation of the common peroneal nerve evokes in the PSTHs of quadriceps units a peak of excitation that appears with a low threshold (0.6 × MT) and a central delay of 3–4 ms (Forget *et al.*, 1989b). Here again, the low threshold and abrupt onset (see Fig. 10.12(*b*)) suggest that the excitation is mediated through an oligosynaptic pathway, the long central

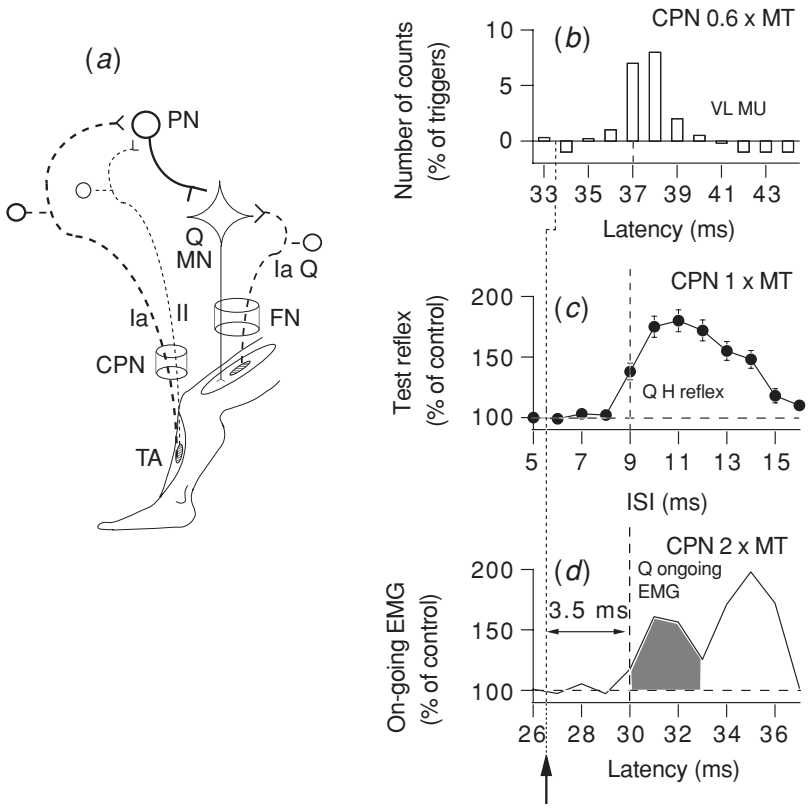


Fig. 10.12. Methods to estimate peripheral propriospinally mediated excitation of lumbar motoneurones. (*a*) Sketch of the presumed pathways. Group I and group II afferents from tibialis anterior (TA) activate propriospinal neurones (PN) projecting to quadriceps (Q) motoneurones (MN). (*b*) Effect of common peroneal nerve (CPN) stimulation at 0.6 × MT in the PSTH (after subtraction of the background firing, 1-ms bin width) of a vastus lateralis (VL) motor unit (MU). (*c*) The size of the Q (vastus intermedius) H reflex (expressed as a percentage of its control value) conditioned by a volley to the CPN (1 × MT) is plotted against the interstimulus interval (ISI). (*d*) Facilitation of the on-going rectified voluntary EMG of the Q (vastus intermedius, conditioned EMG as a percentage of control EMG) by a conditioning volley to the CPN (2 × MT). The early peak has a low threshold and is elicited by group I afferents (grey area), whereas the late peak has a higher threshold and is due to group II afferents (see Chapter 7). The difference between the afferent conduction times of Ia volleys in femoral (FN) and CP nerves was 5.5 ms. The zero central delay (arrow and dotted vertical line) corresponds to the 33.5 ms latency in (*b*) (the peak of femoral-induced monosynaptic Ia excitation occurred at the 28 ms latency, without allowance for the trigger delay of the unit), the 5.5 ms ISI in (*c*), and 26.5 ms in (*d*) (the latency of the quadriceps H reflex was 21 ms). The dashed vertical line indicates the onset of the excitation. Modified from Forget *et al.* (1989b) (*b*), Forget *et al.* (1989a) (*c*), Marchand-Pauvert *et al.* (2005) (*d*), with permission.

delay being explained by the conduction time to and from interneurones located at different spinal segments than motoneurones. As in the cervical enlargement, the excitation mediated through this pathway also differs from a segmentally mediated effect by its widespread input pattern: in a given unit, propriospinally mediated excitation may be observed after stimulation of afferents from virtually any leg or thigh muscle, including antagonists (cf. p. 494). The limitations are the same as those for

the PSTH method in studies of cervical propriospinal pathways (pp. 457–8).

Non-monosynaptic excitation of compound EMG responses

Quadriceps H reflex

Non-monosynaptic facilitation of the quadriceps H reflex occurs with a long central delay and a low threshold (<1 × MT) when the reflex is conditioned by common peroneal nerve stimulation (Fig. 10.12(*c*); Forget *et al.*, 1989a, b). When the conditioning stimulus intensity is above the threshold of group II afferents (1.2 × MT, Simonetta *et al.*, 1999), the early group I peak is followed by a second peak (the onset of which overlaps the end of the early peak; see Fig. 7.4(*b*) in Chapter 7). Whatever the stimulus intensity, the first 3 ms of the reflex facilitation are not contaminated by the group II effect and may be attributed to the activation of the relevant interneurones by group I afferents. Initially this reflex facilitation was erroneously attributed to disynaptic Ib excitation through an intersegmental pathway (cf. Chapter 6, pp. 258–60). The method is simple but, during a quadriceps contraction >10% of MVC, the H reflex may be suppressed by convergence of the peroneal volley with afferents in the femoral test volley on interneurones mediating autogenetic 'Ib inhibition' (see Marchand-Pauvert *et al.*, 2002; Chapter 1, pp. 14–16). This constitutes an important limitation of the technique.

Modulation of the on-going EMG

There is no such limitation when investigating the modulation of the on-going rectified quadriceps EMG by conditioning stimuli to the common peroneal nerve because there is no femoral test volley. Figure 10.12(*d*) shows that the resulting facilitation of the EMG occurs similarly with a 3.5-ms central delay. Stimulation >1.2 × MT activates group II afferents, and a second peak of excitation overlaps the declining phase of the early peak, but the initial part (grey area in Fig. 10.12 (*d*)) is purely group I in origin.

Table 10.2. Central delay of lumber propriospinal excitation

MN pool	Rostro-caudal location	Central delay
Vastus lateralis	L2 L3 L4	3.91 ± 0.28
Tibialis anterior	L4 L5	4.38 ± 0.31
Peroneus brevis	L4 L5 S1	4.46 ± 0.22
Soleus	L5 S1	4.93 ± 0.32
Biceps femoris	L5 S1 S2	5.00 ± 0.68
Gastrocnemius medialis	S1 S2	5.19 ± 0.99

Mean (±SEM) central delay (ms) of propriospinal excitation, calculated as the difference between the latency of non-monosynaptic and monosynaptic Ia excitations, for six motoneurone pools (MN) listed from top to bottom with respect to their rostro-caudal location in the spinal cord. From Chaix *et al.* (1997).

Rostral location of the relevant interneurones

Evidence for rostral location of the relevant interneurones

Table 10.2 shows the central delay of the peripheral *homonymous* non-monosynaptic excitation, calculated for single motor units as the difference between the latencies of monosynaptic and non-monosynaptic excitations. The central delay is longer the more caudal the motoneurone pool in the spinal cord (Chaix *et al.*, 1997). As expected, given the convergence of femoral and common peroneal group I volleys onto common interneurones (see below), the central delays of the homonymous non-monosynaptic excitation and heteronymous peroneal-induced non-monosynaptic excitation of quadriceps motoneurones are similar. Because the presumed propriospinal neurones investigated in humans receive a strong peripheral excitatory input, they presumably correspond to the mid-lumbar ventromedial propriospinal neurones of the cat. The

segmental location within the lumbar spinal cord is different in humans (who have five lumbar segments) and the cat (which has seven lumbar segments). Quadriceps motoneurones are in L5–L6 in the cat and in L2–L4 in humans. Accordingly, short-axoned propriospinal neurones in L3–L5, rostral to motoneurones in the cat, should be above L1–L2 in humans. It is of interest that evidence for a spinal excitatory pathway ('mid-thoracic nucleus') that projects from the vertebral T8 level to lower limb motoneurones has been found in humans during stimulation of the spinal cord during surgery for spinal deformity (Taylor, Ridding & Rothwell, 1995).

Critique

Again, the increase in the central delay of the excitation with the caudal location of the motoneurone pool suggests that the relevant neurones are located rostral to motoneurones, much as are lumbar propriospinal neurones in the cat. However, the data in Table 10.2 are less conclusive than the data in Table 10.1 for the cervical level, because the studies involved only the peripheral homonymous excitation, whereas the data for the cervical projection include studies of cutaneous inhibition (which has not been found at lumbar level in the absence of cortical stimulation, see below) and corticospinal excitation (see Pierrot-Deseilligny, 1996, 2002). For the lumbar system, corticospinal excitation has been investigated mainly in the common peroneal-quadriceps paradigm.

Organisation and pattern of connections

Peripheral excitatory input to excitatory lumbar propriospinal neurones

Diffuse distribution

For any given motor unit, excitation has been observed after stimulation of group I afferents in the nerves innervating virtually all leg and thigh muscles, including those supplying antagonists (Chaix *et al.*, 1997). Group I afferents from the plantar muscles evoke a low-threshold, medium-latency excitation frequently in tibialis anterior (Fig. 10.14(*b*)) and peroneus brevis units, rarely in thigh muscles and never in ankle extensors (Marque *et al.*, 2001a).

Differences with the organisation at cervical level

Peripheral excitation of lumbar propriospinal neurones differs from that of cervical propriospinal neurones in three important aspects.

Afferents responsible for the activation of propriospinal neurones

The low threshold for the excitation indicates a group I effect, and there is evidence for a contribution from Ia afferents (Fournier *et al.*, 1986; Forget *et al.*, 1989b). However, the main input to these neurones seems to be from group II afferents, except in the common peroneal–quadriceps combination, where group I and group II inputs are of equal importance (see Simonetta-Moreau *et al.*, 1999; Chapter 7).

Strength of the peroneal group I excitation to quadriceps

Another important difference with the cervical system concerns the potency of the peripheral group I excitation in the common peroneal nerve–quadriceps combination. Thus, increasing common peroneal stimulus intensity can result in a very large facilitation in quadriceps units (cf. Fig. 10.13(*b*)–(*d*)). Similarly, Fig. 10.12(*c*) shows a very large facilitation of the H reflex at rest, something that is generally absent at cervical level (see p. 458). This could be attributed to the fact that peripheral excitation is not counteracted by feedback inhibition elicited from the same afferents (see below). However, the size of the peak of excitation in Fig. 10.12(*b*), at an intensity close to the threshold

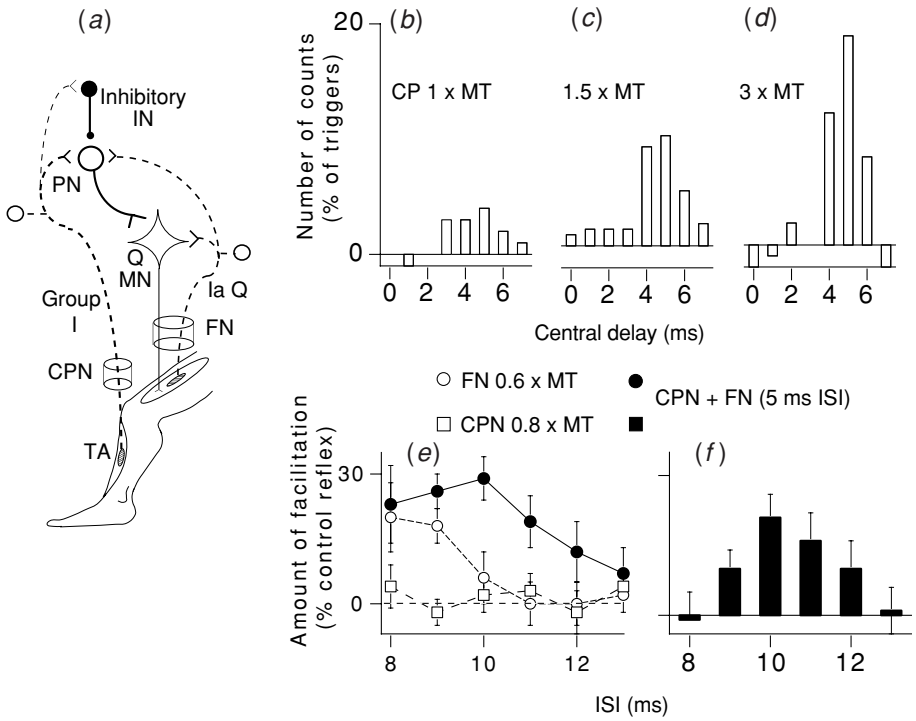


Fig. 10.13. Peripheral propriospinally mediated excitation of lumbar motoneurones. (*a*) Sketch of the presumed pathways. Group I afferents from tibialis anterior (TA) and quadriceps (Q) converge on common propriospinal neurones (PN) projecting to Q motoneurones (MN). The projection of TA Ia afferents to inhibitory interneurones (IN) inhibiting PNs is weak (thin dashed line). (*b*)–(*d*) PSTHs (after subtraction of the background firing, 1ms bin width), with the number of counts (as a percentage of the number of triggers) plotted against the central delay (latency after the arrival of the conditioning group I volley at the segmental level of the MN). Propriospinally mediated excitation elicited in the same vastus lateralis (VL) unit by common peroneal nerve (CPN) stimuli of increasing intensity ((*b*), 1, (*c*), 1.5, (*d*), 3 × MT). The increase in stimulus intensity above 1 × MT was possible because there is no recurrent inhibition from CPN to Q MNs to mask the propriospinally mediated excitation (Meunier, Pierrot-Deseilligny & Simonetta-Moreau, 1994). (*e*), (*f*) Time course of the spatial facilitation between CPN and femoral nerve (FN) volleys assessed with the Q H reflex. The amount of reflex facilitation (conditioned *minus* control reflex, as a percentage of the control reflex) is plotted against the interstimulus interval (ISI) between CPN and test volleys (ISI between conditioning CPN and subliminal FN volleys constant at 5 ms). (*e*) Effect of separate CPN (0.8 × MT, □, producing no facilitation in this subject at that intensity), separate FN (0.6 × MT, ○, with the decline of the homonymous monosynaptic Ia facilitation), and combined (CPN + FN, ●) stimuli. (*f*) Time course of extra facilitation on combined stimulation (difference between the facilitation on combined stimulation and the sum of effects of separate stimuli). Each symbol in (*e*), (*f*) is the mean of 60 measurements. Vertical bars 1 SEM. Modified from Chaix *et al.* (1997) ((*b*)–(*d*)) and Forget *et al.* (1989b) ((*e*), (*f*)), with permission.

of group I afferents, indicates that the group I peroneal-induced propriospinally mediated excitation of quadriceps is much stronger than peripheral excitation mediated through cervical propriospinal neurones. Notwithstanding, equivalently potent projections have not been found to motoneurones of hamstrings or leg muscles, whatever the conditioning nerve. The potency of the propriospinally mediated group I excitation could thus be specific to the peroneal–quadriceps combination.

Excitatory convergence of group I afferents from different muscles

A third important difference is the existence of significant peripheral excitatory convergence onto lumbar propriospinal neurones, revealed using spatial facilitation of the H reflex (Forget *et al.*, 1989b). Thus, peroneal and femoral volleys without effect by themselves produce significant facilitation of the quadriceps H reflex on combined stimulation (Fig. 10.13(*e*)). The extra facilitation has a time course (Fig. 10.13(*f*)) similar to that of the facilitation elicited by a stronger stimulation of the common peroneal nerve (see Fig. 10.12(*c*)). The similar time course suggests facilitation at premotoneuronal level. This convergence is quite specific because no convergence has been detected between femoral Ia afferents and low-threshold afferents in the posterior tibial and plantar nerves or various cutaneous afferents. This finding, together with the potency of the group I excitation, raises the question whether the organisation of the excitation of quadriceps motoneurones from the pretibial flexors is unique in the lumbar enlargement.

Peripheral inhibitory inputs to lumbar propriospinal neurones

Homonymous suppression

Weakness of the 'homonymous' inhibition

Figure 10.13(*b*)–(*d*) shows that increasing common peroneal nerve stimulation results in a continuous increase in the propriospinally mediated excitation of a quadriceps unit. The absence of depression was observed in 95% of motor units and contrasts strongly with the suppression of peripheral excitation to cervical propriospinal neurones, consistently observed when the intensity of peripheral stimulation is increased above 0.8–0.9 × MT (p. 464).

Probable existence of a 'homonymous' group I inhibition

There is probably a pathway mediating 'homonymous' inhibition (i.e. evoked by group I afferents in the same nerve as those eliciting excitation) of lumbar propriospinal neurones. When investigating common peroneal-induced effects on quadriceps units, suppression was repeatedly observed in one subject (Simonetta-Moreau *et al.*, 1999), and the brief duration of the early peak in the PSTHs in the other subjects suggests a depression truncating the group I propriospinally mediated excitation (Figs. 10.12(*b*), 10.13(*b*)–(*d*)). However, the main evidence for the existence of this pathway is the strong inhibition which becomes apparent when common peroneal and cortical stimulations are combined (see p. 500). The absence of an early group I depression of the quadriceps H reflex at rest (Fig. 10.12(*c*)) and during weak tonic Q contractions (Fig. 10.15(*b*)), even when the peroneal stimulus intensity was increased far above 1 × MT (Marque, Pierrot-Deseilligny & Simonetta-Moreau, 1996), argues against an IPSP evoked in motoneurones, because an IPSP should depress the H reflex as well (see pp. 471–3). It is therefore suggested that the suppression seen in the presence of corticospinal stimulation is due to disfacilitation resulting from inhibition of propriospinal neurones.

Cutaneous effects

Cutaneous inhibition has only been disclosed in the presence of cortical stimulation (p. 500). In the absence of TMS, only cutaneous excitatory effects were observed (afferents in the sural nerve onto peroneus brevis motoneurones, Chaix *et al.*, 1997; cutaneous afferents from the heel onto tibialis anterior motoneurones, Marque *et al.*, 2001a) and, except for their long latency, there was no evidence that these effects were mediated through propriospinal neurones.

Lateral inhibition between conditioning volleys applied to two different nerves

In contrast, a lateral 'heteronymous' suppression is often seen. Thus, the propriospinally mediated excitation elicited in the PSTHs of single units by stimulation of one nerve (common peroneal, posterior tibial, femoral) was reduced in 68% of the cases when there were volleys in two nerves (Forget *et al.*, 1989b;

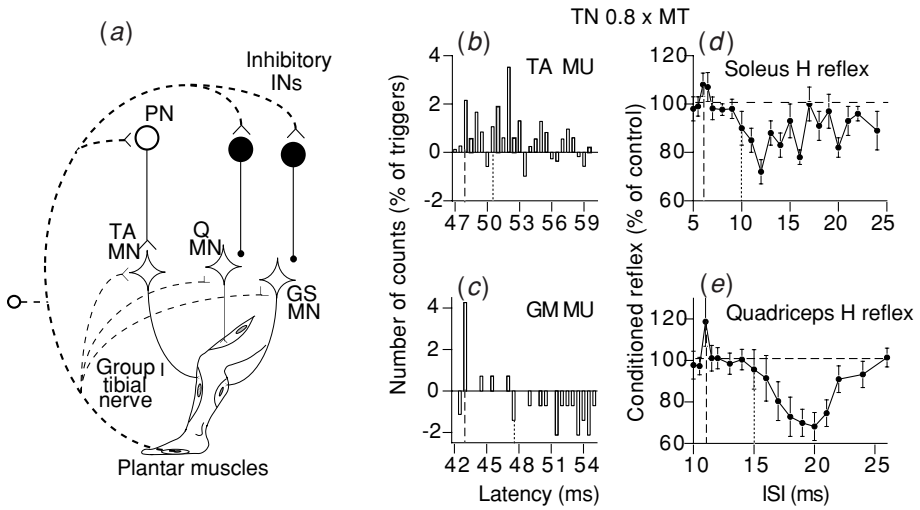


Fig. 10.14. Projections of group I afferents from intrinsic foot muscles to motoneurone pools of TA, quadriceps and triceps surae. (*a*) Sketch of the presumed pathways. Ia afferents from intrinsic plantar foot muscles have monosynaptic Ia and non-monosynaptic excitatory projections to tibialis anterior (TA) motoneurones (MN), and monosynaptic Ia excitatory and non-monosynaptic inhibitory projections to quadriceps (Q) and gastrocnemius-soleus (GS) MNs. (*b*)–(*e*) Effects evoked by a stimulation of the tibial nerve (TN) at 0.8 × MT. Vertical dashed and dotted lines indicate the latency of the monosynaptic excitation and of the non-monosynaptic effect, respectively. (*b*), (*c*) PSTHs (after subtraction of the background firing, 0.5 ms bin width) in a TA (*b*) and a gastrocnemius medialis (GM) (*c*) motor unit (MU). (*d*), (*e*) The size of the soleus (*d*) and of the quadriceps (*e*) H reflex (expressed as a percentage of the control reflex) is plotted against the interstimulus interval (ISI). Each symbol represents the mean of 20 measurements. Vertical bars ±1 SEM. Modified from Marque *et al.* (2001a), with permission.

Chaix *et al.*, 1997). Evidence has been presented that this suppression presumably reflects disfacilitation of the motoneurone due to inhibition of excitatory propriospinal neurones (Chaix *et al.*, 1997).

Peripheral inhibition of motoneurones

Group I inhibition from foot muscles

Stimulation of the tibial nerve at the ankle elicits a weak heteronymous monosynaptic Ia facilitation in all leg and thigh muscles, followed by inhibition 3–5 ms later in triceps surae and quadriceps (Fig. 10.14(*c*); Marque *et al.*, 2001a). This inhibition suppresses the H reflexes of soleus and quadriceps at rest (Fig. 10.14(*d*),(*e*)), and therefore results from IPSPs in motoneurones. Because it is not produced by separate stimulation of cutaneous afferents and has the same low threshold as the monosynaptic heteronymous group I excitation, it is likely to be of group I origin. Here again, the low threshold and abrupt onset of the inhibition (see Fig. 10.14(*d*),(*e*)) suggest transmission through an oligosynaptic pathway, the long central delay being explained by interneurones located at different spinal segments than motoneurones.

Medium-latency reciprocal inhibition

During voluntary dorsiflexion of the foot, group I volleys in the common peroneal nerve evoke a medium-latency inhibition of the soleus H reflex (1–3 ms longer than disynaptic reciprocal Ia inhibition). This medium-latency inhibition is superimposed on the disynaptic reciprocal Ia inhibition and has been seen only during active dorsiflexion, where it appears ~50 ms before tibialis anterior EMG activity, and is correlated with the strength of tonic dorsiflexion (Crone & Nielsen, 1989). Because of its

low threshold, it was again assumed that this inhibition could be mediated through a disynaptic pathway with interneurones located at different spinal segments than motoneurones. The fact that this medium-latency inhibition is not seen at rest can be explained by a weak afferent input. It is readily facilitated during *tonic* voluntary dorsiflexion (Crone *et al.*, 1987), even when mechanisms such as post-activation depression and presynaptic inhibition of Ia terminals are active (Chapter 5, pp. 220–1). This is another indication that the group I input to this pathway is relatively weak and the supraspinal input relatively strong (Crone, 1993), as in other propriospinal pathways.

Which interneurones?

It is likely that the interneurones which mediate the above inhibitions are located at a different segmental level than their target motoneurones (and are therefore by definition 'propriospinal'). However, there is no evidence that these interneurones belong to the system of short-axoned lumbar propriospinal neurones located rostral to motoneurones. Indeed, the central delay of the tibial nerve-induced inhibition of extensors, assessed with the H reflex (Fig. 10.14(*d*),(*e*)) or in the PSTHs of single units is, if anything, longer in quadriceps than in triceps surae motoneurones located more caudally (Marque *et al.*, 2001a). Further experiments are therefore required to elucidate the exact nature of the interneurones mediating medium-latency inhibition(s) exerted directly on motoneurones.

Corticospinal control

Corticospinal control of peripheral excitation

Spatial facilitation between peripheral and corticospinal volleys

The same spatial facilitation technique as in the upper limb has been used to demonstrate that corticospinal and common peroneal volleys converge onto premotoneurones interposed in the corticospinal pathway to quadriceps motoneurones (Marchand-Pauvert, Simonetta-Moreau & Pierrot-Deseilligny, 1999b). Thus, Fig. 10.15(*b*) shows that, at early ISIs, common peroneal nerve stimulation facilitates the quadriceps MEP, sparing the initial part of the MEP (Fig. 10.15(*c*)). This result was confirmed when investigating the PSTHs of single units, since the effect on combined stimulation was greater than the sum of effects of separate stimuli and, here again, the initial part of the corticospinal peak was not facilitated (Fig. 10.15(*d*),(*e*)), indicating summation of EPSPs in premotoneurones (see pp. 461–3). A similar statistically significant extra facilitation has been found consistently in all tested units at an ISI corresponding to the simultaneous arrival of the peroneal volley and the effective component of the corticospinal volley (D or I wave) at the level of the relevant premotoneurones. Corticospinal volleys also facilitate transmission in the pathway mediating group I excitation from intrinsic foot muscles to tibialis anterior and peroneus brevis motoneurones. Finally, spatial facilitation between corticospinal and group I volleys has also allowed the disclosure of excitatory connections between leg muscles (from gastrocnemius medialis to tibialis anterior, and vice versa), connections that were rarely detected in the absence of cortical stimulation (Lourenço *et al.*, 2005).

Which interneurones?

The number of positive results in caudal motoneurones (gastrocnemius medialis in S1–S2) is low and cortical stimulation at threshold used in these experiments elicited excitation with a variable latency (presumably because the effective I wave varied from trial to trial). It was therefore not possible to be certain of the central delay of the extra facilitation of the corticospinal peak, and to determine whether the central delay is longer the more caudal the motoneurone pool. Thus, so far, it has not been demonstrated that the premotoneurones transmitting corticospinal excitation are lumbar propriospinal neurones, even though this is probable. The finding that peripheral inhibition of propriospinal neurones can

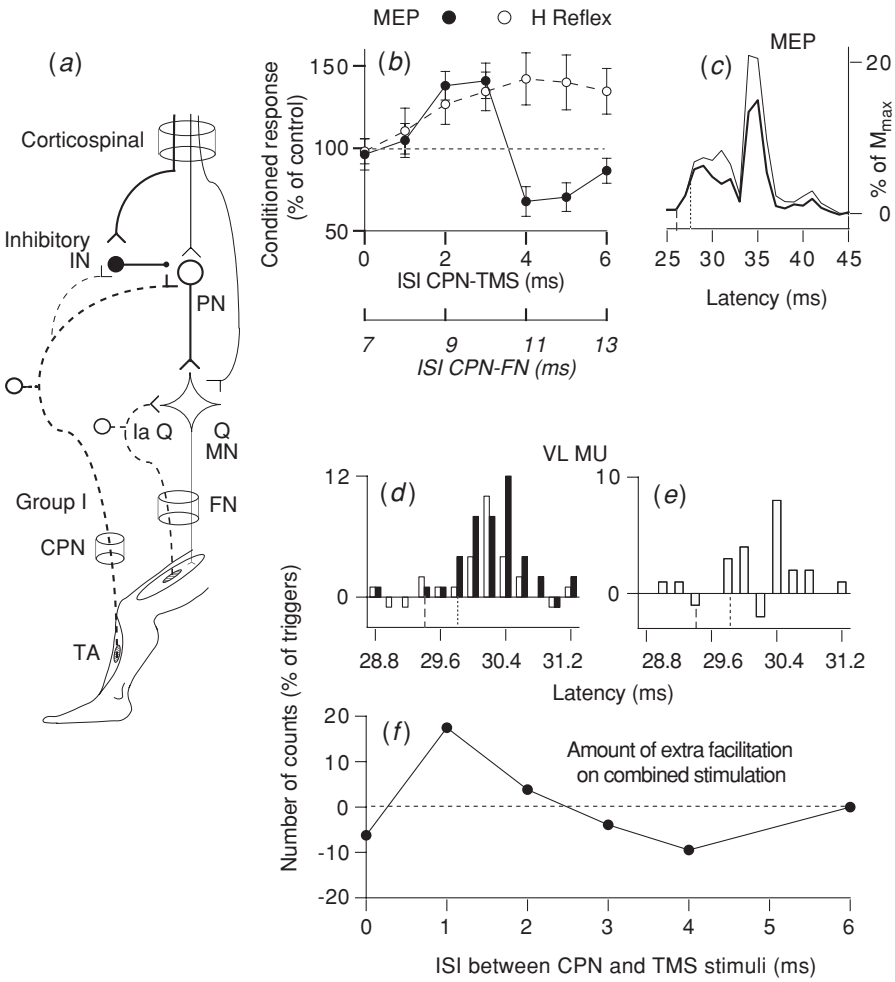


Fig. 10.15. Corticospinal projections to lumbar propriospinal neurones. (*a*) Sketch of the presumed pathways. Corticospinal fibres have monosynaptic excitatory projections to quadriceps (Q) motoneurones (MNs), propriospinal neurones (PN) and feedback inhibitory interneurones (IN) (the latter projection being the more potent, as indicated by the thickest line). (*b*) Time course of the early effects (due to group I afferents) elicited by a common peroneal nerve (CPN) volley (2 × MT) on the MEP (●) and the H reflex (○) of the Q during a weak Q voluntary contraction involving only a few motor units. The conditioned responses (expressed as a percentage of the control responses) are plotted against the interstimulus interval (ISI) between CPN and TMS (upper abscissa) and CPN and femoral nerve (FN) stimuli (lower abscissa, in italics), the two abscissae being aligned to start at the simultaneous arrival of conditioning and test volleys at the segmental level of the Q MN pool. Each symbol represents the mean of 20 measurements. Vertical bars ±1 SEM. (*c*), Mean control and conditioned (facilitated) rectified Q MEPs (20 sweeps, thick and thin lines, respectively, percentage of M_{max}) at the 1 ms ISI (a different subject than in (*b*)). (*d*), (*e*) PSTHs for a vastus lateralis (VL) motor unit (MU) (after subtraction of the background firing, 0.2 ms bin width). (*d*) The sum of effects elicited by separate CPN and cortical stimuli (□) is compared to the effect on combined stimulation (1 ms ISI, ■). (*e*) Extra facilitation on combined stimulation, i.e. the difference between filled and open columns in (*d*). Dashed and dotted lines in (*c*)–(*e*) indicate the onset of the MEP (*c*) or the corticospinal peak ((*d*), (*e*)) and of the extra facilitation on combined stimulation, respectively. (*f*) The amount of extra facilitation on combined stimulation for a VL unit (same unit as in (*d*), (*e*)) is plotted against the ISI. Modified from Marchand-Pauvert, Simonetta-Moreau & Pierrot-Deseilligny (1999), with permission.

reduce the corticospinal excitation of motoneurones below its unconditioned value (see below) suggests that part of the corticospinal volley is transmitted to motoneurones by propriospinal neurones.

Cortical control of peripheral inhibition

Convergence of corticospinal and peripheral volleys onto inhibitory interneurones

During a weak voluntary contraction of quadriceps, the early group I facilitation of the MEP by common peroneal stimulation ends abruptly 1–2 ms after its onset, and is then reversed to inhibition. This contrasts with the progressive decline of the group I facilitation of the H reflex (Fig. 10.15(*b*)). The suppression of the MEP is not due to occlusion in propriospinal neurones of the effects of cortical and peripheral excitatory inputs because the peroneal facilitation of the MEP was reduced below its control level. This indicates an inhibitory process. A similar suppressive effect was confirmed in the PSTHs for single motor units of quadriceps. In Fig. 10.15(*f*), the extra facilitation elicited by common peroneal stimulation was only significant at the 1-ms ISI, and was reversed to inhibition at the 3–4 ms ISIs. This suppression on combined stimulation was found consistently in all tested units and contrasts with the facilitation elicited by separate peroneal stimulation. These findings indicate that peripheral volleys (group I and possibly cutaneous), insufficient to activate inhibitory interneurones in the absence of TMS, become effective when their synaptic actions are potentiated by TMS, and that inhibitory interneurones receive corticospinal excitation, much as do excitatory propriospinal neurones. A similar effect has been observed from gastrocnemius medialis to semitendinosus.

Which interneurones?

The suppression implies a truncation of EPSPs by IPSPs, probably at the level of the excitatory propriospinal neurones (producing a disfacilitation of the motoneurones, see p. 496).

Conclusions

Corticospinal volleys have two effects on the lumbar propriospinal system: facilitation of propriospinal neurones and facilitation of inhibitory interneurones mediating feedback inhibition to propriospinal neurones. Overall the dominant effect of corticospinal volleys on the lumbar propriospinal system seems to be excitation of feedback inhibition. This could explain the results obtained during contraction (see below).

Motor tasks and physiological implications

So far, only changes in the facilitation of the quadriceps H reflex produced by conditioning stimulation of the femoral or the deep peroneal nerve have been compared at rest and during voluntary contraction. However, because of the suppression of the H reflex by the convergence between conditioning and test volleys onto interneurones mediating 'autogenetic Ib inhibition', such changes can only be interpreted safely during relatively weak contractions (<10% of MVC, see p. 493). Data on the changes in transmission in lumbar propriospinal pathways during voluntary contractions are therefore limited.

Propriospinally mediated changes in the quadriceps H reflex during weak contractions

Increased facilitation of the quadriceps H reflex during voluntary contraction

At the onset of a weak voluntary contraction of quadriceps, the common peroneal-induced group I facilitation of the quadriceps H reflex was increased over that at rest at the early ISIs of 9 and 10 ms (Fig. 10.16(*b*); Forget *et al.*, 1989a). It was also increased during tonic contraction at the 10-ms ISI when weak peroneal stimulus intensities were used (<0.8 × MT, Fig. 10.16(*e*)). Given the convergence of peroneal and

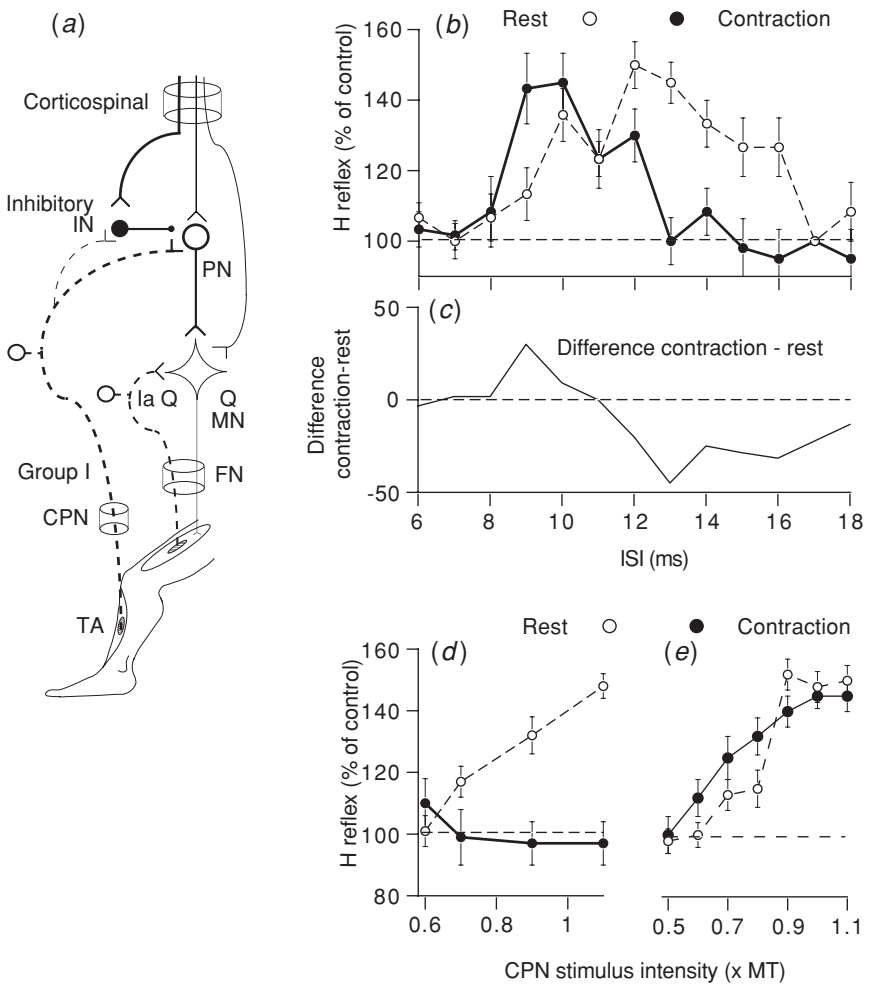


Fig. 10.16. Changes in the CPN facilitation of quadriceps at the onset of a quadriceps voluntary contraction. (*a*) Sketch of the presumed pathways. Corticospinal projections revealed when using TMS are activated at the onset of contraction. Corticospinal fibres have monosynaptic excitatory projections to quadriceps (Q) motoneurones (MNs), propriospinal neurones (PN) and feedback inhibitory interneurones (IN), the latter projection being the more potent, as indicated by the thickest line. (*b*)–(*e*) Changes in the Q H reflex (expressed as a percentage of its unconditioned value) are compared at rest (○) and at the onset of ((*b*)–(*d*)) or during tonic (*e*) voluntary contraction of the quadriceps involving only a few motor units (●). Each symbol represents the mean of 20 measurements. Vertical bars ±1 SEM. (*b*) Time courses of the changes evoked by a common peroneal nerve (CPN) stimulation at 1 × MT at rest and at the onset of contraction. (*c*) Time course of the difference between the changes during contraction and at rest (i.e. the difference between filled and open circles in (*b*)). (*d*), (*e*) Effects of varying the CPN stimulus intensity at the 13 ms ISI at rest and at the onset of contraction (*d*), and at the 10 ms ISI at rest and during tonic contraction (*e*). Modified from Forget *et al.* (1989a), with permission.

femoral volleys onto common propriospinal neurones, it is not surprising that the femoral-induced facilitation of quadriceps motoneurones was similarly enhanced at the onset of a weak quadriceps contraction (Hultborn *et al.*, 1986). Since the conditioning-test stimulus pair was triggered in advance of any afferent discharge evoked by the voluntary contraction, the increased reflex facilitation is presumably of descending origin. There is no unequivocal evidence whether it results from increased excitability of the relevant lumbar propriospinal neurones and/or decreased presynaptic inhibition of group I afferents synapsing with them.

Decreased facilitation of the H reflex

Decreased facilitation of the quadriceps H reflex at the onset of a quadriceps voluntary contraction was however the dominant effect at ISIs >10 ms (Fig. 10.16(*b*)–(*d*)). The time course of the difference between the amount of reflex facilitation during contraction and at rest (Fig. 10.16(*c*)) is reminiscent of the time course representing the peroneal-induced variations of the MEP, with an initial facilitation rapidly truncated by inhibition. At the 10 ms ISI, during tonic contraction, the increased facilitation observed at weak stimulus intensities was reversed to decreased facilitation when the stimulus intensity was >0.8 × MT (Fig. 10.16(*e*)).

Which mechanism?

Occlusion in excitatory pathways between the peripheral volley and the descending excitation could explain the reversal from increased to decreased facilitation at higher stimulus intensities in Fig. 10.16(*e*), but could not easily account for the total absence of facilitation observed at 0.7 × MT at the 13 ms ISI at the onset of a contraction involving only a few motor units (Fig. 10.16(*d*)). This would imply that all propriospinal neurones mediating the peroneal-induced facilitation were then recruited, which is unlikely. A consistent finding was that, as in Fig. 10.16(*d*), increasing the stimulus intensity from 0.7 to 1.1 × MT at the 13 ms ISI caused the excitation to disappear but did not depress the reflex below its unconditioned value (Forget *et al.*, 1989a). This argues against an inhibition exerted directly on motoneurones and suggests, instead, disfacilitation due to descending facilitation of feedback inhibition exerted on propriospinal neurones.

Modulation of the on-going EMG during different motor tasks

Propriospinally mediated excitation produced by deep peroneal nerve stimulation in the rectified quadriceps EMG activity has been compared during different motor tasks, at equivalent EMG activity levels, with co-contraction of quadriceps and pretibial flexors: voluntary contraction and the initial part of the stance phase of gait (Marchand-Pauvert & Nielsen, 2002), or voluntary contraction and active maintenance of posture while leaning backwards (Marchand-Pauvert *et al.*, 2005). The early group I excitation was similar in the different tasks, but there was increased group II excitation during stance and gait. This suggests that the overall excitability of lumbar propriospinal neurones is the same in the different tasks, and that the increased group II excitation may be due to a decrease in the monoaminergic gating of group II pathways (i.e. to disinhibition, see Chapter 7, p. 314). However, during gait, ischaemic blockade of group I afferents causes the group II excitation to disappear, probably because group II excitation requires depolarisation of propriospinal neurones by the group I afferent discharge to manifest itself (see Chapter 7, p. 318).

Functional implications

Quadriceps contractions

During weak quadriceps contractions, the dominant descending effect is facilitation of feedback inhibitory interneurones inhibiting lumbar

propriospinal neurones, and this probably acts to focus the command on the few motoneurones involved in such contractions.

Relaxation of antagonists

Medium-latency propriospinally mediated inhibition of antagonistic motoneurones contributes significantly to the relaxation of the antagonists during flexion-extension movements (see Chapter 11, pp. 519–20).

Stance phase of walking

(i) The group I discharge from the pretibial flexors is needed to depolarise propriospinal neurones so that the increased group II excitation mediated through the same interneuronal pathway can manifest itself.

(ii) It is also important that soleus activity be overcome by dorsiflexion forces if the body is to be brought forward when walking (see Chapter 11, p. 547). Propriospinally mediated group I inhibition from intrinsic plantar muscles could be one of the mechanisms which allows this to occur: it is activated in mid-stance by group I discharges from contracting plantar muscles, and is facilitated by cutaneous afferents from the sole of the foot (Abbruzzese, Rubino & Schieppati, 1996).

Studies in patients and clinical implications

Spasticity

Stroke patients

The peroneal-induced facilitation of the quadriceps H reflex is similar in normal subjects and on the unaffected side of stroke patients, but is more prominent on the affected side (Fig. 10.17(*b*); Marque *et al.*, 2001b). Because the greater facilitation involves the early group I (ISI, 10 ms) and the late group II (ISI, 16–20 ms) peaks of excitation to the same extent, a common underlying mechanism is probable. A good candidate would be increased excitability of the propriospinal neurones co-activated by group I and II afferents, due to interruption of the strong corticospinal control on feedback inhibitory interneurones (see Chapter 7, pp. 322–4).

Patients with spinal cord lesions

Peroneal facilitation of the quadriceps H reflex

Facilitation of the quadriceps H reflex by common peroneal nerve stimulation is also increased in patients with spinal cord lesions (Rémy-Néris *et al.*, 2003). The increase was sometimes limited to the early group I peak (Fig. 10.17(*c*)), but more often both the group I and group II peaks were significantly enhanced, with a greater increase in the late group II peak (Fig. 10.17(*d*)). Here again, the finding that both peaks are increased suggests an increase in the excitability of the propriospinal neurones resulting from a change in their descending control. The larger increase in the late group II-mediated excitation is considered in Chapter 7 (pp. 324–5).

PSTHs of single soleus units

In soleus motor units, a longer-latency excitation elicited by stimuli below 1 × MT, presumably group I in origin, has been observed in patients with traumatic spinal cord lesions (Mailis & Ashby, 1990). It was assumed to be mediated by the same neurones as the propriospinally mediated excitation described above, but this is doubtful, given its much longer central delay (11–15 ms).

Patients with Parkinson's disease

No change in the early group I propriospinally mediated excitation of quadriceps motoneurones has been found in patients with Parkinson's disease (Simonetta-Moreau *et al.*, 2002; Chapter 7, p. 326).

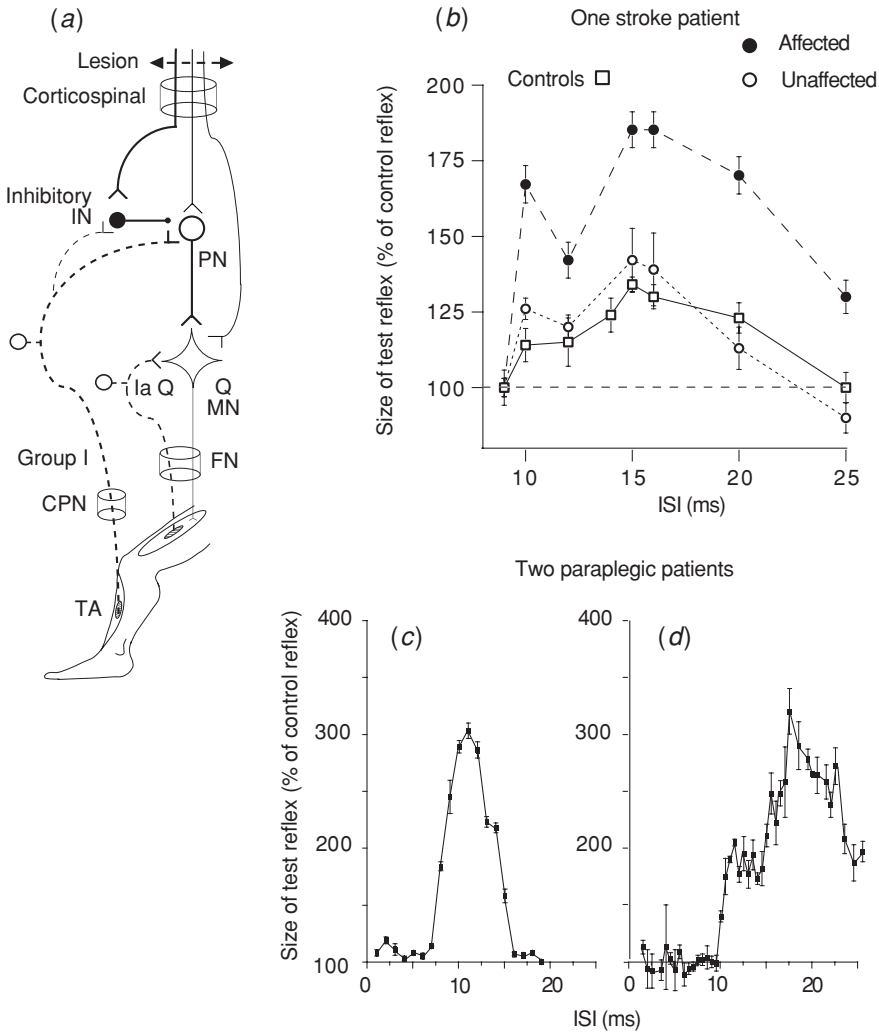


Fig. 10.17. Changes in the CPN facilitation of quadriceps motoneurones in spastic patients. (*a*) Sketch of the presumed pathways. Corticospinal projections revealed by TMS are interrupted by the lesion (horizontal dashed arrow) in spastic patients. The net result of the corticospinal lesion would be disfacilitation of feedback inhibitory interneurones (IN) inhibiting propriospinal neurones (PN). (*b*)–(*d*) Changes in the quadriceps H reflex (expressed as a percentage of its unconditioned value) elicited by common peroneal nerve stimulation at 3 × MT (*b*) or 2 × MT ((*c*), (*d*)) are plotted against the interstimulus interval (ISI). (*b*) Changes are compared in a healthy subject (□, continuous line) and on the affected (●, dashed line) and unaffected (○, dotted line) sides of a stroke patient. Each symbol represents the mean of 20 measurements. (*c*), (*d*) Data for two paraplegic patients ((*c*) and (*d*)). Vertical bars ±1 SEM. Modified from Marque *et al.* (2001b) (*b*) and from Rémy-Néris *et al.* (2003) ((*c*), (*d*)), with permission.

Conclusions

Organisation of the lumbar propriospinal system

Striking differences exist between the organisation of the lumbar and cervical propriospinal systems.

(i) The peripheral group I excitatory input appears to be much stronger to lumbar propriospinal neurones, though this could be specific to the common peroneal nerve–quadriceps combination.

(ii) Peripheral excitation is not counteracted by 'homonymous' inhibitory feedback, unless the corticospinal system is activated.

(iii) In the absence of cortical stimulation, there is no evidence for cutaneous inhibition of the relevant interneurones. Corticospinal excitation of feedback inhibitory interneurones seems to be stronger than that of the propriospinal neurones themselves.

Voluntary contractions

The main descending input during weak voluntary contractions seems to be to feedback inhibitory interneurones, presumably to focus the command on the few motoneurones involved in the contraction.

Changes in patients

The excitability of propriospinal neurones is increased in spastic patients, probably because of the disruption of the strong corticospinal control on feedback inhibitory interneurones.

Résumé

Background from animal experiments

Two systems of short-axoned lumbar propriospinal neurones have been described: (i) dorsolateral, located in L3–L5, projecting to distal motoneurones, the input of which is mainly (if not exclusively) from the corticospinal and rubrospinal tracts; (ii) ventrolateral, located in L2–L4, projecting to proximal motoneurones with a strong input from peripheral afferents (in particular group II afferents) and from vestibulospinal and reticulospinal tracts.

Methodology

Most studies have been limited to the facilitation of quadriceps motoneurones by volleys in the common peroneal nerve, though, as at cervical level, the distribution of propriospinally mediated excitation is quite diffuse. Group I volleys evoke in the PSTHs of lower limb motor units an excitation occurring with a central delay that is 3–6 ms longer than the monosynaptic Ia latency. The more caudal the motoneurone pool in the spinal cord, the longer central delay, again suggesting mediation through premotoneurones located rostral to motoneurones. Peroneal-induced facilitation of the quadriceps H reflex occurs with a 3–3.5-ms central delay. Over its first 3 ms, this facilitation is purely group I in origin. With allowance for the difference in the lengths of the afferent pathways, the amount of group I facilitation can be measured at the 10-ms ISI to assess the excitability of the lumbar propriospinal neurones. The suppression of the H reflex produced by the convergence of peroneal and femoral test volleys onto interneurones mediating autogenetic 'Ib inhibition' constitutes an important limitation of the method during quadriceps contractions of 10% of MVC. Facilitation of the on-going quadriceps EMG by common peroneal nerve stimulation is a simple method, which can be used to compare propriospinally mediated excitation during different motor tasks.

Organisation and pattern of connections

Peripheral excitation of lumbar propriospinal neurones

This peripheral excitation differs from that to cervical propriospinal neurones in several respects.

(i) Lumbar propriospinal neurones are co-activated by group I and II afferents.

(ii) The peripheral excitation is considerably stronger, even taking into account that it is not counteracted by 'homonymous' inhibition.

(iii) Group I afferents from quadriceps and pretibial flexors converge onto common propriospinal neurones. However, both the potency of the group I excitation and the above convergence could be specific to the common peroneal nerve-quadriceps combination, the only one so far investigated in detail.

Peripheral inhibition of lumbar propriospinal neurones

In the absence of TMS, inhibition of propriospinal neurones has not been found after cutaneous stimulation and is weak and usually absent in homonymous group I pathways. As a result the facilitation can increase with the stimulus intensity far above $1 \times$ MT, at least in the common peroneal nerve–quadriceps combination. By contrast, 'lateral' inhibition between the effects elicited by two different nerves is often found.

Inhibition of motoneurones

Inhibition of motoneurones has been regularly observed in motoneurones of leg and thigh extensors after stimulation of the tibial nerve but, despite its low threshold and long latency, its pathway remains uncertain. During voluntary dorsiflexion of the foot, there is a 'longer-latency' inhibition of soleus motoneurones. This inhibition is superimposed on the disynaptic reciprocal Ia inhibition, occurs only during active dorsiflexion and, although fed by group I afferents, is mainly of supraspinal origin.

Corticospinal excitation

TMS produces activation of both propriospinal neurones and inhibitory interneurones projecting to propriospinal neurones. On combined stimulation, the latter effect dominates.

Motor tasks and physiological implications

During weak contractions, the dominant descending effect is facilitation of feedback inhibitory interneurones inhibiting propriospinal neurones, probably to focus the command to the few motoneurones involved in such contractions. During gait, the peroneal group I discharge is needed to depolarise propriospinal neurones so that the increased group II excitation of quadriceps motoneurones mediated through the same interneuronal pathway can manifest itself.

Studies in patients and clinical implications

The excitability of propriospinal neurones is increased in spastic patients, whether the corticospinal lesion is hemispheric or spinal. This increased group I-induced excitability could be due to the disruption of the strong corticospinal control on feedback inhibitory interneurones. The greater increase in excitation in patients with spinal cord injury is considered in Chapter 7. There is no change in propriospinal group I excitation in parkinsonian patients.

REFERENCES

Abbruzzese, G., Rubino, V. & Schieppati, M. (1996). Task-dependent effects evoked by foot muscle afferents on leg muscle activity in humans. *Electroencephalography and Clinical Neurophysiology*, **101**, 339–48.

Alstermark, B. & Kümmel, H. (1990). Transneuronal transport of wheat germ agglutinin conjugated horseradish peroxidase into last order spinal interneurones projecting to acromio- and spinodeltoideus motoneurones in the cat. *Experimental Brain Research*, **80**, 90–103.

Alstermark, B. & Lundberg, A. (1992). The C3–C4 propriospinal system: target-reaching and food-taking. In *Muscle Afferents and Spinal Control of Movement*, ed. L. Jami, E. Pierrot-Deseilligny & D. Zytnicki, pp. 327–54. Oxford: Pergamon Press.

Alstermark, B. & Sasaki, S. (1986). Integration in descending motor pathways controlling the forelimb in the cat. 14. Differential projection to fast and slow motoneurones from excitatory C3–C4 propriospinal neurones. *Experimental Brain Research*, **63**, 530–42.

Alstermark, B., Lindström, S., Lundberg, A. & Sybirska, E. (1981a). Integration in descending motor pathways controlling the forelimb in the cat. 8. Ascending projection to the lateral reticular nucleus from C3–C4 propriospinal neurones also projecting to forelimb motoneurones. *Experimental Brain Research*, **42**, 282–98.

Alstermark, B., Lundberg, A., Norrsell, U. & Sybirska, E. (1981b). Integration in descending motor pathways controlling the forelimb in the cat. 9. Differential behavioural defects after spinal cord lesions interrupting defined pathways from higher centres to motoneurones. *Experimental Brain Research*, **42**, 299–318.

Alstermark, B., Lundberg, A. & Sasaki, S. (1984a). Integration in descending motor pathways controlling the forelimb in the cat. 10. Inhibitory pathways to forelimb motoneurones via C3–C4 propriospinal neurones. *Experimental Brain Research*, **56**, 279–92.

(1984b). Integration in descending motor pathways controlling the forelimb in the cat. 11. Inhibitory pathways from higher motor centres and forelimb afferents to C3–C4 propriospinal neurones. *Experimental Brain Research*, **56**, 293–307.

(1984c). Integration in descending motor pathways controlling the forelimb in the cat. 12. Interneurones which may mediate descending feed-forward inhibition and feed-back inhibition from the forelimb to C3–C4 propriospinal neurones. *Experimental Brain Research*, **56**, 308–22.

Alstermark, B., Gorska, T., Johannisson, T. & Lundberg, A. (1986). Hypermetria in forelimb target-reaching after interruption of the inhibitory pathway from forelimb afferents to C3–C4 propriospinal neurones. *Neuroscience Research*, **3**, 457–61.

Alstermark, B., Kümmel, H., Pinter, M. J. & Tantisira, B. (1990). Integration in descending motor pathways controlling the forelimb in the cat. 17. Axonal projection and termination of C3–C4 propriospinal neurones in the C6–Th1 segments. *Experimental Brain Research*, **81**, 447–61.

Alstermark, B., Isa, T., Ohki, T. & Saito, T. (1999). Disynaptic pyramidal excitation in forelimb motoneurones mediated via C3–C4 propriospinal neurones in *Macaca fuscata*. *Journal of Neurophysiology*, **82**, 3580–5.

Araki, T., Eccles, J. C. & Ito, M. (1960). Correlation of the inhibitory post-synaptic potential of motoneurones with the latency and time course of inhibition of monosynaptic reflexes. *Journal of Physiology (London)*, **154**, 354–77.

Bawa, P. & Lemon, R. N. (1993). Recruitment of motor units in response to transcranial magnetic stimulation in man. *Journal of Physiology (London)*, **471**, 445–64.

Benecke, R., Meyer, B. U. & Freund, H. J. (1991). Reorganisation of descending motor pathways in patients after hemispherectomy and severe hemispheric lesions demonstrated by magnetic brain stimulation. *Experimental Brain Research*, **83**, 419–26.

Burke, D. (2001). Clinical relevance of the putative C3–4 propriospinal system in humans. *Muscle and Nerve*, **24**, 1437–9.

Burke, D., Gracies, J. M., Mazevet, D., Meunier, S. & Pierrot-Deseilligny, E. (1992a). Convergence of descending and various peripheral inputs onto common propriospinal-like neurones in man. *Journal of Physiology (London)*, **449**, 655–71.

Burke, D., Gracies, J. M., Meunier, S. & Pierrot-Deseilligny, E. (1992b). Changes in presynaptic inhibition of afferents to propriospinal-like neurones in man during voluntary contractions. *Journal of Physiology (London)*, **449**, 673–87.

Burke, D., Gracies, J. M., Mazevet, D., Meunier, S. & Pierrot-Deseilligny, E. (1994). Non monosynaptic transmission of the cortical command for voluntary movement in man. *Journal of Physiology (London)*, **480**, 191–207.

Chaix, Y., Marque, P., Meunier, S., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1997). Further evidence for non-monosynaptic group I excitation of motoneurones in the human lower limb. *Experimental Brain Research*, **115**, 35–46.

Cheney, P. D. & Fetz, E. E. (1980). Functional classes of primate corticomotoneuronal cells and their relation to active force. *Journal of Neurophysiology*, **44**, 773–91.

Crone, C. (1993). *Reciprocal Ia Inhibition in Man*. 16 pp. Copenhagen: Laegeforeningens Forlag.

Crone, C. & Nielsen, J. (1989). Spinal mechanisms in man contributing to reciprocal inhibition during voluntary dorsiflexion of the foot. *Journal of Physiology (London)*, **416**, 255–72.

Crone, C., Hultborn, H., Jespersen, B. & Nielsen, J. (1987). Reciprocal Ia inhibition between ankle flexors and extensors in man. *Journal of Physiology (London)*, **389**, 163–85.

Crone, C., Hultborn, H., Mazières, L., Morin, C., Nielsen, J. & Pierrot-Deseilligny, E. (1990). Sensitivity of monosynaptic test reflexes to facilitation and inhibition as a function of the test reflex size: a study in man and the cat. *Experimental Brain Research*, **81**, 35–45.

Davies, H. E. & Edgley, S. A. (1994). Inputs to group II-activated midlumbar interneurones from descending motor pathways in the cat. *Journal of Physiology (London)*, **479**, 463–73.

Dietz, V. (2002). Do human bipeds use quadrupedal coordination? *Trends in Neurosciences*, **25**, 462–7.

Forget, R., Hultborn, H., Meunier, S., Pantieri, R. & Pierrot-Deseilligny, E. (1989a). Facilitation of quadriceps motoneurones by group I afferents from pretibial flexors in man. 2. Changes occurring during voluntary contraction. *Experimental Brain Research*, **78**, 21–7.

Forget, R., Pantieri, R., Pierrot-Deseilligny, E., Shindo, M. & Tanaka, R. (1989b). Facilitation of quadriceps motoneurones by group I afferents from pretibial flexors in man. 1. Possible interneuronal pathway. *Experimental Brain Research*, **78**, 10–20.

Fournier, E., Meunier, S., Pierrot-Deseilligny, E. & Shindo, M. (1986). Evidence for interneuronally mediated Ia excitatory effects to human quadriceps motoneurones. *Journal of Physiology (London)*, **377**, 143–69.

Gracies, J. M., Meunier, S., Pierrot-Deseilligny, E. & Simonetta, M. (1991). Pattern of propriospinal-like excitation to different species of human upper limb motoneurones. *Journal of Physiology (London)*, **434**, 151–67.

Gracies, J. M., Meunier, S. & Pierrot-Deseilligny, E. (1994). Evidence for corticospinal excitation of presumed propriospinal neurones in man. *Journal of Physiology (London)*, **475**, 509–18.

Hallett, M. (2001). Plasticity of the human motor cortex and recovery from stroke. *Brain Research Reviews*, **36**, 169–74.

Hultborn, H., Meunier, S., Pierrot-Deseilligny, E. & Shindo, M. (1986). Changes in polysynaptic Ia excitation to quadriceps motoneurones during voluntary contraction in man. *Experimental Brain Research*, **63**, 436–8.

Illert, M., Lundberg, A. & Tanaka, R. (1977). Integration in descending motor pathways controlling the forelimb in the cat. 3. Convergence on propriospinal neurones transmitting disynaptic excitation from the corticospinal tract and other descending tracts. *Experimental Brain Research*, **29**, 323–46.

Illert, M., Lundberg, A., Padel, Y. & Tanaka, R. (1978). Integration in descending motor pathways controlling the forelimb in the cat. 5. Properties of and monosynaptic excitatory convergence on C3–C4 propriospinal neurones. *Experimental Brain Research*, **33**, 101–30.

Jankowska, E. (1992). Interneuronal relay in spinal pathways from proprioceptors. *Progress in Neurobiology*, **38**, 335–78.

Kirkwood, P. A., Maier, M. A. & Lemon, R. N. (2002). Interspecies comparisons for the C3–C4 propriospinal system: unresolved issues. *Advances in Experimental Medicine and Biology*, **508**, 299–308.

Kostyuk, P. G. (1967). Neuronal mechanisms of cortico-spinal motor systems. *Sechenov Physiological Journal of USSR*, **53**, 1311–21 (in Russian).

Kozhanov, V. M. & Shapovalov, A. L. (1977). Synaptic organization of the supraspinal control of propriospinal ventral horn interneurons in cat and monkey cord. *Neurophysiology USSR*, **1**, 5–14.

Lemon, R. N. (1999). Pathways for corticospinal control of motoneurones in man and other primates. *Journal of Physiology (London)*, **518**, 31S.

Lloyd, D. P. C. (1941a). Activity in neurons of the bulbospinal correlation system. *Journal of Neurophysiology*, **4**, 115–34.

(1941b). Spinal mechanism of the pyramidal system in cats. *Journal of Neurophysiology*, **4**, 525–46.

Lourenço, G., Simonetta-Moreau, M., Pierrot-Deseilligny, E. & Marchand-Pauvert, V. (2005). Cortical control of spinal reflex pathways in the human lower limb. *Electroncephalography and Clinical Neurophysiology*, in preparation.

Lundberg, A. (1992). To what extent are brain commands for movements mediated by spinal interneurones? *Behavioral and Brain Sciences*, **15**, 775.

(1999). Descending control of forelimb movements in the cat. *Brain Research Bulletin*, **50**, 323–4.

Maertens de Noordhout, A., Rothwell, J. C., Day, B. L. *et al.* (1992). Effect of digital nerve stimuli on responses to electrical or magnetic stimulation of the human brain. *Journal of Physiology (London)*, **447**, 535–48.

Maertens de Noordhout, A., Rapisarda, G., Bogacz, D. *et al.* (1999). Corticomotoneuronal synaptic connections in normal man. An electrophysiological study. *Brain*, **122**, 1327–40.

Maier, M., Illert, M., Kirkwood, P. A., Nielsen, J. & Lemon, R. N. (1998). Does a C3–C4 propriospinal system transmit corticospinal excitation in the primate? An investigation in the macaque monkey. *Journal of Physiology (London)*, **511**, 191–212.

Mailis, A. & Ashby, P. (1990). Alterations in group Ia projections to motoneurones following spinal lesions in humans. *Journal of Neurophysiology*, **64**, 637–47.

Malmgren, K. & Pierrot-Deseilligny, E. (1987). Evidence that low threshold afferents both evoke and depress polysynaptic excitation of wrist flexor motoneurones in man. *Experimental Brain Research*, **67**, 429–32.

(1988a). Evidence for non-monosynaptic Ia excitation of wrist flexor motoneurones, possibly via propriospinal neurones. *Journal of Physiology (London)*, **405**, 747–64.

(1988b). Inhibition of neurones transmitting non-monosynaptic Ia excitation to human wrist flexor motoneurones. *Journal of Physiology (London)*, **405**, 765–83.

Marchand-Pauvert, V. & Nielsen, J. B. (2002). Modulation of non-monosynaptic excitation from ankle dorsiflexor afferents to quadriceps motoneurones during human gait. *Journal of Physiology (London)*, **538**, 647–57.

Marchand-Pauvert, V., Mazevet, D., Pierrot-Deseilligny, E., Pol, S. & Pradat-Diehl, P. (1999a). Handedness related asymmetry in non-monosynaptic transmission of cortical excitation to human forearm motoneurones. *Experimental Brain Research*, **125**, 323–34.

Marchand-Pauvert, V., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (1999b). Cortical control of spinal pathways mediating group II excitation to thigh motoneurones. *Journal of Physiology (London)*, **517**, 301–13.

Marchand-Pauvert, V., Mazevet, D., Nielsen, J., Petersen, N. & Pierrot-Deseilligny, E. (2000). Distribution of non-monosynaptic excitation to early and late recruited units in human forearm muscles. *Experimental Brain Research*, **134**, 274–8.

Marchand-Pauvert, V., Mazevet, D., Pradat-Diehl, P., Alstermark, B. & Pierrot-Deseilligny, E. (2001). Interruption of a relay of corticospinal excitation by a spinal lesion at C6–C7. *Muscle and Nerve*, **24**, 1554–61.

Marchand-Pauvert, V., Nicolas, G., Burke, D. & Pierrot-Deseilligny, E. (2002). Suppression of the H reflex by disynaptic autogenetic inhibitory pathways activated by the test volley. *Journal of Physiology (London)*, **542**, 963–76.

Marchand-Pauvert, V., Marque, P., Nicolas, G., Iglesias, C. & Pierrot-Deseilligny, E. (2005). Posture-related increase in group II excitation from pretibial flexors to quadriceps motoneurones. *Journal of Physiology (London)* (in press).

Marque, P., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1996). Evidence for excitation of the human lower limb motoneurones by group II muscle afferents. *Experimental Brain Research*, **109**, 357–60.

Marque, P., Nicolas, G., Marchand-Pauvert, V., Gautier, J., Simonetta-Moreau, M. & Pierrot-Deseilligny, E. (2001a). Group I projections from intrinsic foot muscles to motoneurones of leg and thigh muscles in humans. *Journal of Physiology (London)*, **536**, 313–27.

Marque, P., Simonetta-Moreau, M., Maupas, E. & Roques, C. F. (2001b). Facilitation of transmission in heteronymous group II pathways in spastic hemiplegic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 36–42.

Mazevet, D. & Pierrot-Deseilligny, E. (1994). Pattern of descending excitation of presumed propriospinal neurones at the onset of voluntary movement in man. *Acta Physiologica Scandinavica*, **150**, 27–38.

Mazevet, D., Pierrot-Deseilligny, E. & Rothwell, J. C. (1996). A propriospinal contribution to EMG responses evoked in wrist extensor muscles by transcranial stimulation of the motor cortex in man. *Experimental Brain Research*, **109**, 495–9.

Mazevet, D., Meunier, S., Pradat-Diehl, P., Marchand-Pauvert, V. & Pierrot-Deseilligny, E. (2003). Changes in propriospinally-mediated excitation of upper limb motoneurones in stroke patients. *Brain*, **126**, 988–1000.

Meunier, S., Pierrot-Deseilligny, E. & Simonetta-Moreau, M. (1994). Pattern of heteronymous recurrent inhibition in the human lower limb. *Experimental Brain Research*, **102**, 149–59.

Muir, R. B. & Lemon, R. N. (1983). Corticospinal neurons with a special role in the precision grip. *Brain Research*, **261**, 312–16.

Nakajima, K., Maier, M. A., Kirkwood, P. A. & Lemon, R. N. (2000). Striking differences in transmission of corticospinal excitation to upper limb motoneurones in two primate species. *Journal of Neurophysiology*, **84**, 698–709.

Nicolas, G., Marchand-Pauvert, V., Burke, D. & Pierrot-Deseilligny, E. (2001). Corticospinal excitation of presumed cervical propriospinal neurones and its reversal to inhibition in humans. *Journal of Physiology (London)*, **533**, 903–19.

Nielsen, J. & Petersen, N. (1994). Is presynaptic inhibition distributed to corticospinal fibres in man? *Journal of Physiology (London)*, **477**, 47–58.

Nielsen, J. & Pierrot-Deseilligny, E. (1991). Pattern of cutaneous inhibition of the propriospinal-like excitation to human upper limb motoneurones. *Journal of Physiology (London)*, **434**, 169–82.

Nielsen, J., Morita, H., Baumgarten, J., Petersen, N. & Christensen, L. O. (1999). On the comparability of H-reflexes and MEPs. *Electroencephalography and Clinical Neurophysiology*, **Suppl. 51**, 93–101.

Olivier, E., Baker, S. N., Nakajima, K., Brochier, T. & Lemon, R. N. (2001). Investigation into non-monosynaptic corticospinal excitation of macaque upper limb single motor units, *Journal of Neurophysiology*, **86**, 1573–86.

Pauvert, V., Pierrot-Deseilligny, E. & Rothwell, J. C. (1998). Role of spinal premotoneurones in mediating corticospinal input to forearm motoneurones in man. *Journal of Physiology (London)*, **508**, 301–12.

Pierrot-Deseilligny, E. (1996). Transmission of the cortical command for human voluntary movement through cervical premotoneurones. *Progress in Neurobiology*, **48**, 489–517.

(2002). Propriospinal transmission of part of the corticospinal excitation in humans. *Muscle and Nerve*, **26**, 155–72.

Pierrot-Deseilligny, E. & Mazevet, D. (1993). Propriospinal transmission of voluntary movement in humans. In *Spasticity: Mechanisms and Management*, ed. A. Thilmann, D. J. Burke, & W. Z. Rymer, pp. 40–56. Berlin: Springer.

Pierrot-Deseilligny, E., Morin, C., Bergego, C. & Tankov, N. (1981). Pattern of group I fibre projections from ankle flexor and extensor muscles in man. *Brain Research*, **42**, 337–50.

Pierrot-Deseilligny, E., Mazevet, D. & Meunier, S. (1995). Cutaneous inhibition of the descending command passing through the propriospinal relay might contribute to curtail human movements. In *Alpha and Gamma Motor System*, ed. A. Taylor, M. H. Gladden & R. Durbaba, pp. 607–15. New York: Plenum.

Pol, S., Vidailhet, M., Meunier, S., Mazevet, D., Agid, Y. & Pierrot-Deseilligny, E. (1998). Overactivity of cervical premotoneurones in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **64**, 166–71.

Rémy-Néris, O., Denys, P., Daniel, O., Barbeau, H. & Bussel, B. (2003). Effect of intrathecal clonidine on excitation transmitted by interneurones activated by groups I-II afferents in paraplegics. *Experimental Brain Research*, **148**, 509–14.

Rothwell, J. C. (2002). Spinal interneurones: reevaluation and controversy. *Advances in Experimental Medicine and Biology*, **508**, 259–63.

Sasaki, S., Isa, T., Pettersson, L. G. *et al.* (2004). Dexterous finger movements in primate without monosynaptic corticomotoneuronal excitation. *Journal of Neurophysiology*, **92**, 3142–7.

Schomburg, E. D. (1990). Spinal sensorimotor systems and their supraspinal control. *Neuroscience Research*, **7**, 265–340.

Shapovalov, A. I. (1975). Neuronal organization and synaptic mechanisms of supraspinal motor control in vertebrates. *Reviews of Physiological and Biochemical Pharmacology*, **72**, 1–54.

Simonetta-Moreau, M., Marque, P., Marchand-Pauvert, V. & Pierrot-Deseilligny, E. (1999). The pattern of excitation of human lower limb motoneurones by probable group II muscle afferents. *Journal of Physiology (London)*, **517**, 287–300.

Simonetta-Moreau, M., Meunier, S., Vidailhet, M., Pol, S., Galitzky, M. & Rascol, O. (2002). Transmission of group II heteronymous pathways is enhanced in rigid lower limb of de novo patients with Parkinson's disease. *Brain*, **125**, 2125–33.

Stinear, J. W. & Byblow, W. D. (2004). The contribution of cervical propriospinal premotoneurons in recovering hemiparetic stroke patients. *Journal of Clinical Neurophysiology*, **21**, 426–34.

Taylor, B. A., Ridding, M. C. & Rothwell, J. C. (1995). Some evidence for a mid-thoracic nucleus in the human motor pathway. In *Alpha and Gamma Motor Systems*, ed. A. Taylor, M. H. Gladden & R. Durbaba, pp. 629–31. New York: Plenum.

Turton, A., Wroe, S., Trepte, N., Fraser, C. & Lemon, R. N. (1996). Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. *Electroencephalography and Clinical Neurophysiology*, **101**, 316–28.

11

Involvement of spinal pathways in different motor tasks

If one excludes discrete movements of the fingers (cf. p. 522), most motor tasks are accompanied by changes in transmission in spinal pathways, due to both the descending activity and changes in the peripheral afferent feedback related to the movement itself ('reafference'). Both types of input are largely mediated through common spinal interneurones (cf. Jankowska & Lundberg, 1981). In the preceding chapters, changes in transmission in segmental spinal pathways during various motor tasks have been described, and the presumed origin of these changes discussed. In addition, because of the focusing due to the stronger inhibitory control of propriospinal neurones in primates, it has been suggested that the propriospinal system might be used for a more diversified motor repertoire than in the cat (Chapter 10, see Lemon *et al.*, 2004). The present chapter presents an overview of the relative contributions of different spinal pathways to various natural motor tasks: isometric tonic contractions, flexion–extension movements at hinge and ball joints, coordination of multi-joint movements, co-contractions of antagonists at the same joint, postural adjustments, and gait. Despite the risk inherent in speculation, it is important to present an overview of the role of spinal cord circuits in the control of movement. This includes (i) a description of the relative contribution made by spinal pathways to the different features of movement in various motor tasks, and (ii) an attempt to show how these pathways work together harmoniously to achieve the movement. Experimental data on which this overview relies have been discussed in the preceding chapters, and reference to the relevant sections is made. Reference is also made to original data and some papers which were not considered in the preceding chapters.

Absence of redundancy

A given motor task, for example, the excitation of the agonists and the inhibition of the antagonists during flexion–extension movements at hinge joints, is accompanied by changes in transmission in several pathways. This might give the impression that there is some functional redundancy between the different spinal circuits. In fact, as discussed below, the different features of the movement (such as force, smoothness, selectivity, resistance to fatigue, timing, etc.) are not controlled to the same extent and at the same stage of the movement by the same pathways. In pathological conditions, the function of one spinal pathway may be partially taken over by another pathway (see Chapter 12), but the smooth development of force and accurate achievement of the desired trajectory of a movement still require the integrity of the different pathways.

It must be emphasised that several reasons make the overview presented below speculative

(i) Most of the available data dealing with changes in transmission in spinal pathways during voluntary 'movements' were obtained during isometric contractions.

(ii) Given the different descending control of some spinal pathways in the cervical and lumbar enlargements, extrapolations from lumbar to cervical level are uncertain.

(iii) It cannot be taken for granted that spinal interneurones respond similarly to the phasic

artificial volleys generally used in the experiments described in the previous chapters and to a tonic input, as in the normal *modus operandi* of the central nervous system. In this respect, the newer techniques of cross-correlation and coherence analysis should allow further development of neuronal signals to be studied without external interference (see pp. 48–9).

(iv) Experiments described in the earlier chapters do not necessarily provide a quantitative assessment of the normal input to motoneurones, e.g. a reduction by half of the motoneurone pool response when suppressing an input does not imply that the input provided 50% of the excitatory drive to motoneurones. The motoneurone discharge is produced by the spatial and temporal summation of several inputs, and removal of any one could have a large effect (e.g. see pp. 316, 474).

Isometric tonic contractions

Contraction under near-isometric circumstances occurs during many motor tasks, e.g. carrying luggage, grasping an object while displacing it, or postural contractions of trunk and lower limb muscles. The excitation of agonist motoneurones is initiated by descending tracts, but their maintained activity may be favoured by different spinal mechanisms (cf. Fig. 11.1(*a*), (*b*)): (i) fusimotor-driven spindle afferent feedback, (ii) cutaneomuscular responses, and (iii) suppression of the transmission in some inhibitory pathways. Many isometric contractions involve co-contraction of antagonistic muscles (see pp. 531–5).

Fusimotor-driven inflow from primary and secondary endings

Activation of α motoneurones

Ample evidence has been provided that, during tonic isometric contractions: (i) there is an enhanced inflow from primary and secondary spindle endings driven by fusimotor neurones, (ii) this afferent inflow has an overall autogenetic excitatory effect at spinal level and contributes significantly to maintaining the firing of α motoneurones, but (iii) it has a limited role in compensating for muscle fatigue (see pp. 133–5). This excitatory effect is not limited to homonymous motoneurones. Heteronymous Ia and group II excitatory connections are widespread and often bidirectional in the lower limb and strong from distal to proximal muscles in the upper limb, and their existence contributes to appropriate contractions of the synergistic muscles involved in a given task (see pp. 528–9).

Servo-assistance through monosynaptic Ia connections

The background discharge of spindles provides them with a dynamic working range, because their discharge can increase and decrease in response to external load variations. However, the 'servo assistance' from Ia afferent discharges is limited by post-activation depression (see pp. 96–9) and presynaptic inhibition of Ia terminals (see p. 358), both of which would keep the efficacy of the Ia fibre-motoneurone synapse at a relatively low level during voluntary movements. The resulting low gain for the stretch reflex helps to prevent oscillations and clonus from developing (see Matthews, 1972; Rack, 1981).

Servo-assistance through group II pathways

Group II excitation is not limited by post-activation depression, which is probably absent at synapses between spindle group II afferents and the relevant interneurones (see pp. 292, 310). Fusimotor activation of primary and secondary endings in γ_s-assisted contractions can produce multiple mutual reinforcing interactions between the discharges from the two receptors, because lumbar propriospinal neurones mediating group II excitation are co-activated by Ia afferents and transmit part of the corticospinal command to motoneurones (see Chapter 7; see Fig. 11.1(*b*)). Thus: (i) both

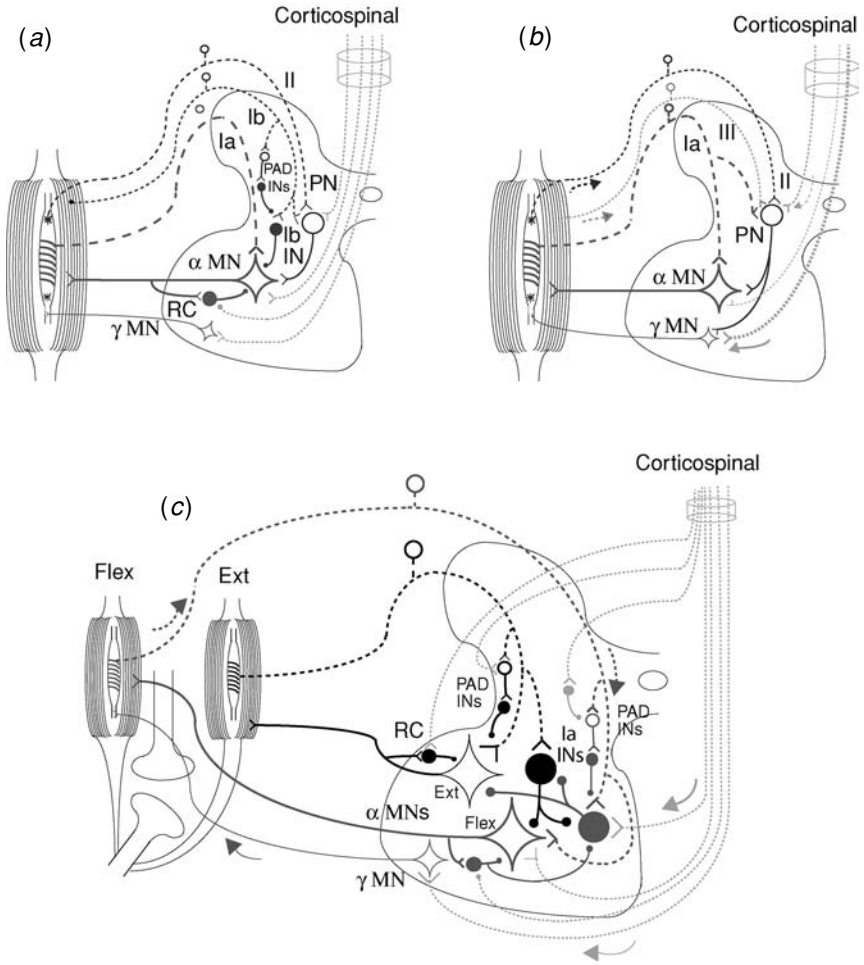


Fig. 11.1. Changes in transmission in spinal pathways during voluntary contraction at a hinge joint. In this and subsequent figures, excitatory synapses are represented by Y-shaped bars and inhibitory synapses by small filled circles, excitatory interneurones by open circles and inhibitory interneurones by large filled circles. α and γ motoneurones (MN) of a contracting flexor muscle, Renshaw cells (RC), Ia afferents ((*a*)–(*c*) with their presynaptic inhibition (PAD INs, (*c*)) and Ia inhibitory interneurones (Ia IN) to antagonist extensor MNs (*c*) sketched in red; corresponding pathways of the extensor in black (*c*). Group II afferents exciting MNs through propriospinal neurones (PN) in blue ((*a*), (*b*)). Ib afferents, with their presynaptic inhibition (PAD INs), and Ib inhibitory INs in brown (*a*). Group muscle III afferents converging on PNs in violet (*b*). Descending tracts (corticospinal) in green. (*a*) Changes in some spinal pathways contributing to agonist excitation. The descending command (i) activates α MNs, γ MNs and PNs, all of which are also affected by afferent inputs, (ii) inhibits RCs, and (iii) suppresses transmission in Ib inhibitory pathways (Ib IN) by presynaptic gating (PAD INs). (*b*) The 'FRA hypothesis': a movement, initiated by descending activation of MNs and/or PNs (thin dotted green arrow), is subsequently maintained by the combined effect of group II afferents (dotted blue arrow) driven by descending activation of γ_s MNs (thick continuous green arrow) and by the contraction-induced group III afferent activity (dotted violet arrow). [Note that this hypothesis has so far not been supported by experimental evidence.] (*c*) Inhibition of antagonist extensor MNs during voluntary flexion. Flexor-coupled Ia INs (red) project both to extensor MNs and the 'opposite' (extensor-coupled) Ia INs (black), and are inhibited from corresponding RCs. The descending command (green arrows) (i) activates flexor α MNs, γ MNs and corresponding flexor-coupled Ia INs, which are also excited by the Ia discharge through the γ loop (red arrows), but (ii) depresses flexor-coupled RCs and presynaptic inhibition (PAD INs) on flexor Ia terminals. In contrast, extensor MNs and corresponding extensor-coupled Ia INs are inhibited by the flexor-coupled Ia INs, while the descending command facilitates extensor-coupled RCs and presynaptic inhibition (PAD INs) on extensor Ia terminals. The pathway of propriospinally mediated reciprocal inhibition has been omitted.

Ia and group II discharges contribute to the activation of the relevant interneurones; (ii) at motoneuronal level, servo-assistance given by Ia monosynaptic connections depends on depolarisation of α motoneurones evoked through interneurones supported by secondary spindle afferents and vice versa.

An hypothesis regarding the role of group II excitation has been advanced by Lundberg (1973, 1979; Lundberg, Malmgren & Schomburg, 1987). The hypothesis relies on: (i) the activation by the contraction of high-threshold muscle afferents (groups III–IV, see Schomburg, 1990); (ii) the convergence of these afferents onto group II interneurones (see Lundberg, 1973, 1979); and (iii) the spatial specificity of the descending control of γ_s motoneurones (see Hulliger, 1984). A contraction could be initiated by descending activation of group II interneurones, but might then be maintained by the combined effect of spindle secondaries activated by descending excitation of γ_s motoneurones and by high-threshold muscle afferent activity evoked by the contraction (the 'FRA hypothesis', see p. 389; Fig. 11.1(*b*)). As in the original 'follow-up length servo' hypothesis (Merton, 1953), it was assumed that some stages of a contraction can be governed from the brain solely or mainly via γ_s motoneurones. However, Lundberg's hypothesis postulates that the excitatory group II reflex connections are too weak at rest to activate motoneurones during passive movement, and that the increase in the gain of transmission during an active contraction is supplied by the contraction itself. The strong excitation of group II afferents on γ motoneurones may assist in sustaining their activation by positive feedback (see p. 291), and this would provide further excitation for the active α motoneurones. A parallel descending activation of inhibitory pathways would prevent activation of muscles not required for a given contraction. This focusing action might be achieved through the corticospinal excitation of feedback inhibitory interneurones inhibiting the relevant propriospinal interneurones, and/or the monoaminergic gating from the brainstem of transmission in group II pathways (see pp. 311, 314). Intellectually, this hypothesis has many attractions, particularly for postural co-contractions which could be maintained without significant voluntary intervention (see p. 538). However, it has yet to be substantiated for the cat, and direct corticospinal activation of the motoneurone pool provides a simpler mechanism for initiating a voluntary contraction, particularly in human subjects (as acknowledged by Lundberg, 1979).

Cutaneomuscular responses

Tactile cutaneous inputs produce early excitatory cutaneomuscular responses that are spinally mediated. In the upper limb, spinal cutaneomuscular excitatory responses (E1) of different distal upper limb motor pools are facilitated during a power grip. The resulting reinforcement of the grip prevents grasped objects from slipping from the hand (see p. 428). Early excitatory cutaneomuscular responses in the lower limb could play a role in postural contractions when balance becomes unstable (see pp. 430, 540).

Suppression of transmission in inhibitory pathways

Excitation of active motoneurones is also favoured by the suppression of transmission in inhibitory pathways activated by the contraction-induced afferent discharge (autogenetic Ib inhibition) or the discharge of motoneurones (recurrent inhibition) (Fig. 1.11(*a*)). The control of the transmission in these inhibitory pathways contributes to adjusting the force of the contraction.

Changes in recurrent inhibition

Changes during voluntary movement vary with the force of the contraction (see pp. 174–9). There is a descending facilitation of Renshaw cells during weak contractions. The resulting low gain for the motoneurone pool would allow supraspinal

centres to operate over a large part of their working range causing only small changes in muscle force, and this should improve resolution in the control of motor output. In contrast, during strong contractions, transmission in homonymous and heteronymous recurrent pathways directed to active motoneurones is suppressed. This suppression is probably corticospinal in origin, and helps secure a high output gain for the active motoneurone pool(s). In addition, the removal of recurrent inhibition from homonymous silent motoneurones would facilitate their recruitment, thus helping overcome fatigue.

Suppression of autogenetic Ib inhibition

Suppression of autogenetic Ib inhibition to active motoneurones increases with contraction force during sustained contractions, presumably because of presynaptic gating of Ib terminals by the contraction-induced Ib discharge (see pp. 268–71). This suppression is functionally appropriate, because otherwise Ib inhibition evoked by the activation of Golgi tendon organs would hinder the maintained firing of active motoneurones and interfere with the recruitment of new units when the effort had to be increased. However, (i) even at strong tonic forces, there is suppression rather than complete abolition of Ib inhibition, and this allows an operating level of inhibition that can be modulated in either direction, and (ii) Ib inhibition is active when there are rapid increases in contraction force in order to help smooth the force profile (see p. 271). On the other hand, Ib inhibition can be restored when necessary because transmission in Ib pathways can be facilitated by other peripheral afferent inputs which converge onto the relevant Ib interneurones, and there is descending facilitation of the transmission of these other inputs during strong contractions (see p. 267).

Conclusions

Several spinal mechanisms contribute to maintaining isometric tonic contractions.

(i) The fusimotor-driven spindle afferent discharge contributes to the discharge of α motoneurones, and the background spindle afferent discharge may be used to provide servo-assistance to the contraction; the combined effect of spindle secondaries activated by γ_s motoneurones and of high-threshold afferent activity evoked by the contraction probably helps to maintain the contraction.

(ii) Cutaneomuscular spinal responses in the upper limb may be used to prevent grasped objects from slipping from the hand and, in the lower limb, they play a role in postural contractions.

(iii) Suppression of recurrent and Ib inhibitions to active motoneurones increases with contraction force, and thus contributes to regulating the force of isometric contractions.

Flexion–extension movements involving hinge joints

During a selective voluntary contraction of one muscle, changes in transmission occur in all tested spinal pathways (Chapters 2–10). Such changes are often used in attempts to explain the mechanisms underlying the activation of the agonists and/or the relaxation of the antagonists in flexion-extension movements. However, because these data were obtained during isometric contractions, extrapolation to changes occurring in transmission in spinal pathways during dynamic movements should be made with caution. The control of muscles operating at ball joints (e.g. wrist) differs in many points from that of muscles acting at hinge joints (ankle, elbow, knee), and the former is considered in a separate section (pp. 522–6).

Afferent discharges accompanying a voluntary flexion–extension movement

Flexion–extension movements produce activity in a variety of afferents.

(i) Spindle Ia and group II discharges depend on the efficacy of the γ drive in activating spindle

primary and secondary endings during a voluntary movement and the contraction-induced changes in muscle length (see pp. 133–5). Shortening (in a 'concentric' contraction) will unload spindle endings, and an increase in spindle discharge will then occur only in slow contractions. During an unloaded phasic shortening contraction, it is likely that the discharge of muscle spindle endings in the contracting muscle will decrease and many will be silenced, and afferent cues of spindle origin then come mainly from the stretched antagonistic muscle(s). However, when the contracting muscle is working against a load so that greater effort is required to perform the same movement, the discharge pattern becomes less modulated by the change in muscle length, and spindle endings behave more like tension-transducing organs. During an 'eccentric' contraction, as, for example, when easing down an object, fusimotor activity combined with muscle stretch produces a marked increase in spindle activity in parallel with the declining α motor activity (see pp. 135, 521).

(ii) Ib afferents discharge readily during shortening contractions, even in the absence of an external load, the discharge increasing throughout the contraction as EMG builds up (see pp. 267–8).

(iii) Joint afferents are activated as the joint approaches the extremes of movement (Chapter 6, p. 272).

(iv) Cutaneous afferents will be also activated by contact with a target or an unexpected obstacle, but some cutaneous receptors are activated during movement without contact with an external object (Chapter 9, p. 388), largely due to stretching of the skin.

Excitation of active motoneurones

Excitation of agonist motoneurones is favoured both by facilitation of transmission in excitatory pathways to active motoneurones and suppression of transmission in inhibitory pathways to those motoneurones.

Facilitation of the transmission in excitatory pathways

Monosynaptic Ia excitation

During eccentric contractions and loaded concentric contractions, the fusimotor-driven Ia discharge provides excitatory feedback to homonymous and heteronymous motoneurones involved in the movement. The non-linear characteristics of primary endings allow them to respond briskly to the initiation of a length change, and the short-latency of the segmental stretch reflex makes this feedback capable of providing fast motor reactions to absorb mechanical disturbances. If the mechanical disturbance is an unexpected obstruction to movement, such that there is a mismatch between the intended and the achieved movement, misalignment between intended and actual muscle length would increase the firing of Ia afferents. If the disturbances result from irregularities in α motor outflow during active, graded movements, the reflex can counterbalance the unwanted changes in trajectory. It might be argued that the γ-driven Ia discharge is modest during shortening contractions, even when they are loaded, and that its efficacy in activating motoneurones is reduced by post-activation depression at the Ia fibre-motoneurone synapse. However, at the onset of a voluntary contraction, there is a prominent decrease in presynaptic inhibition on Ia terminals on active lower-limb motoneurones, pre-programmed at cortical level according to both the strength and the speed of the movement (see p. 359). Thus, at the beginning of a movement, when the exact load is not yet known, even a modest Ia discharge could help compensate rapidly and automatically for any errors in the programmed movement.

Propriospinally mediated excitation

Propriospinal neurones are excited by the γ-driven spindle discharge, and this may provide servo-assistance to motoneurones at propriospinal level, in addition to servo-assistance provided through segmental circuitry. Propriospinal neurones receive additional excitation from the Ib input, related

to muscle contraction rather than muscle length. Because the group I excitation of cervical propriospinal neurones is weak and gated by presynaptic inhibition during voluntary contraction, it is unlikely to provide significant reflex support in the absence of other drives. However, despite its weakness, the group I input is able to produce potent facilitation of that part of the corticospinal command passing through the propriospinal relay, and could thereby provide a safety factor to propriospinal neurones that are being activated by on-going descending activity. This view is supported by the finding that descending excitation is focused on the subset(s) of propriospinal neurones receiving the afferent feedback from the contracting muscle (see pp. 476–7).

Inhibition of the transmission in inhibitory pathways

Suppression of the transmission in spinal segmental inhibitory pathways to active motoneurones also favours the excitation of these motoneurones. Thus, there is suppression of: (i) recurrent inhibition to homonymous motoneurones towards the end of ramp contractions, due to corticospinal inhibition of Renshaw cells (see p. 179); (ii) autogenetic Ib inhibition, via presynaptic gating of Ib afferents (see pp. 268–71); (iii) reciprocal Ia inhibition from stretched antagonists (see pp. 223–5). Suppression of the transmission in these three pathways would help sustain the agonist contraction.

Control of different features of the movement

Changes in transmission in spinal pathways may contribute to controlling several features of flexion–extension movements: selectivity, mechanical characteristics (force and speed), termination.

Selectivity of the movement

The focusing of the descending commands responsible for a given flexion–extension movement is helped by the descending control of several spinal pathways.

(i) Presynaptic inhibition of Ia terminals is decreased at the onset of movement on active motoneurones but increased on inactive motoneurones linked in Ia synergism. This differential corticospinal control of presynaptic inhibition, selectively 'opening' Ia transmission to voluntarily activated motoneurones while 'closing' transmission to motoneurones of relaxed muscle(s), prevents those motoneurones from receiving heteronymous Ia excitation and increases the contrast between the active muscle and inactive synergists (see pp. 359–60).

(ii) Ib inhibition from the contracting muscle is suppressed to active motoneurones but increased on inactive synergists. Again, the resulting focusing action would increase 'motor contrast' (see pp. 272–3).

(iii) Spindle activation occurs even in rapid shortening movements before the limb has actually started to move, but occurs only for spindles in the contracting muscle(s) (see p. 135).

(iv) Increased recurrent inhibition of homonymous motoneurones at the onset of movement (Chapter 4, pp. 174–5) helps sharpen activity within the active motoneurone pool(s) in the initial part of the movement.

(iv) In the propriospinal system, muscle and cutaneous volleys produced by the movement excite feedback inhibitory interneurones. Selection by the corticospinal command of the relevant feedback inhibitory interneurones prevents the activation of propriospinal neurones not required for the movement, and helps focus the propriospinally mediated part of the descending command on the active motoneurones (see p. 477).

Control of mechanical features (force, speed)

Adjustment of biomechanical features, such as the force and speed of the movement, can be achieved by appropriate descending inputs to motoneurones. However, the descending control of spinal pathways may also contribute to adjusting these features.

Force produced by the movement

The stronger the force pre-programmed at the end of the dynamic phase of a ramp contraction, the stronger the suppression of various inhibitions directed to active motoneurones (see above): (i) autogenetic Ib inhibition, (ii) homonymous recurrent inhibition, (iii) reciprocal inhibition from antagonistic stretched muscles (see pp. 223–5), and (iv) presynaptic inhibition of Ia terminals in the initial phase of the movement. (v) In addition, the servo-assistance provided by the γ-driven spindle discharge increases with the load on the contracting muscle (see p. 135).

Speed of the movement

Suppression of recurrent inhibition and presynaptic inhibition of Ia terminals is also regulated according to the speed of the desired movement. Thus, whatever the duration of the dynamic phase of a ramp movement, the suppression of recurrent inhibition is adjusted to be maximal at the end of the dynamic phase (see p. 174), while presynaptic inhibition reappears during the decelerating (braking) phase (see p. 358).

Control through propriospinal pathways

Group I inhibitory projections to propriospinal neurones can modulate the corticospinal excitation passing through this relay thereby helping to adjust the force and speed of the movement by controlling the gain in the feedback inhibitory loop (see p. 477).

Termination of the movement

On several occasions, Lundberg has argued that it would be appropriate for a spinal mechanism to ensure termination of a movement, because termination must be one of the most difficult parameters of a movement for the brain to calculate (e.g. Lundberg, Malmgren & Schomburg, 1977). Several spinal mechanisms are capable of contributing to this role in human subjects.

Cutaneous inhibition of propriospinal neurones

The specific pattern of the cutaneous inhibition of cervical propriospinal neurones suggests a role in curtailing movement. The exteroceptive volley evoked by contact with the target or with an unexpected obstacle would inhibit the descending command passing through propriospinal neurones, helping to terminate the movement. This view is supported by the finding that feedback inhibitory interneurones mediating cutaneous inhibition of propriospinal neurones receive a stronger descending drive at the offset of a visually guided movement than at its onset (see p. 478).

Restoration of Ib inhibition

Ib inhibition to active motoneurones is suppressed during voluntary movements, but may reappear when Ib pathways are facilitated by inputs from other peripheral afferents. Thus, cutaneous facilitation of transmission in Ib pathways, which has a precise local sign, could be used to curtail an exploratory movement meeting an obstacle (see pp. 271–2). Similarly, facilitation of Ib inhibition from joint receptors activated at the extremes of joint movement will increase Ib inhibition and automatically contribute to curtailing the movement as it approaches the extremes of joint rotation (see p. 272).

Recruitment of different types of motor units

During voluntary contractions, motoneurones are generally recruited in an orderly sequence from small motoneurones supplying slow-twitch motor units to large motoneurones supplying fast-twitch units. Thus, the thresholds of units in the first dorsal interosseus for abduction of the index finger are ranked according to size both in slow ramp and in ballistic contractions, irrespective of whether the contractions are performed under isotonic or isometric conditions (see Desmedt, 1983). However, there are circumstances when the preferential recruitment of high-threshold, more powerful, motor units would be advantageous.

(i) Descending excitation mediated through the cervical propriospinal relay is evenly distributed to early- and late-recruited motoneurones. This distribution could be important when it is necessary to activate a wide range of motoneurones more or less simultaneously (see p. 477).

(ii) During the natural cutaneous stimulation involved in precision grip and active manipulation, significant decreases in the recruitment threshold of high-threshold more powerful motor units in hand muscles occur, and this could make prehension and manipulation stronger (see pp. 425–7).

(iii) A lengthening contraction, when easing down a load at a constant smooth velocity, would be helped by recruiting fast-twitch units with a faster relaxation time (Nardone, Romanò & Schieppati, 1989).

Inhibition of antagonists

Effective inhibition of the antagonistic muscle(s) is required during phasic flexion–extension movements. For simplicity, this is discussed below with regard to a voluntary flexion, but similar principles apply to extension movements at all hinge joints. A movement of flexion produces a stretch-induced Ia discharge from the antagonistic extensor muscle, especially when movement is rapid. This extensor Ia discharge could produce two undesirable effects: (i) excitation of extensor motoneurones, producing a contraction that would slow the flexion movement, and (ii) activation of 'corresponding' extensor-coupled Ia interneurones inhibiting flexor motoneurones involved in the voluntary movement (see the sketch in Fig. 11.1(*c*)). There are no direct corticospinal inhibitory projections onto motoneurones, and the necessary inhibition of the antagonists is due to the activation of several spinal inhibitory pathways.

Different spinal pathways contribute to inhibiting the antagonists

Reciprocal Ia inhibition

This is the best known spinal mechanism inhibiting the antagonists during flexion–extension movements, and has been the most thoroughly investigated. When the fusimotor drive maintains a Ia discharge from a contracting muscle, the efficacy of this discharge will be enhanced around the onset of the contraction by decreased presynaptic gating, and this may be able to activate Ia inhibitory interneurones, especially if they are depolarised by a descending drive and not inhibited by recurrent inhibition (Fig. 11.1(*c*)). However, post-activation depression could help keep the efficacy of the Ia fibre–Ia interneurone synapse at a relatively low level during γ-assisted movements. In addition, activation through the γ loop only occurs during eccentric contractions and slow or loaded concentric contractions (see p. 516). Thus, during a rapid unloaded shortening contraction, i.e. the type of contraction that has greatest potential to trigger a stretch-induced Ia discharge from the antagonist, it is likely that many muscle spindle endings in the contracting muscle will be silenced. Unwanted activation of both extensor motoneurones and extensor-coupled Ia inhibitory interneurones would then require that flexor-coupled Ia inhibitory interneurones receive a strong descending drive, sufficient to fire them without the support from Ia afferents in the contracting muscle (see pp. 222–3).

Presynaptic inhibition of Ia terminals

Presynaptic inhibition of Ia terminals on antagonistic extensor motoneurones is increased during voluntary flexion (Fig. 11.1(*c*); see pp. 360–1). The increase in presynaptic inhibition is modest, and is due mainly to the activation of PAD interneurones by the group I afferent discharge from contracting flexors.

Longer-latency propriospinally mediated inhibition

The longer-latency propriospinally mediated inhibition of extensor motoneurones antagonistic to active flexor motoneurones is revealed only during active movement, where it appears ~50 ms before EMG activity, increases during the dynamic phase of the movement and is correlated with the strength of flexion (see pp. 497–8). The fact that

this inhibition is not seen at rest is consistent with a weak afferent input to propriospinal neurones, and this implies that the descending drive provides sufficient facilitation of the relevant propriospinal inhibitory interneurones to fire them during voluntary movement.

Recurrent inhibition

During a phasic flexor contraction, extensor-coupled Renshaw cells receive descending facilitation. This may also contribute to curtailing a stretch reflex in the antagonist: the first motoneurones firing in the stretch reflex would activate extensor-coupled Renshaw cells, which would inhibit other motoneurones and thus curtail the stretch reflex (Fig. 11.1(*c*); see p. 180).

Non-reciprocal group I inhibition

Interneurones mediating non-reciprocal group I inhibition to antagonistic extensor motoneurones receive corticospinal facilitation at the onset of a voluntary contraction of flexors (see p. 273). The stretch-induced Ia discharge in the antagonistic extensor would activate facilitated interneurones mediating non-reciprocal group I inhibition to extensor motoneurones, and this would help prevent a stretch reflex in that muscle.

Absence of redundancy between the mechanisms inhibiting the antagonists

All spinal inhibitory pathways that can be tested contribute to the relaxation of antagonistic muscles during flexion–extension movements (see above). However, there is no redundancy between the different pathways, because they differ in their afferent input, their target neurones and the stage of the movement when they become active.

(i) Propriospinally mediated inhibition is an almost purely descending mechanism, independent of afferent feedback and of controls on Renshaw cells, directed only to antagonistic motoneurones. The correlation of this inhibition with the strength and timing of the agonist contraction suggests a parallel corticospinal control of the relevant interneurones and α motoneurones.

(ii) Reciprocal Ia inhibition could be used to provide servo-assistance to the contraction of agonists and relaxation of antagonists in those movements modulated by the γ-driven Ia discharge from the contracting muscle. Ia interneurones are also activated by corticospinal drives, but the resulting motoneurone inhibition contributes less than the propriospinally mediated inhibition to relaxation of the antagonist. This weaker effect could result from the suppression of reciprocal Ia inhibition by recurrent inhibition activated by the agonist motor discharge. However, recurrent inhibition progressively decreases towards the end of the dynamic phase of the movement in order to leave reciprocal Ia interneurones to exert their inhibitory action fully (see pp. 174–9). Effective reciprocal Ia inhibition could then be functionally crucial, because Ia inhibitory interneurones also inhibit 'opposite' Ia interneurones and can prevent the inhibition of active motoneurones by the stretch-induced Ia discharge in the antagonistic muscle (Fig. 11.1(*c*)).

(iii) Given the weak sensitivity of the stretch reflex to presynaptic inhibition of Ia terminals, the main role of increased presynaptic inhibition on Ia terminals on antagonistic motoneurones could be to help prevent the Ia discharge produced by stretch of the antagonist (extensor) from firing extensor-coupled Ia inhibitory interneurones and thus from inhibiting active flexor motoneurones (see p. 361).

(iv) Facilitation of recurrent and non-reciprocal group I inhibitions directed to antagonistic motoneurones contributes to curtailing a stretch reflex in the antagonistic muscle, thereby smoothing the execution of the movement.

Timing of the different effects

Onset of movement

Mechanisms ensuring selectivity are then favoured: (i) increased recurrent inhibition within the active motoneurone pool; (ii) decreased presynaptic

inhibition on Ia terminals on active motoneurones, and increased presynaptic inhibition on inactive synergistic motoneurones; (iii) Ib inhibition, decreased on active motoneurones and increased on synergistic inactive motoneurones; and (iv) before the limb has commenced moving, γ-driven Ia discharge focused on motoneurones of the contracting muscles. This focusing action is consistent with results in the monkey showing suppression of the activity of many cervical interneurones prior to a voluntary movement, preventing the overt expression of the movement (cf. Fetz *et al.*, 2002).

Movements in progress

Mechanisms favouring a stronger muscle contraction progressively appear as the movement develops: (i) suppression of autogenetic Ib inhibition increases with muscle force; (ii) homonymous recurrent inhibition decreases towards the end of the dynamic phase, helping maintain a high output gain; (iii) suppression of recurrent inhibition also favours increased reciprocal Ia inhibition which, via inhibition of opposite Ia inhibitory interneurones, prevents the Ia discharge from the stretched antagonist from inhibiting the active motoneurones; (iv) increased presynaptic inhibition of Ia terminals on antagonist-coupled Ia inhibitory interneurones contributes to preventing this undesirable inhibition of the active motoneurones; (v) increased afferent feedback, in particular Ib, from the contracting muscle provides enhanced facilitation of corticospinal commands passing through the propriospinal relay; and (vi) recruitment of more powerful fast-twitch motor units of hand muscles by contact of appropriate skin regions with an object will increase grip force. In parallel, relaxation of antagonists is ensured by: (vii) descending facilitation of propriospinally mediated inhibition of antagonistic motoneurones; and (viii) increased reciprocal Ia inhibition. The latter is fed by the γ-driven Ia discharge from the contracting muscle no longer gated by presynaptic inhibition of Ia terminals, facilitated by corticospinal excitation of Ia interneurones, and is disinhibited by the progressive suppression of recurrent inhibition.

Easing off a contraction

Braking and decelerating a movement when easing down an object is controlled by (i) the servo-assistance provided by the γ-driven spindle discharge associated with the lengthening contraction; and (ii) the recruitment of fast-twitch motor units which have a faster relaxation time.

Cutaneous control of the end of movement

The exteroceptive volley evoked by contact with the target or an unexpected obstacle helps terminate the movement because it causes facilitation of: (i) Ib interneurones mediating autogenetic group I inhibition to active motoneurones so that the obstacle is not displaced; and (ii) feedback inhibitory interneurones inhibiting the part of the corticospinal command passing through the propriospinal relay.

Different strategies for proximal and distal movements

Given the large repertoire of human movement, the changes in transmission in spinal pathways will vary according to the requirements of an infinite number of possible movements. Different strategies may be required for movements at proximal and distal joints, as discussed below for the upper limb.

Elbow muscles

Elbow muscles have a load-bearing function for which the γ-driven spindle discharge may provide useful servo-assistance, and have much spinal circuitry at their disposal for reflex assistance: (i) a well-developed monosynaptic spinal stretch reflex, which contributes to the response of the triceps brachii in subjects falling intentionally forward onto their arms (see p. 89); (ii) potent reciprocal Ia inhibition (see p. 210); (iii) potent recurrent inhibitory projections to homonymous motoneurones and corresponding Ia inhibitory interneurones (see pp. 169–71); and (iv) corticospinal commands transmitted to

motoneurones through the propriospinal relay, where they can be modulated by the peripheral feedback from the moving limb (see p. 477).

Hand muscles

Hand muscles are required to perform skilled manual tasks, which may involve rapid, essentially unloaded movements in which afferent-induced changes in motoneurone discharge could lag far behind the phase of movement that generated the feedback. It would therefore be sensible if such movements were performed with feedforward control, without potentially disruptive feedback. Accordingly, in these muscles, in which the largest responses to Ia input have been found in high-threshold units (see p. 81), the spinal Ia stretch reflex is poorly developed and positional servo-assistance is provided by a transcortical Ia pathway or by conscious intervention (see p. 92). Distal movements are also not subjected to recurrent inhibition, because of the absence of recurrent collaterals from motor axons innervating the relevant muscles (see p. 169). In addition, there are no projections of propriospinal neurones to the intrinsic muscles of the human hand (see p. 460). Many hand movements, such as writing, involve near-isometric contractions of intrinsic muscles and those of the forearm. Under these circumstances, feedback from cutaneous and muscle receptors, acting through transcortical rather than spinal pathways (e.g. see Datta, Harrison & Stephens, 1989) can have significant effects on the active motoneurone pools.

Conclusions

Hypotheses concerning the involvement of the different spinal pathways in movements at hinge joints have been inferred from data obtained during isometric ramp contractions. It cannot be taken for granted that the descending control is the same when the brain programs isotonic movements at a single joint, or *a fortiori* a complex movement involving muscles operating at different joints and performing various shortening and lengthening contractions, weight-bearing or unloaded. This holds particularly for upper limb movements, given their large motor repertoire. Now that techniques have been developed, which enable one to explore changes in transmission in spinal pathways during gait (see pp. 545–50), it is important that future research uses such techniques in upper limb movements (such as reaching, grasping, manipulation).

Movements involving ball joints

Different organisation of the human spinal circuitry at wrist level

Information regarding ball joints, i.e. joints with several degrees of freedom, is limited, for both human subjects and the cat. 'This bears the problem that many hypotheses have been derived from the situation at simple joints, which display only a rigid and stereotyped motor behaviour. It has to be expected that research of more differentiated and flexible motor synergies will lead to drastic modifications of many of the present concepts' (Hultborn & Illert, 1991). As discussed below, the organisation of the human spinal circuitry at wrist level differs from that at hinge joints (cf. the sketch in Fig. 11.2). This might result from an adaptive evolution to different requirements. (i) FCR and ECR may act as antagonists in flexion–extension movements of the wrist, but they operate as synergistic muscles in wrist abduction movements. (ii) Some wrist flexion–extension movements are rapid movements and, in them, muscle spindle endings in the contracting muscle will be unloaded and reflex cues may need to come from other receptors (see p. 135).

The organisation of spinal circuits at wrist level differs from that at hinge joints in many aspects

(i) There is mutual recurrent inhibition between 'antagonistic' FCR and ECR motor nuclei (see p. 171).

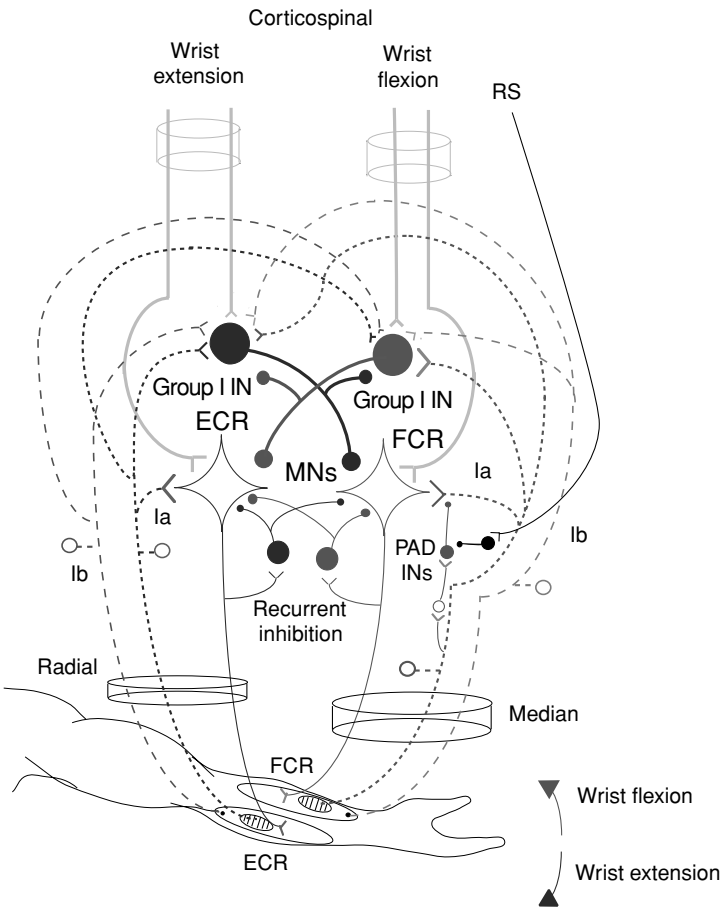


Fig. 11.2. Some spinal pathways to wrist flexors and extensors. α Motoneurones (MNs), Renshaw cells (RC) and Ia afferents, with their presynaptic inhibition (PAD INs) and their projection to interneurones mediating non-reciprocal group I inhibition of antagonist MNs (Group I IN) in red for FCR and blue for ECR. Ib afferents in brown for FCR and violet for ECR. RCs activated by recurrent motor axon collaterals from one muscle project to MNs innervating both FCR and ECR, but not to INs mediating non-reciprocal group I inhibition. FCR-coupled Group I INs inhibit ECR MNs and ECR-coupled Group I INs, are activated both by Ia and Ib FCR afferents, and also receive excitatory projections from ECR group I afferents, and vice versa for ECR-coupled Group I INs. Corticospinal in green. During a voluntary wrist flexion, the corticospinal command activates FCR MNs and FCR-coupled Group I INs, which inhibit opposite ECR-coupled Group I INs. After the onset of contraction, the group I feedback from the contracting muscle (and the Ia discharge from the antagonist stretched ECR) are channelled back into the reflex path already activated by corticospinal excitation, because transmission in the opposite pathway is inhibited, and vice versa for voluntary wrist extension. Presynaptic inhibition (PAD INs) of FCR Ia terminals is depressed by a descending inhibition, possibly reticulospinal (RS) in origin.

(ii) Radial-induced group I inhibition of the FCR H reflex and median-induced inhibition of the ECR H reflex are mediated through the pathway of non-reciprocal group I inhibition, not through Ia inhibitory interneurones transmitting reciprocal Ia inhibition (see pp. 211–14).

(iii) Group I afferents contained in the median and radial nerves converge onto the interneurones mediating disynaptic non-reciprocal group I inhibition of FCR and ECR motoneurones (see p. 212).

(iv) Despite this convergence, these interneurones are arranged in subsets specialised with regard to their target motoneurones (see below).

(v) Because of the mutual inhibition between the interneurones mediating non-reciprocal group I inhibition to FCR and ECR motoneurones, activation of FCR-coupled group I interneurones produces inhibition of ECR-coupled group I interneurones, and vice versa (see p. 214).

(vi) Corticospinal volleys facilitate presynaptic inhibition on Ia terminals on wrist motoneurones, while they depress it on Ia terminals on lower limb motoneurones (see p. 353).

Non-reciprocal group I inhibition

Non-reciprocal group I inhibition of wrist motoneurones is more profound at rest than any other non-reciprocal group I (or reciprocal Ia) inhibition at other joints: a conditioning volley at 0.95 × MT usually reduces the test reflex to ~50% of its unconditioned value. This is in keeping with the finding that, in the cat, non-reciprocal group I inhibition is larger in the forelimb than in the hindlimb (Illert, Lundberg & Tanaka, 1976).

Corticospinal control

Stimulation of the motor cortex produces potent disynaptic suppression of the radial-induced inhibition of the FCR H reflex. Through mutual inhibition of 'opposite' interneurones, corticospinal facilitation of FCR-coupled group I inhibitory interneurones would produce inhibition of ECR-coupled group I inhibitory interneurones (Fig. 11.2; Rothwell *et al.*, 1984). This reveals a more potent corticospinal facilitation of non-reciprocal group I interneurones than found at ankle level (see p. 265).

Non-reciprocal group I inhibition during wrist movements

Non-reciprocal group I inhibition during voluntary wrist flexion

In two exceptional subjects, in whom it was possible to evoke an ECR H reflex which did not disappear during the contraction of the antagonistic FCR, median-induced non-reciprocal group I inhibition of the ECR was found to be increased at the onset of FCR contraction (R. Katz & J. C. Lamy, unpublished data). In the other direction, the disynaptic radial-induced non-reciprocal group I inhibition of the FCR H reflex is suppressed prior to, and during voluntary wrist flexion, and the stronger the contraction the more marked the suppression (Day, Rothwell & Marsden, 1983; Day *et al.*, 1984). The finding that the above effects occur before the contraction-induced afferent feedback has reached the spinal cord, indicates a descending control. Given that corticospinal volleys produce parallel facilitation of FCR motoneurones and corresponding group I inhibitory interneurones (cf. above; Fig. 11.2), the above effects are consistent with corticospinal facilitation of FCR-coupled group I inhibitory interneurones, with: (i) facilitation of group I inhibition to ECR motoneurones, and (ii) suppression of group I inhibition to FCR motoneurones, through mutual inhibition of opposite group I inhibitory interneurones.

Non-reciprocal group I inhibition during voluntary wrist extension

Is there descending facilitation of the pathway?

The difficulty in proving descending facilitation of ECR-coupled group I inhibitory interneurones during voluntary wrist extension contrasts with the ease with which corticospinal facilitation of FCR-coupled group I inhibitory interneurones can be demonstrated during voluntary wrist flexion. Prior to voluntary wrist extension, radial-induced inhibition of

the FCR H reflex has been reported to be increased, suggesting descending facilitation of ECR-coupled group I inhibitory interneurones (Day, Rothwell & Marsden, 1983), but this result has not been confirmed by Raoul *et al.* (1999) and is not seen at the onset of the movement (Cavallari *et al.*, 1984). During tonic wrist extension, radial-induced inhibition of the FCR H reflex may be increased or unchanged in different subjects (Cavallari *et al.*, 1984; Raoul *et al.*, 1999). However, when the natural peripheral feedback from the contracting wrist extensors is interrupted by a block of the radial nerve using lignocaine injected distal to the stimulation site, the radial-induced inhibition of the FCR H reflex is enhanced during attempted tonic wrist extension (Day *et al.*, 1984). The most parsimonious explanation is that the descending facilitation of the relevant interneurones is difficult to define because of an interaction between the peripheral feedback from the contracting muscle and the conditioning volley. Much as in the case of reciprocal Ia inhibition (see pp. 220–1), several mechanisms dependent on the natural group I discharge during voluntary contraction could contribute to the decreased efficacy of the conditioning volley in activating group I inhibitory interneurones: occlusion at interneuronal level, presynaptic inhibition of the conditioning volley, and possibly post-activation depression at the synapse between group I fibres and inhibitory interneurones at wrist level.

Synergy between ECR and finger flexors

The functional synergy between wrist extensors and finger flexors in clenching and grasping (see Livingston *et al.*, 1951) and the lack of selectivity of the recording conditions might account for the difficulty in proving descending facilitation of ECR-coupled group I interneurones. The H reflex of forearm flexor muscles to stimulation of the median nerve in relaxed subjects originates from both wrist and finger flexors (cf. Day *et al.*, 1984). Thus, subliminal excitation of finger flexor motoneurones accompanying isometric 'synergistic' wrist extension could favour their recruitment in the median-induced H reflex. Intuitively, there are no good reasons for these motoneurones receiving reciprocal inhibition from the conditioning radial volley, unless there is an associated voluntary finger extension. Variable results between subjects, and different groups, could result simply from whether care was taken that the wrist extension was accompanied or not by finger extension.

Functional implications

Corticospinal excitation of the appropriate pathway

During FCR contractions, FCR-coupled group I inhibitory interneurones projecting to ECR motoneurones receive descending facilitation, while 'opposite' interneurones projecting to FCR motoneurones are inhibited. This differential control indicates that interneurones mediating non-reciprocal group I inhibition to wrist motoneurones are arranged in subsets specialised with regard to their target motoneurones. The corticospinal facilitation of group I inhibitory interneurones precedes the parallel discharge of the corresponding motoneurones, and its main function is probably to select the appropriate subset of group I interneurones, i.e. the subset directed to antagonistic motoneurones. These interneurones also inhibit inhibitory interneurones projecting to active motoneurones. After the onset of contraction, the group I feedback from the contracting muscle is channelled back into the reflex path already activated by corticospinal excitation, because transmission in the opposite pathway is inhibited (see Fig. 11.2). Activation of the inhibitory pathway to antagonistic motoneurones prevents a stretch reflex in this muscle, while inhibition of the opposite interneurones prevents the Ia discharge from the stretched antagonists from inhibiting the active motoneurones.

Peripheral activation of the relevant interneurones

During rapid unloaded shortening contractions of wrist muscles, the discharge of spindle endings

in the contracting muscle will decrease (see p. 516). However, inhibitory group I interneurones to wrist motoneurones also receive Ib inputs, which are related to muscle contraction, not to muscle length. Moreover, the Ia afferent discharge from the stretched antagonists may also contribute to activation of the selected pathway because of the convergence of group I volleys from flexors and extensors onto common interneurones (see p. 524). Thus, the particular organisation of the pathways of non-reciprocal group I inhibition to wrist motoneurones ensures that the relevant interneurones receive peripheral feedback, even during rapid movements.

Changes in presynaptic inhibition on Ia terminals on wrist motoneurones

Non-specific decrease in presynaptic inhibition

Presynaptic inhibition of Ia terminals on FCR motoneurones is moderately depressed at the onset of and during isometric voluntary contractions of either FCR or ECR. It has been speculated that this non-specific effect might be due to reticulospinal depression acting on the last-order PAD interneurones (p. 363). The *isometric* contractions resemble postural co-contractions of wrist muscles. Assuming that there is the same descending control of PAD interneurones in postural contractions, decreased presynaptic inhibition on Ia terminals on wrist motoneurones would reinforce the servo-assistance provided by the monosynaptic Ia stretch reflex of wrist muscles and improve the reflex support to manipulatory movements of the fingers.

Corticospinal facilitation of PAD interneurones

The corticospinal facilitation of presynaptic inhibition on Ia terminals on wrist motoneurones, seen using stimulation of the motor cortex (p. 353), has not been reproduced during the voluntary contractions so far tested (see pp. 362–3). This might be due to the isometric nature of the contractions studied. Facilitation of PAD interneurones could be selected by the motor cortex in order to turn off the monosynaptic Ia assistance during rapid unloaded wrist movements, in which reflex feedback could have deleterious effects (see p. 522). Testing this hypothesis would require further experiments using rapid isotonic movements.

Other spinal pathways possibly involved in wrist movements

Mutual recurrent inhibition between FCR and ECR motoneurones

This particular pattern has been described during voluntary contractions of the target muscle in studies of the modulation of the discharge of single motor units and of the on-going EMG activity, but there are no data on how transmission in the relevant pathways is modulated during other types of contraction. A functional explanation for these connections is proposed below (p. 534).

Cutaneomuscular responses

Cutaneomuscular responses can be elicited in voluntarily active wrist muscles by low-intensity stimuli to the fingers. In normal adult subjects, these responses are dominated by the long-latency transcortical excitatory response. So far, there are limited data on the modulation of the responses in wrist muscles during different motor tasks (though such changes are well-documented for the intrinsic muscles; Fig. 9.13).

Propriospinal pathways

Propriospinal pathways transmit some of the corticospinal command for isometric contractions of wrist muscles (pp. 471–4). The extent to which they are involved in the transmission of the command for different motor tasks requires further studies.

Co-ordinated activation of various synergies

No natural movement involves just one muscle. Even planar movements at single joints involve the activation of synergists operating at the same joint, and relaxation (or disfacilitation) of antagonists. Only under contrived conditions, such as the artificial constraints of the laboratory, does a natural movement consist of action at just one hinge joint. More often there is a co-ordinated activation of muscles across several joints. Thus, for example, reaching with the upper limb involves displacements at shoulder, elbow, wrist and fingers, while kicking a ball involves displacements at hip, knee and ankle. The correct spatial and temporal pattern of muscle activation is crucial for smooth and coordinated movements, and the question is where motor synergies are laid down in the central nervous system.

Where are motor synergies laid down?

Spinal origin?

Although even the simplest movements involve a large number of muscles, the pattern of muscle activity is generally constant for a defined type of movement (locomotion, postural adjustments [see, however, ankle and hip strategies in posture, p. 542]). This led Beevor (1904, cited by Hultborn & Illert, 1991) to claim that the neuronal arrangements for relatively stereotyped movements were laid down in the spinal cord. In the cat, the isolated spinal cord can generate complex activities such as scratching and locomotion. Accordingly, Sherrington (1906) believed that the spatial and temporal patterning of muscle activity was driven by afferent input and linked by the pathways subserving reflex arcs. This view had been proposed by Michael Forster in his *Textbook of Physiology* (1879, cited by Hultborn, 2001). He wrote that 'reflex action may be said to be, *par excellence*, the function of the spinal cord', but added that 'the cord contains a number of more or less complicated mechanisms capable of producing, as reflex results, co-ordinated movement altogether similar to those which are called forth by the will. Now it must be an economy to the body that the will should make use of these mechanisms already present, by acting directly on their centres, rather than it should have recourse to a special apparatus of its own of a similar kind'. As discussed below, several spinal circuits may be used both in the coordination of muscle synergies involved in complex movements and in the flexibility of these synergies.

Hierarchical control schema

Spinal pathways and higher centres also contribute to muscle synergies in complex co-ordinated movements. According to this view, originally raised by Bernstein (1967) and recently developed by Macpherson (1991), motor control would be organised on the basis of hierarchical control schema in which descending motor commands are sent to groups of muscles that are then co-activated through appropriate spinal pathways. The higher level parameters of any motor act would be global and related to the goals of the movement. These global parameters would participate in determining the values of the more local, lower level variables. For example, 'in a voluntary movement, such as goal-directed reaching movement, the end point position of the hand, and possibly its trajectory, would be higher level variables related to the goal of target acquisition. Specified at a lower level are the individual joint angular displacements and the muscle activation patterns needed to achieve adequate movement of the arm. . . The problem of selecting the correct muscles to be activated is simplified by certain basic rules of combination, rules that are probably formed during motor learning. One rule could be to minimise expenditure or energy, and another to make use of predictable forces such as gravity or inertial perturbation among the body segments' (Macpherson, 1991). It is suggested below that the command for propriospinally mediated reaching represents a good example of movement so organised.

Synergies based on 'hardwired' spinal connections

Heteronymous projections of different afferents to a variety of motoneurones link muscles of the ipsilateral, and often contralateral, limbs in various synergies, represented by different groups of interneurones or monosynaptic connections. These correspond to Sherrington's concept of a number of 'spinal common paths', in contrast to the 'final common path', i.e. the motoneurones. The classical example is furnished by the muscles which contract and relax in the flexion withdrawal reflex (see pp. 404–5), although the responsible nociceptive afferents are not involved in the control of normal movement (however, see p. 389). It is likely that the brain acts by mobilising these spinal mechanisms during 'voluntary' movements. Whether monosynaptically or interneuronally mediated, synergies transmitted through these spinal connections are flexible because of the control exerted on the interneurones intercalated in their pathways and/or PAD interneurones mediating presynaptic inhibition of primary afferent terminals.

Heteronymous monosynaptic Ia connections

Heteronymous monosynaptic Ia connections represent the simplest example of 'hardwired' connections. Speculation about their function is based on the assumption that, in movements, an adequate contribution of Ia afferent activity to motor output depends not only on the fusimotor drive but also the direct depolarisation by the central command of the relevant α motoneurones (Hultborn & Illert, 1991).

Lower limb

Contractions of lower-limb muscles are usually weight-bearing and often eccentric. These are circumstances when the co-activated γ drive can represent a powerful input to muscle spindle endings (see p. 137). In striking contrast with data for the cat and baboon hindlimb, transjoint monosynaptic Ia connections are the rule in the human lower limb and are often bidirectional (Chapter 2, Table 2.1). The fact that this pattern exists indicates that the widespread Ia connections found in humans are of functional importance, adapted to provide the reflex assistance required for bipedal stance and gait (see pp. 538, 550). Projections from a muscle to 'antagonists' operating at another joint do not occur in the cat or baboon hindlimb, but are quite common in the human lower limb (see p. 83). They may be explained in terms of the versatile synergisms required to accomplish the various postural tasks that are more variable in bipedal than in quadrupedal stance (see p. 94).

Upper limb

In the human upper limb, heteronymous monosynaptic Ia projections are diffuse from distal muscles to both the flexors and extensors of proximal joints. Proximal muscles have a load-bearing function during grasping and manipulatory movements and, again, the co-activated γ drive can represent a powerful input to muscle spindle endings. Distal-to-proximal Ia connections might then be used to stabilise the wrist and elbow to provide a firm support for the hand (see p. 94).

Relaxation of antagonistic muscles

Co-ordinated synergies also imply relaxation of antagonistic muscles, whether by inhibition or disfacilitation. Discharge of remote motoneurones through heteronymous Ia excitation presupposes the direct depolarisation of the connected α motoneurones by the central command (see above; Hultborn & Illert, 1991). The relaxation of the antagonists at different joints during multi-joint movements may therefore be due to activation by the descending drive of the same spinal pathways as those ensuring the inhibition of the antagonists during single hinge (pp. 519–20) or ball (pp. 524–6) joint movements.

Flexible synergies

At times, an invariant diffuse pattern of monosynaptic Ia connections in the human lower limb could be functionally inconvenient, because the activation of Ia afferents from a contracting muscle might then result in the automatic activation of unwanted muscle(s) linked in Ia synergism. Two mechanisms allow the selection of the heteronymous Ia connections appropriate for a given task: (i) increased presynaptic inhibition of Ia afferents directed to 'unwanted' motoneurones (see pp. 259–60); and (ii) matched recurrent inhibition of 'unwanted' motoneurones (see pp. 183–4, 538).

Activation of excitatory group II pathways. The FRA hypothesis

The hypothesis regarding the role of group II pathways in supporting isometric contractions, presented above for one muscle (see p. 514), could be extended to complex movements involving several muscles, as proposed by Lundberg (1973). The FRA hypothesis suggests that a diffuse feedback system with a multisensory input, including group II afferents, could be used for the selective reinforcement and prolongation of the descending command (see p. 389 and Fig. 9.1(*c*)). In the human lower limb, heteronymous group II excitatory projections are widespread and strong (Chapter 7, Table 7.3). The group II excitatory input activated in γ-assisted lengthening contractions could therefore help to maintain contractions initiated by descending drives on motoneurones and/or group II interneurones. Again, the parallel descending activation of feedback inhibitory interneurones inhibiting excitatory interneurones might prevent activation of muscles not required in a given co-contraction. Available experimental data provide more evidence for an important role of group II pathways in posture and gait (see pp. 537–49) than in voluntary movements (see pp. 310–12). This role should be seen as supporting the contraction, not driving it, much as the role of the fusimotor system is now known to be supportive (Matthews, 1972).

Cervical propriospinal system

Synergies through the propriospinal system

A substantial part of the corticospinal command to motoneurones of human upper-limb muscles is transmitted through the propriospinal relay rostral to motoneurones (see pp. 471–4). There is indirect evidence that, as in the cat, human propriospinal neurones have divergent projections to motoneurones of various muscles acting at different joints (see p. 476). In the cat, propriospinal neurones have also been shown to project to Ia inhibitory interneurones, thus contributing to the relaxation of the antagonists (Chapter 10, p. 453). This creates a network adequate for translation of descending commands for multi-joint movements into the appropriate coordinated muscle synergies which underlie those movements. Synergies produced by such a network are less limited than the 'hardwired' monosynaptic Ia and corticospinal projections onto specific and smaller sets of motoneurones. The extensive convergence of descending excitation, feedforward inhibition and feedback inhibition onto C3–C4 propriospinal neurones allows the cortical command to be updated at the premotoneuronal level. Because of the prewired connections of each subset of propriospinal neurones with the different motoneurones involved in a multi-joint movement, integration at a premotoneuronal level would allow the command to all these motoneurones to be simultaneously and 'economically' modulated by the same peripheral volleys (see pp. 477–8).

Reaching: an example of hierarchical control

It is likely that, as in the cat, the human cervical propriospinal system is involved in the control of reaching movements. Georgopoulos & Grillner (1989) have proposed that, much as in locomotion, a significant

part of such movements may be accomplished in the spinal cord, illustrating the concept of hierarchical control of co-ordinated synergies mentioned above. Thus, specification of the direction and probably speed of the movement would be elaborated by supraspinal motor structures, especially the motor cortex (the higher level). This contribution of the motor cortex to the initiation of reaching is partly channelled through the spinal propriospinal system (the lower level). The required co-ordinated motions of the shoulder, elbow and wrist are then assisted by the divergent projections of propriospinal neurones to motoneurones and Ia inhibitory interneurones, while the movement is controlled accurately by the feedforward and feedback inhibitory interneurones of the propriospinal system.

State-dependent modulation of sensory feedback

The spinal cord contains the substrate for many complex motor actions (e.g. nociceptive withdrawal reflexes, locomotion, scratching). Interneurones involved in generating these complex movements are lumped together in 'functional units', but the interneurones participating in the 'functional units' are not independent and may be involved in many types of movement. 'The understanding of how functionally distinct neuronal circuits can be built by altering the properties of individual neurones and their communication is now emerging from studies on simpler circuits in invertebrates with obvious implications for the vertebrates. This requires a dynamic regrouping of interneurones to construct different functional networks. . . As would be expected from this conceptual framework, experiments on *reflex* control of muscle activity during various forms of movements, have revealed that the action from specific sensory inputs are not only gated, but actually *re-routed* and mediated via different neuronal networks' (Hultborn, 2001). State-dependent modulation of sensory feedback is well exemplified by the reflex reversal of Ib inhibition under resting conditions to Ib excitation during gait (see pp. 248, 273–5), and constitutes a support for variable muscle synergies.

Motor learning

The motor performance of deafferented patients shows that reflex support is not indispensable to performing or grading a contraction, at least in laboratory tasks. However, there is good evidence that afferent feedback and the resulting activity in spinal circuitry are important in refining the motor output (see pp. 136–7), and probably play a crucial role in motor learning.

γ drive

When learning a motor task, movements are slow and often involve co-contraction of antagonists to brace the joint. Such contractions would be associated with an effective increase in γ drive to the contracting muscles (see below). The feedback from spindle endings would be important, not only for smoothing the movement trajectory but also for providing the sensory cues that allow a more refined voluntary command. This holds for both homonymous and heteronymous γ-driven spindle discharges. As skill is acquired, the importance of spindle support for the contraction lessens, in parallel with a change in movement performance that decreases the efficacy of the γ drive (see p. 138).

Projections to ascending tracts

Many 'automatic' movements are acquired by the internalisation of learnt programmes, and perfection of the movement depends on trial and error. As learning progresses, a motor programme is shaped which is subsequently available to command the movement (see Windhorst *et al.*, 1991). Setting up and maintaining a motor programme depends on detailed information from both the reafferent cues activated by the movement and the spinal circuitry ('the lower motor centres') fed by these cues. Interneurones activated during movement, whether projecting to motoneurones or mediating presynaptic inhibition of primary afferents, also have

collateral projections to cell bodies of ascending tracts, especially spinocerebellar, which can signal information regarding the different spinal pathways (see Lundberg, Malmgren & Schomburg, 1987). This information is essential for calling up the coordinated synergies that characterise the movement when the motor programming has been learnt.

Efference copy

C3–C4 propriospinal neurones in the cat have ascending collaterals to the lateral reticular nucleus (LRN). Via these ascending collaterals, the LRN, which projects to the cerebellum, receives mirror information of the action that reaches motoneurones via the propriospinal neurones, and this constitutes a perfect efference copy. This may allow the cerebellum to take corrective measures with a minimal delay, for which purpose it has at its disposal the rubrospinal and reticulospinal tracts which project directly to C3–C4 propriospinal neurones (Chapter 10, p. 454). Internal feedback of this type may regulate a forthcoming movement at its onset. Feedback inhibitory interneurones also have ascending projections to the LRN, indicating that correction of the movement takes into account the output from propriospinal neurones and the input that they receive from feedback inhibitory interneurones. Such copies of the propriospinally mediated input to motoneurones and of their feedback inhibition could play a crucial role when using trial and error in motor learning. Evidence for similar ascending projections of the cervical propriospinal relay has so far not been sought in human subjects, but they exist in the macaque monkey (Chapter 10, p. 455), and there are so many analogies between the propriospinal systems in the cat and the human that the projections are likely.

Co-contractions of antagonists at the same joint

Since Sherrington's demonstration of the reciprocal innervation of opposing muscles, it was for long thought that antagonistic muscles were inactive during most voluntary movements. Co-activation of antagonistic finger and wrist muscles is used in the precision grip and the power grip. Co-contractions of antagonists also occur in many voluntary tasks, such as when unpredictable perturbations may be encountered or when learning a new motor task (cf. Smith, 1981; Akazawa, Milner & Stein, 1983; Llewellyn, Yang & Prochazka, 1990).

Control of spinal pathways during co-contraction of antagonists

Hinge joints

A comprehensive review of the extensive work by Jens Nielsen on co-contraction at the ankle joint has been published in a thesis (1998).

Reciprocal Ia inhibition

Reciprocal Ia inhibition between antagonistic ankle muscles is almost completely suppressed when dorsiflexors and plantar flexors are voluntarily activated simultaneously (see pp. 225–7). The suppression is greater than expected from the sum of the effects of separate dorsiflexion and plantar flexion contractions, and results from a suppressive central control specific to co-contraction (see below). Reciprocal Ia inhibition is depressed maximally even at low co-contraction levels, and there is no modulation as the strength of co-contraction increases.

Homonymous recurrent inhibition

Homonymous recurrent inhibition of soleus motoneurones is increased during co-contractions with respect to rest, regardless of the strength of the contraction (see pp. 180–1). Because of the descending inhibition of Renshaw cells during separate strong contractions of soleus (cf. p. 515), the higher the contraction strength the greater is increased the recurrent inhibition during co-contraction when compared to plantar flexion at equivalent

EMG activity. Increased recurrent inhibition during co-contraction is greater than expected from the sum of the effects evoked by separate dorsiflexion and plantar flexion and, again, this points to a control specific to co-contraction. The control could simply be a suppression of the descending inhibition of the recurrent pathway observed during separate plantar flexion, leaving the motor discharge-induced excitation of Renshaw cells unopposed by descending inhibition. However, suppression of the descending control cannot account for all of the features of the increased recurrent inhibition during co-contraction, suggesting the existence of a supplementary descending facilitation of Renshaw cells (see Chapter 4, p. 181). The increased recurrent inhibition has two effects: (i) reduction of the gain of the motor output (see p. 534), and (ii) suppression of reciprocal Ia inhibition, via recurrent depression of Ia interneurones.

Presynaptic inhibition of Ia terminals

Presynaptic inhibition on Ia terminals on motoneurones of soleus and tibialis anterior is increased during voluntary co-contraction of the two muscles. This increased presynaptic inhibition is largely due to a descending control that could be specific for co-contraction (see p. 361). Increased presynaptic inhibition also has two effects: (i) suppression of the monosynaptic Ia excitation of the involved motoneurone pools (see p. 534), and (ii) suppression of reciprocal Ia inhibition because of the reduction of the input to Ia inhibitory interneurones.

Fusimotor drive

Co-contractions may involve greater fusimotor drive to the contracting muscles than occurs during isolated contractions producing equivalent EMG (see p. 135). The increased γ drive would be required to maintain an effective Ia feedback despite increased presynaptic inhibition on Ia terminals (see above), and would be in line with the fusimotor activation found in the cat in balancing tasks in which the animal has to co-contract antagonistic muscles (Hulliger *et al.*, 1989).

Reciprocal Ia inhibition vs. recurrent inhibition

There is a conflict between the control of reciprocal Ia inhibition and that of the motor pool output by recurrent inhibition at hinge joints: marked recurrent inhibition is required during strong co-contractions to suppress reciprocal Ia inhibition, but the more active the recurrent inhibition the smaller the gain of the motoneurone pool (see p. 179). Thus strong co-contractions that produce high joint stiffness (see below) occur at the expense of a relatively low output gain. This probably explains why, at hinge joints, less voluntary EMG is produced during co-contraction tasks than during isolated contractions of single muscles (Tyler & Hutton, 1986).

Ball joints

Non-reciprocal group I inhibition

Radial-induced non-reciprocal group I inhibition of FCR motoneurones is moderately reduced during the co-contraction of antagonistic wrist muscles. The inhibition was greater than the sum of the inhibitions during separate ECR and FCR voluntary contractions in the two subjects investigated by Nielsen & Kagamihara (1992) during a power grip, but of the same magnitude in a larger population during co-contraction of ECR and FCR producing tonic wrist abduction (Raoul *et al.*, 1999). It is likely that more forearm and hand muscles would have been active in the former task than the latter.

Presynaptic inhibition of Ia terminals

Presynaptic inhibition on Ia terminals on FCR motoneurones is decreased to a similar extent during separate wrist flexion or extension and during co-contraction of wrist muscles, whether associated with tonic wrist abduction or a power grip (R. Katz & J. C. Lamy, unpublished data).

Control of the decreased inhibition between antagonists

The suppression of reciprocal inhibition, whether Ia inhibition at hinge joints or non-reciprocal group I inhibition at ball joints, allows antagonistic motoneurone pools to be activated together without the effects of the interposed reciprocal inhibition.

Spinal mechanisms

During co-contraction reciprocal inhibition between antagonistic ankle muscles is depressed with respect to rest, and this suggests that transmission through the pathway mediating reciprocal inhibition is actively depressed. Increases in recurrent inhibition and presynaptic inhibition on Ia terminals (see above) contribute to an active inhibition. However, the relationship between these mechanisms and the strength of the contraction is different: reciprocal Ia inhibition is maximally depressed even at low co-contraction levels, but recurrent inhibition and presynaptic inhibition on Ia terminals increase with the strength of co-contraction. Moreover, there are no projections from Renshaw cells to the interneurones of non-reciprocal group I inhibition between wrist muscles (see pp. 207–8), and presynaptic inhibition on Ia terminals on wrist motoneurones is decreased during co-contraction (see above). This implies that other mechanisms contribute to the decoupling of motoneurones and interneurones mediating reciprocal Ia or non-reciprocal group I inhibition.

Different cortical drive for flexion-extension movements and co-contractions

Results in the monkey

The results suggest that there is a different cortical drive for these two types of contraction.

(i) Some cortical cells are active during co-contraction tasks, but not during flexion-extension movements (Humphrey & Reed, 1983).

(ii) Fetz & Cheney (1987) found that some corticospinal neurones with a 'reciprocal' pattern during activity of antagonistic wrist motoneurones (i.e. with facilitation of agonist and inhibition of antagonist) were vigorously active during flexion–extension movements, but could stop firing during a power grip involving co-contraction of wrist flexors and extensors. Conversely, during power grip there was activation of cortical neurones that only excited agonist motoneurones (i.e. without inhibition of the antagonist). Because only 2% of the corticospinal (but 15% of the rubrospinal) cells have monosynaptic excitatory projections on both antagonistic wrist flexors and extensors (Fetz *et al.*, 1989), Humphrey & Tanji (1991) suggested that the cortical command for co-contraction of antagonists must be mediated through common driving of cortico-motoneuronal cells which themselves innervate only one set of synergists, or through an oligosynaptic pathway with diverging projections on antagonistic motoneurones. The propriospinal system would be a good candidate since, apart from propriospinal neurones that project to both motoneurones and Ia inhibitory interneurones, others project only to motoneurones and are assumed to subserve the co-contraction of antagonists (Alstermark *et al.*, 1990).

Results in human subjects

Experiments using magnetic stimulation of the motor cortex have provided evidence for differential cortical control of flexion–extension movements and co-contractions (Nielsen *et al.*, 1993). This finding is also suggested by analyses of coherence in the time and frequency domains (cf. Chapter 1, pp. 48–9) for tibialis anterior and soleus units during co-contraction (Hansen *et al.*, 2002).

Joint stiffness

Joint stiffness measured during voluntary contraction as the stretch-induced torque increment, i.e. the resistance to external load, has two components, part caused by reflex mechanisms (reflex

stiffness), and the rest (non-reflex stiffness) by the active and passive properties of the muscle (building of cross-bridges, tendon compliance, etc). Strong co-contraction results in greater stiffness of the limb about the joint than with activity of any of the two antagonistic muscle groups separately. This holds true at all joints investigated: elbow, interphalangeal joints of the fingers, thumb, and ankle (Feldman, 1980; Akazawa, Milner & Stein, 1983; Carter, Crago & Gorman, 1993; Nielsen *et al.*, 1994). It has been shown at ankle level that the increased stiffness during co-contraction occurs too early after application of the external load to be mediated through a reflex mechanism (Nielsen *et al.*, 1994). Thus, the main cause of the greater stiffness during co-contraction with respect to separate activation of one of the antagonists could simply be that more muscles are then active (i.e. at ankle, not only the antagonistic pretibial flexors and soleus, but also the gastrocnemius medialis and peroneus longus).

Control of the stretch reflex at hinge joints

Because co-contraction of the different muscles operating at the ankle will stabilise the joint in difficult tasks (see above), there may be no need for additional stiffness through an active stretch reflex. On the contrary a low gain, ensured by increased presynaptic inhibition of Ia terminals and by facilitated (or at least unsuppressed) recurrent inhibition (see above), will prevent oscillations and clonus from developing (see Matthews, 1972; Rack, 1981). Accordingly, the stretch reflex is reduced during weak, and mainly unchanged during strong co-contractions (Nielsen *et al.*, 1994).

Control of the excitation at ball joints

Renshaw cells

A different control of the motor output is likely at wrist level, because of the particular pattern of Renshaw cell projections (see p. 171).

(i) Mutual recurrent inhibition between FCR and ECR motoneurones allows the gain of the motor output to be modulated in parallel in wrist flexors and extensors during co-contractions. Thus, in a co-contraction intended to produce a power or precision grip in a given wrist position, Renshaw cell discharge produced by the dominating contraction of either muscle (extensors or flexors) can automatically adjust the contraction of the antagonist.

(ii) The absence of projections from Renshaw cells to inhibitory interneurones mediating non-reciprocal group I inhibition between wrist flexors and extensors enables a parallel increase in the output gain and joint stiffness at this joint. This is not possible at hinge joints (see above).

In conclusion, during co-contractions, the particular organisation of recurrent inhibition at wrist level allows automatic adjustment of the output gain in the antagonistic pair, and a more flexible descending control of Renshaw cells because, during strong co-contractions, they can be inhibited without jeopardising joint stiffness.

Stretch reflex

The findings that increased recurrent inhibition is not required and that presynaptic inhibition is not increased (see above) fit with the need for a firmer mechanical *muscle* support during co-contractions at ball than at hinge joints. Under these conditions, several non-exclusive mechanisms might prevent the stretch reflex braking into oscillations.

(i) Reciprocal Ia inhibition is almost completely suppressed at hinge joints, but non-reciprocal group I inhibition between wrist muscles is only moderately suppressed, and the group Ia and Ib feedback activated during isometric contractions can still produce significant activation of the relevant inhibitory interneurones.

(ii) Tactile cutaneous receptors provide critical information for the control of grip force according to the physical properties (weight, slipperiness, shape and mass distribution) of the manipulated object. This is evidenced by the finding that subjects adapt to the loss of tactile sensibility by applying strong grip

forces regardless of these properties (see Johansson, 2002).

(iii) Although presynaptic inhibition is not increased during tonic co-contractions, this does not imply that the strong corticospinal facilitation of presynaptic inhibition on Ia terminals on wrist motoneurones cannot be activated if necessary (see p. 526).

(iv) Similarly, the fact that recurrent inhibition may be suppressed during strong co-contraction at wrist level does not mean that the flexible control of Renshaw cells cannot produce their facilitation if necessary.

Conclusions

The main cause of the greater joint stiffness during co-contraction is simply that more muscles are then active, not an increase in stretch reflex activity. The decoupling of motoneurones and group I inhibition (whether Ia inhibition at hinge joints or non-reciprocal group I inhibition at ball joints) contrasts with the linkage seen during simple flexion-extension movements, and allows the simultaneous activation of antagonistic motoneurone pools to be relatively unhindered by reciprocal inhibition. This decoupling results from different drives for the two types of movements from higher centres. In addition, the different organisation of the connections at hinge and ball joints accounts for the finding that, at hinge joints, the decoupling is completed by increased recurrent inhibition and presynaptic inhibition of Ia terminals. The absence of such mechanisms at ball joints allows more flexible descending control of co-contractions.

Maintenance of bipedal stance

Only the maintenance of upright bipedal stance is considered here. Postural adjustments occur in many other situations, e.g. in the upper limb to provide support to hand movements, and have been considered above, with isometric contractions or co-contractions. Similarly postural adjustments occur in the lower limbs in standing subjects when the upper limbs are moved. Unlike the quadrupedal digitigrade stance of the cat, humans balance on their skeleton as an inverted pendulum (see below). They expend little energy in doing so, using limited muscle activity to correct reflexly for destabilising sway. The control of body sway during quiet stance and of responses to destabilising perturbations to stance may involve different mechanisms and are therefore treated separately.

Normal quiet standing

Because the centre of gravity is maintained over a relatively small base of support, human standing posture is inherently unstable. Body instability, therefore, has a high potential energy, leading to the priority of equilibrium control during almost all motor tasks including quiet standing. During quiet standing, the body's centre of mass is maintained a few centimetres in front of the ankle joint. This posture requires a background triceps surae activity, which is, however, not continuous, and little muscular activity is needed to maintain balance (Bonnet *et al.*, 1976). The main body sway occurs in the sagittal plane, where there are quasi-random spontaneous alternating movements of the centre of mass, which happen mostly at the ankle joint (e.g. Diener *et al.*, 1984a; Horak & Nashner, 1986; Gatev *et al.*, 1999). It has therefore become common to regard the body as an inverted pendulum pivoted at the ankle joint (e.g. Gurfinkel & Osevets, 1972; Fitzpatrick *et al.*, 1992; Fitzpatrick, Burke & Gandevia, 1996; Winter *et al.*, 1998; Loram, Kelly & Lakie, 2001). Smaller sway movements also occur in the frontal plane, mostly at hip level, where they are stabilised by hip abductor–adductor activity (Deniskina & Levik, 2001).

Multiple sources of feedback

Afferent cues from multiple sources

Several sources of afferent feedback are used to stabilise body sway during quiet standing: visual,

vestibular, proprioceptive, and tactile. Many studies have shown that, when various sensory systems are manipulated, body sway is affected: (i) absence of visual input increases the amplitude and speed of the fluctuations of the body (e.g. Day *et al.*, 1993) and postural responses are induced by moving visual scenes (Dichgans *et al.*, 1972; Lestienne, Soechting & Berthoz, 1977); (ii) loss of vestibular function alters low-frequency stabilisation of the body (Dichgans & Diener, 1989), and postural responses may be induced by galvanic vestibular stimulation (Lund & Broberg, 1983; Fitzpatrick, Burke & Gandevia, 1994; Day *et al.*, 1997); (iii) ischaemic blockade of group I afferents produces 1 Hz sway (Mauritz & Dietz, 1980), and postural responses are induced by vibration of ankle muscles (Eklund, 1972); (iv) a role of group II muscle afferents is suggested by balance abnormalities observed in patients with different types of peripheral neuropathy (Chapter 7, p. 320); (v) blockade of the afferent input from the foot sole by cooling the feet increases body sway (Magnusson *et al.*, 1990), and specific postural responses are induced by vibration of various zones of the sole of the foot (Kavounoudias, Roll & Roll, 1999).

Redundancy of the different feedbacks?

Signals coming from these multiple sensory sources co-vary with every postural change. Because exclusion of any of the above cues may be compensated for in normal subjects with a small (but significant) increase in body sway, the question of redundancy arises. However, once again, redundancy is more apparent than real. For instance, tactile afferents from the sole of the foot are involved in the regulation of small-amplitude sway, whereas the muscle afferent discharge from ankle muscles is greater for larger and faster body movements at the ankle. In addition, evidence for the necessity of an interaction between information from multiple sensory sources comes from investigations showing that the direction of the postural response produced by one cue varies with the position of the limb, trunk or head (for references see Kavounoudias, Roll & Roll, 2001). Such an integration is necessary because (i) precise information about the movement of the centre of gravity with regard to the feet is necessary at all times, and (ii) balance has to be maintained during body configurations that may be continuously changing.

Intrinsic stiffness of the ankle

Intrinsic spring-like properties of the calf muscles

The extent to which the intrinsic spring-like properties of the calf muscles contribute to stabilising the body during standing has recently become the subject of much debate. A model has been proposed in which the intrinsic elastic properties of the activated ankle musculature alone would be sufficient to stabilise the upright posture. The stabilisation of quiet standing would then be an essentially passive process without any significant active or reactive component, except for the background setting of the triceps surae tonic activity. In this case, any deflection from the body's equilibrium position would generate a restoring torque that would cause it to regain that position after a decrementing series of oscillations; as the body sways the energy could be stored and released in the stretching and shortening of the spring (Horak & Macpherson, 1996; Winter *et al.*, 1998, 2001).

Contrary arguments

However, attractive as it may be, this simple hypothesis does not explain a number of findings. (i) Other calculations have shown that ankle stiffness was overestimated in the above model and is actually insufficient to stabilise the body (Morasso & Schieppati, 1999; Morasso & Sanguineti, 2002). (ii) Aponeurosis, tendon and foot rather than muscle fibres appear to be the main source of ankle stiffness in quiet standing (Loram & Lakie, 2002b). (iii) There is clear evidence that the EMG is modulated in anticipation of postural sway (see below), and this is directly contrary to the theory that the central nervous system is not involved in regulating balance sway by sway. (iv) In different subjects and patients with modifications of their

postural patterns the main problem is not a reduction of muscle force (and thus of muscle stiffness) but, rather, a sensory deficit. In them, the reduced efficacy of predictive control due to unreliable sensory information is frequently compensated for by increased ankle stiffness resulting from co-contraction of ankle muscles (Morasso & Sanguineti, 2002).

Stretch reflex

It was initially assumed that shifts in the centre of gravity stimulated stretch afferents of postural muscles that contracted reflexively (Hellebrandt, 1938). This strategy was questioned because the angular motion at the ankle was less than necessary to elicit a stretch reflex (Kelton & Wright, 1949). It was then demonstrated repeatedly that spinal stretch reflexes are not relevant to the maintenance of quiet standing (Gurfinkel, Lipshits & Popov, 1974; Soames & Atha, 1981; Loram & Lakie, 2002a). Accordingly, (i) quiet stance is only slightly destabilised by selective suppression of the group I input from ankle muscles (see pp. 89–90), and (ii) reflex responses evoked in the soleus by changes in the proprioceptive afferent input due to near-physiological perturbations have a low loop gain (~1), which is insufficient to explain stable standing as a feedback control task (Fitzpatrick, Burke & Gandevia, 1996). This low gain may be due in part to increased presynaptic inhibition on Ia terminals on soleus motoneurones in quiet standing (see pp. 363–5), and is desirable because the combination of high gain and the long latencies of human stretch reflexes might have introduced instability (Matthews, 1972; Rack, 1981).

Anticipatory control of the body sway

The low loop gain of the soleus EMG response evoked by small perturbations and the fact that they lead ankle movements with a phase advance that increases with frequency are consistent with a *feedforward* process (Fitzpatrick *et al.*, 1992; Fitzpatrick, Burke & Gandevia, 1996). Thus, the afferent information produced by one sway would be used to predict and generate an appropriate reflex response for future sway. Positive correlations, with time lags in cross-correlations of 200–300 ms between triceps surae EMG activity and antero-posterior motion of the centre of gravity have been interpreted similarly as a feedforward modulation of muscle activity. This modulation would aim at establishing the minimal ankle stiffness needed to restrict the allowable amount of sway (Gatev *et al.*, 1999). Finally, the low intrinsic ankle stiffness found by Loram & Lakie (2002a,b) implies the existence of an active neural control for modulating ankle torque, and they suggest that this control is predictive, possibly originating from muscle spindles. Interestingly, changes in voluntary set can minimise body sway when the subject attempts to be still (Fitzpatrick *et al.*, 1992), but the predictive process is also operative when the subject is paying minimal attention (Loram & Lakie, 2002a).

Conclusions

In quiet standing, attenuation of body sway is due to a combination of the visco-elastic stiffness of the ankle and a predictive neural response to sway. Afferent cues from multiple sources evoked by previous swaying movements interact to organise a predictive neural response producing the least ankle stiffness needed to keep the extent of sway minimal.

Unstable postural tasks requiring prolonged muscle contractions

During quiet standing, because the knee joint is locked in extension and crossed by the gravitational action line, there may be little or no activity in thigh muscles (Kelton & Wright, 1949; Clemensen, 1951; Joseph, 1962; de Vries, 1965; Soames & Atha, 1981). In contrast, when leaning backward or forward, co-contractions of quadriceps and tibialis anterior or hamstrings and triceps surae, respectively, are required to maintain the upright stance, and quadriceps and triceps surae are co-contracted when standing on tip of toes with knees and hips

slightly flexed (a position referred to as 'preparation for hopping', see p. 183).

Spinal mechanisms contributing to the maintenance of balance during unstable stance

Muscle spindle discharges

In the postural tasks described above, excessive sway would produce a lengthening contraction. The co-activated γ drive would then represent a powerful input to muscle spindle endings and produce large Ia and group II afferent discharge from the receptor-bearing muscle(s). In this respect, even the very weak tonic or phasic contractions occurring during quiet stance to maintain balance are accompanied by increased fusimotor drive sufficient to affect spindle afferent discharge (see p. 135), and co-contraction is associated with increased fusimotor activity. Ia and group II discharges contribute to maintaining firing of homonymous motoneurones (cf. p. 512). They also favour the associated co-contraction of heteronymous muscle(s) operating at another joint, through the strong transjoint excitatory connections that link human lower-limb muscles, whether monosynaptic Ia (Chapter 2, Table 2.1) or group II (Chapter 7, Table 7.3) (pp. 528–9).

Group II excitation

Transmission of heteronymous group II excitation from tibialis anterior to quadriceps and from gastrocnemius medialis to semitendinosus is facilitated when leaning backwards and forwards, respectively. This facilitation is probably due to decreased activity in the monoaminergic control of transmission in group II pathways from the locus coeruleus in the brainstem (see pp. 313–14). Transmission of the group II discharge from stretched leg muscles, tuned up by decreased activity in the monoaminergic control system, might thus contribute to the co-contraction of leg and thigh muscles required to maintain bipedal stance when leaning backwards or forwards.

Heteronymous excitation from muscle spindles

Monosynaptic Ia excitation

Transjoint monosynaptic Ia connections often link a muscle or group of muscles to a pair of antagonists operating at another joint (Table 2.1). Through focused corticospinal drive, recurrent inhibition of 'unwanted' motoneurones allows the selection of the heteronymous Ia connections appropriate for a given task (see pp. 183–4).

Heteronymous group II excitation

Group II pathways also link one muscle to antagonists operating at another joint (Table 7.3). The selection of the appropriate group II pathway for a given postural task might be ensured by the parallel activation of inhibitory pathways preventing activation of muscles not required in this task (see p. 514).

Conclusions

During unstable upright stance, co-contractions of ankle and knee muscles are required to maintain posture. Fusimotor-driven spindle discharges contribute to the discharge of homonymous and heteronymous motoneurones, the latter through transjoint excitatory projections of Ia and group II afferents. Transmission of group II excitation is facilitated, possibly due to decreased monoaminergic gating. Ia and group II excitations can be focused by descending control of Renshaw cells and of interneurones controlling the transmission of spindle group II inputs to motoneurones.

Responses to fast transient perturbations of stance

A sudden and unexpected perturbation to posture can occur when standing on unstable ground or on a minimal area. The mechanisms involved in the control of quiet standing are then not sufficient to stabilise the body, and transient perturbations produce

complex reflexes with short-, medium- and long-latency responses involving the stretched muscle, its antagonists and synergists operating at other joints.

Reflex responses in ankle muscles

The responses of ankle muscles have been investigated extensively, and conflicting results have been obtained due to different experimental approaches: (i) perturbations produced by rotating the platform on which the subjects stood (toe-up/toe-down), translating the platform (backward–forward), or by applying brisk acceleration impulses during stance on a treadmill, all stimuli that are unusual in real life, but convenient to analyse the different responses produced by the perturbation; (ii) different velocities of displacement; and (iii) responses in ankle extensors recorded either in the gastrocnemius medialis or in the soleus. The issue is further complicated by discrepancies in the definition of the various EMG responses according to their latencies, and it is not always clear whether latencies were measured to the onset or the peak of the response (latencies to the onset are given below). It is now agreed that, provided the ankle rotation is fast enough ($>40^\circ$ s^{-1}, Diener *et al.*, 1984a), passive ankle dorsiflexion evokes a response with three components: short- and medium-latency responses in the triceps surae, and long-latency responses in the antagonistic tibialis anterior (Diener *et al.*, 1984a; Dietz, Quintern & Berger, 1984; Nardone *et al.*, 1990; Allum *et al.*, 1998). Usually, there is no short-latency response in the tibialis anterior (see p. 90), where the first response produced by passive plantar flexion is a medium-latency response. This is followed by a long-latency response in the triceps surae. These responses have been shown to be mediated through different pathways.

Short-latency responses (M1)

M1 responses occur at latencies compatible with a monosynaptic response, and several other arguments indicate that it can be attributed to the short-latency Ia spinal stretch reflex, without a significant contribution from cutaneous afferents from the foot (see p. 89). They are larger in soleus than in gastrocnemius medialis, in accordance with the greater sensitivity of small motoneurones (slow-twitch motor units) to Ia inputs (see pp. 79–81).

Medium-latency responses (M2)

M2 responses occur with a latency of ~80 ms in the soleus and tibialis anterior (Fig. 7.2(*c*),(*m*); Schieppati *et al.*, 1995; see p. 293). Several lines of evidence indicate that they are mediated through a muscle group II spinal pathway without a significant contribution from cutaneous afferents from the foot (see pp. 297–9). The picture is, however, complicated by three features, which may explain the discrepancies between the different groups: (i) the larger the short-latency response the smaller the medium-latency response in the triceps surae, because of an interaction between group Ia and group II excitations at motoneuronal and interneuronal levels (see p. 301); (ii) because of the mechanical delay produced by muscle stretch, the latencies of both short- and medium-latency responses are slightly longer after translation than after rotation (Schieppati *et al.*, 1995); (iii) a later response often occurs in the stretched muscle (M3, see below) where it may merge with the medium-latency response (Diener *et al.*, 1986).

Long-latency responses in the stretched muscle (M3)

M3 responses have a latency of ~120 ms in the triceps surae. Such long-latency responses in triceps surae were described during stepping, hopping and landing and referred to as the 'functional stretch reflex' (Melvill Jones & Watt, 1971a, b). Then, Nashner (1976), using small platform displacements described a similar 'functional stretch reflex' in the gastrocnemius medialis occurring at 120 ms. The ability of these responses to be modified by will (Melvill Jones & Watt, 1971a, b) suggests that they are, in part, voluntary reactions. However, the possibility exists that a transcortical

reflex pathway is also involved in their generation, even though the latency of the transcortical response evoked by stretch of the tibialis anterior during voluntary contraction is shorter, ~95 ms (see the Discussion in Petersen *et al.*, 1998). In further studies more rapid stretches were shown to produce gastrocnemius medialis responses at earlier latencies (95–120 ms; Nashner, Woollacott & Tuma, 1979; 73–110 ms, Horak & Nashner, 1986), compatible with the medium-latency responses described above.

Long-latency responses in the antagonist

Long-latency responses in the antagonist of the stretched muscle appear with a latency of ~130–140 ms. Thus, after passive dorsiflexion, short- and medium-latency responses in the triceps surae are followed by a long-latency response in the tibialis anterior (Diener *et al.*, 1984a; Nardone *et al.*, 1990; Schieppati *et al.*, 1995), and vice versa after passive plantar flexion. The neural pathway of these responses has not been elucidated. The only existing indications are: (i) they occur at a latency shorter than a voluntary movement triggered by a somatosensory stimulus (Diener *et al.*, 1984a); (ii) skin receptors from the foot and joint receptors from the ankle are not essential for their generation (Diener *et al.*, 1984b); (iii) because, when holding a stable frame, the time courses of the suppression of the medium- and long-latency responses with respect to the go-stimulus are the same, it has been suggested that they would be both mediated through group II afferents and subjected to a similar monoaminergic control from the brainstem (see below; Schieppati & Nardone, 1995); (iv) the finding that, in patients with absent Achilles tendon jerks due to a peripheral neuropathy, the long-latency response in the tibialis anterior is hardly modified (Allum *et al.*, 1998) is also consistent with mediation by group II afferents; and (v) given that the latency of the transcortical response evoked by stretch of the tibialis anterior during voluntary contraction, probably mediated by Ia afferents, is ~95 ms (Petersen *et al.*, 1998), the longer latency of the long-latency responses in antagonists during stance is compatible with a response to stretch fed by group II afferents transmitted over a transcortical pathway.

Cutaneous reflexes

The different responses described above are not modified significantly after ischaemic blockade of cutaneous afferents (Diener *et al.*, 1984b). This finding does not exclude a role for cutaneous information in rapid postural control. In a further investigation, blocking the afferent input from feet and ankles resulted in a change in the strategy (see below) used to restore balance (Horak, Nashner & Diener, 1990). In addition, there is evidence that early excitatory (E1) spinal cutaneous reflexes from the foot, which are not apparent during voluntary contraction, are revealed during active stance, especially when it is unstable (see p. 430). It is also worth noting that the withdrawal responses of tibialis anterior are suppressed when the leg has a supporting role (see p. 414).

Function of the short-, medium- and long-latency responses

The stabilising function of the different responses described above is well illustrated by the marked differences observed in their magnitude (i) when the 'postural set' is changed, and (ii) when changing the nature of the pitch perturbation (rotation or translation) while keeping the same angular velocity at the tibio-tarsal joint (Schieppati *et al.*, 1995). Muscle stretch by itself is not responsible solely for these responses: (i) the responses are greatly attenuated when the same kind of stimulus is applied in seated subjects (Bussel *et al.*, 1980; Diener *et al.*, 1984b); and (ii) the 'functional stretch reflex' provides compensation for postural disturbances only when the reflex is appropriate to the task (Nashner, 1976).

Monosynaptic Ia responses in triceps surae

M1 responses in triceps surae might have a role when subjects have to correct rapid unexpected perturbations of stance (Dietz, Mauritz & Dichgans, 1980),

but their functional value is questioned by the finding that they are not modified when the 'postural set' is changed so that they can make only a limited contribution to maintaining posture (see p. 413). When the perturbation is a rotation, they may actually destabilise balance. The large increase in presynaptic inhibition on Ia terminals on soleus motoneurones during active standing probably helps limit the efficacy of the Ia spinal stretch reflex in this muscle (see pp. 363–5).

Medium-latency group II-mediated responses

Group II-mediated M2 responses are markedly reduced when subjects support themselves by holding onto a stable frame, i.e. when the responses are no longer required to ensure the equilibrium (Nardone *et al.*, 1990). The response suppression is related to the transition to a new stabilised 'postural set'. Presumably there would then be a reduction in descending inhibitory control on the locus coeruleus, leading to increased activity from the locus, and thereby to increased gating of group II volleys. In contrast, when balance is unstable, transmission in group II pathways is tuned upwards by decreased activity in this monoaminergic control system (see pp. 312–14). The influence of the 'central set' on medium-latency responses is demonstrated also when perturbations of various velocities and amplitudes are delivered under variable conditions (Horak, Diener & Nashner, 1989): (i) the scaling of the response disappears when perturbations are randomised; (ii) the response is directionally specific, and related to expectation of the amplitude of perturbation (e.g. a smaller response when a smaller perturbation is expected); and (iii) the response is greater when the velocity of the perturbation is unexpected. Medium-latency responses are minimised with rotations around an axis co-linear with the ankle joint, because such perturbations produce little shift in the centre of mass, and large responses would destabilise posture. In contrast, translations produce a shift in the centre of mass in the opposite direction to the perturbation, and large medium-latency responses are then required to prevent the subject from falling (Schieppati *et al.*, 1995). This is so when the perturbation is produced by unexpected acceleration impulses during stance on a treadmill. Accordingly, medium-latency responses are then larger in the tibialis anterior than in the triceps surae because the shifts in the centre of mass are larger when forward translations are produced (Dietz, Horstmann & Berger, 1988).

Long-latency responses in the antagonist

Long-latency responses in the antagonist of the stretched muscle are suppressed, much as are M2 responses, when the subject holds onto a stable frame and postural reactions are no longer needed (Schieppati & Nardone, 1995). Dependence on postural set is also indicated by the changes in amplitude and latency which occur when the subject actively leans forwards or backwards prior to the platform tilt (Diener *et al.*, 1983; Schieppati *et al.*, 1995). They are also influenced significantly by the type of pitch perturbation. Thus, long-latency responses in the antagonist are consistent and strong after pitch rotations, where they compensate for the destabilisation produced by earlier (short- and medium-latency) responses. In contrast, after pitch plane perturbations, the main postural reaction is exerted by the medium-latency responses, and long-latency responses in the antagonist are attenuated considerably (tibialis anterior) or even absent (triceps surae), because there is little or no need for much further correction. They reappear, however, after translations of unexpected or unpractised amplitude because they aim at correcting the errors in the magnitude of the initial response (Horak, Diener & Nashner, 1989).

Responses in the kinematic chain

Muscles operating at joints other than ankle

Responses produced by transient postural perturbations are not limited to ankle muscles. Short-, medium-, and long-latency stretch responses in the triceps surae are accompanied and completed by analogous activity in the flexor digitorum brevis, which creates a background torque securing

contact of the foot with the ground. Tibialis anterior responses are accompanied by reflexes in the extensor digitorum brevis (Schieppati *et al.*, 1995). Importantly, group II mediated medium-latency responses in ankle muscles also radiate in a distal-to-proximal sequence to thigh and trunk muscles on the same dorsal or ventral aspect, involving triceps surae, hamstrings and paraspinals or tibialis anterior, quadriceps and abdominals (Nashner, 1977; Horak & Nashner, 1986). It is probable that increased transmission in heteronymous group II pathways from ankle to knee muscles contributes to this radiating activation, much as it does in prolonged co-contractions of ankle and knee muscles when leaning forwards and backwards (see p. 538).

Ankle and hip strategies

To maintain stability following a perturbation, the subject must restore the centre of mass to a position within a point of support bounded by the heels and toes. To that end, the nervous system has, at its disposal, two distinct strategies that can either be used separately or be combined to produce adaptable control of the centre of mass in the sagittal plane (Nashner & McCollum, 1985; Horak & Nashner, 1986). In the 'ankle strategy' the body is configured as a single-segment inverted pendulum that sways about the ankle joints. Sway is reduced by exerting torque about the ankles and changing the centre of pressure under the feet. This strategy is achieved with the distal-to-proximal activation of the muscles on the same aspect (see above). For this strategy to be effective mechanically, the support surface must be relatively firm and in contact with the full length of the foot. When the feet are not in full contact with the ground, i.e. when standing on tip of toes, another strategy is required mechanically. This is the 'hip strategy', in which the body configuration is actively changed. Rotations at the hip are used to propel the trunk and produce horizontal shear forces between the feet and the ground. This strategy is achieved by activation of abdominals, quadriceps and tibialis anterior in a proximal-to-distal sequence. The two strategies become mixed when: (i) the support surface is of intermediate size; (ii) the velocity of the pitch plane translation is increased (Runge *et al.*, 1999); or (iii) the somatosensory input from the feet and ankles is blocked by ischaemia (Horak, Nashner & Diener, 1990).

Conclusions

To maintain stability following a perturbation in the sagittal plane, an 'ankle strategy' is generally adopted in which the response initiated in the stretched ankle muscle radiates in a distal-to-proximal sequence to thigh and trunk muscles on the same dorsal or ventral aspect. Besides the monosynaptic stretch reflex, transient postural perturbations produce a medium-latency response in the stretched ankle muscle, mediated through a spinal group II pathway, and a long-latency response in the antagonist, presumably mediated through a transcortical pathway. These two responses depend heavily on 'postural set' and have a functional value in stabilising the upright posture.

Gait

Spinal pathways play two roles in the control of human gait (see Nielsen & Sinkjær, 2002a): (i) a contribution to the activation of muscles during normal unperturbed gait; and (ii) the mediation of some of the reactions to sudden external perturbations during gait. Pioneering studies of the changes in transmission in spinal pathways during human gait were performed by the groups in Edmonton and Nijmegen (for reviews, see Stein & Capaday, 1988; Zehr & Stein, 1999; Duysens, Clarac & Cruse, 2000).

Characteristics of human walking

Biomechanical characteristics

Peculiarities of human walking

Human walking is unique because it is bipedal and plantigrade, with the knee nearly fully extended throughout a stride. Thus, in the main part of the

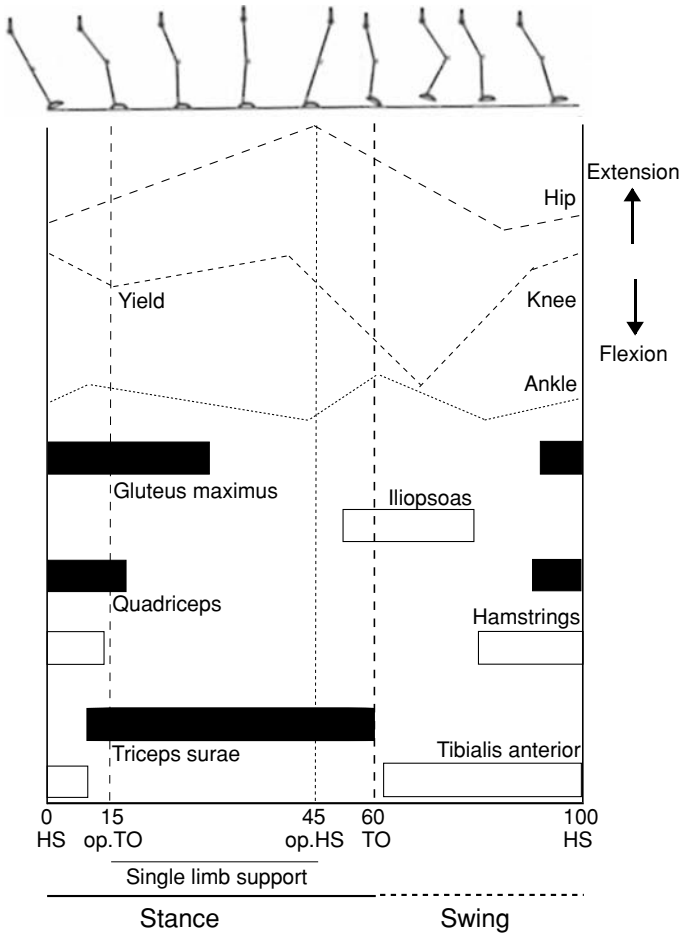


Fig. 11.3. The timing of the movements of lower limb joints and of the EMG activity of the main extensors and flexors during a stride. Vertical lines indicate the time of ipsilateral heel strike (HS, continuous thick lines) and toe-off (TO, thick dashed line), and contralateral toe-off (op.TO, thin dashed line) and heel strike (op.HS, thin dotted line). Abscissa, step cycle normalised as percentage of the duration of one stride from HS (0%) to the next HS (100%). Stance (continuous thick line) and swing (dashed thick line) phases, and the period of single limb support (continuous thin line) are indicated below the abscissa. The movements of the hip, knee and joint are sketched extension upwards, and flexion downwards. The timing of the EMG activity of the main extensors (filled boxes, gluteus maximus at the hip, quadriceps at the knee, triceps surae at the ankle) and flexors (open boxes, iliopsoas at the hip, hamstrings at the knee, tibialis anterior at the ankle) is indicated.

stance phase, when only one leg is on the ground, a sudden perturbation may endanger balance seriously, and reflex mechanisms are required to restore it more than in quadrupeds. The contact with the ground throughout the stance phase is made successively by the heel, foot sole, and toes, with the result that the movements of the knee and ankle are almost out of phase (see Fig. 11.3), contrary to digitigrade animals, such as cats, where they are in phase. Finally, the almost full knee extension throughout a stride allows the lower limbs to be 'used more like struts' (Capaday, 2002) and to minimise

muscle activity, and thus energy expenditure. Indeed, at full extension the tibia rotates slightly on the femur and this 'locks' the knee so that much force is then required to flex it. As a result patients with severe proximal weakness can stand reasonably stably once they are upright. Similarly, they may have less problem when walking with the stance phase than the swing phase, during which the foot must be lifted to clear the ground.

Use of external energy

As in other walking animals, human walking uses external energy. Thus, there is an alternate transfer between gravitational–positional energy and forward kinetic energy within each stride, as takes place in an inverted pendulum pivoted at the ankle joint. This transfer is greatest at intermediate walking speeds and can account for up to 70% of the total energy changes taking place in a stride, leaving only 30% to be supplied by muscles (Cavagna, Heglund & Taylor, 1977). Thus, after the yield of the knee, despite the unipedal stance, knee extension is ensured by the resultant of kinetic and gravitational forces, without quadriceps activity (Fig. 11.3). Similarly, at normal speed, knee flexion is not produced by contraction of hamstrings, but mainly results from the mechanical effect of hip flexion.

Pattern of muscle activation

Timing of activation of the main muscles

The timing of activation of the main extensors and flexors operating at hip, knee and ankle joints, and the movements of these joints throughout a step cycle are sketched in Fig. 11.3. The major groups of muscles are active at or around the beginning and termination of the stance and swing phases, and most of them are quiet during midstance. Thus, at heel strike, contractions of the gluteus maximus, quadriceps and tibialis anterior stiffen the lower limb. In early stance the gluteus maximus continues to extend the hip, quadriceps controls the slight passive flexion of the knee (yield of the knee), and tibialis anterior controls the rapid passive plantar flexion of the ankle. During the ensuing period, the hip continues to extend, the knee begins an extension movement (without quadriceps contraction, see above), and the ankle yields in dorsiflexion. Among muscles represented in Fig. 11.3, triceps surae is then the only one to be active, controlling the rotation of the body about the ankle joint. This contraction is accompanied by that of the intrinsic plantar muscles. In the pre-swing period, the triceps surae contraction produces active ankle extension contributing to the push-off of the body, and initiates knee flexion through the contraction of the biarticular gastrocnemius muscles. At around the time of toe off, the contractions of the iliopsoas and tibialis anterior produce hip and ankle flexion, so that the leg can swing through.

Lengthening loaded contractions

Normal gait is relatively slow, so that many muscles undergo slow loaded contractions, that are often eccentric (e.g. quadriceps during the yield of the knee, tibialis anterior in early stance, triceps surae during most of the stance, see Fig. 11.3). These are circumstances when the co-activated γ drive can represent a powerful input to muscle spindle endings, driving spindle discharges at high rates (see pp. 135, 137).

Conclusions

During the main part of the stance phase of human walking, only one leg is on the ground. In addition, while walking on even ground, muscle contractions are minimised to reduce energy expenditure. Reflex mechanisms must therefore be ready to compensate for any perturbation resulting for unexpected ground unevenness. The inherent instability of human walking may explain the development of some reflex activities (e.g. transcortical) that are particular to humans.

Changes in transmission in spinal pathways during normal walking

Evidence for changes in transmission in spinal pathways

Several lines of evidence show that changes in transmission in spinal pathways occur during human walking. These changes are specific to gait, as revealed by studies comparing transmission in spinal pathways during walking and during voluntary contractions when standing using comparable EMG levels and limb positions.

Monosynaptic Ia excitation of soleus motoneurones

The modulation of the soleus H reflex has been investigated extensively throughout the step cycle. The soleus H reflex increases progressively during stance in parallel with the on-going EMG of soleus, reaching a maximum at ~30% of the step cycle, but it is still inhibited with respect to its size in the standing position. It then decreases abruptly at the end of the stance phase to disappear more or less completely during the swing phase (Capaday & Stein, 1986; Crenna & Frigo, 1987; Yang & Whelan, 1993; Simonsen & Dyhre-Poulsen, 1999; Ferris *et al.*, 2001). The smaller amplitude of the H reflex during walking than standing for comparable EMG levels has been attributed to increased presynaptic inhibition on Ia terminals on soleus motoneurones during gait (Morin *et al.*, 1982; Capaday & Stein, 1987). Evidence for increased presynaptic inhibition was later demonstrated, and it was shown that the modulation of presynaptic inhibition throughout a stride parallels that of the H reflex (Faist, Dietz & Pierrot-Deseilligny, 1996; see p. 366). It has been argued that the phase-dependent presynaptic inhibition of the soleus H reflex results from proprioceptive feedback produced by passive movements about the knee and hip joints (Brooke *et al.*, 1995). However, investigations limiting knee joint movements during walking have demonstrated that the reflex inhibition is of central origin (Garrett, Kerr & Caulfield, 1999; Schneider, Lavoie & Capaday, 2000). The even lower amplitude of the soleus H during difficult beam walking presumably results from a greater increase in presynaptic inhibition of soleus Ia terminals (Llewellyn, Yang & Prochazka, 1990). This finding supports the view that, in difficult motor tasks, increased γ drive (as recorded in the cat, cf. Hulliger *et al.*, 1989) provides supraspinal centres with increased feedback gain and resolution, but that this increased gain could cause instability of the segmental stretch reflex and is therefore controlled by increased presynaptic inhibition on Ia terminals on motoneurones. Increased presynaptic inhibition of homonymous soleus Ia terminals also accounts for two further findings:

(i) The suppression of the on-going soleus EMG caused by unloading soleus during the stance phase is modified little by ischaemic blockade of Ia afferents, though it is slightly delayed. This indicates that these afferents contribute little to the soleus contraction, except by depolarising the relevant propriospinal neurones, thereby potentiating any subsequent excitatory input (see pp. 315–16).

(ii) Transmission of vibration-induced homonymous Ia excitation to soleus motoneurones does not increase during walking (see p. 365).

Monosynaptic Ia excitation of quadriceps motoneurones

The modulation of the quadriceps H reflex also parallels that of the on-going EMG activity throughout a stride, and the reflex is maximal in early stance. At heel strike, there is indirect evidence for a decrease in presynaptic inhibition of homonymous Ia terminals on quadriceps motoneurones. Later, presynaptic inhibition of quadriceps Ia terminals increases progressively to become greater than during standing at the moment of the yield of the knee (see p. 365).

Group II excitation

Homonymous group II excitatory discharges produced by the lengthening contraction of the

triceps surae during the stance phase contribute significantly to the discharge of soleus motoneurones (see pp. 315–16). On the other hand, transmission of heteronymous group II excitation from pretibial flexors to quadriceps motoneurones is facilitated in early stance with respect to voluntary contraction in standing. However, here again depolarisation of the relevant propriospinal neurones by group I afferents might play a crucial role by potentiating the group II excitation. (see pp. 318–20).

Non-reciprocal group I inhibition

Non-reciprocal group I inhibition from pretibial flexors to biceps femoris, seen during voluntary contractions when standing or at the end of the swing phase of walking, is reversed to oligosynaptic group I excitation in early stance (see pp. 274–5).

Recurrent inhibition

Heteronymous recurrent inhibition from soleus to quadriceps is suppressed during the stance phase when there is a simultaneous contraction of soleus and quadriceps (Iles, Ali & Pardoe, 2000).

Reciprocal Ia inhibition

Modulation of reciprocal Ia inhibition between ankle muscles during the walking cycle helps ensure that antagonistic motoneurones are not activated inappropriately (i.e. triceps surae during the swing phase and tibialis anterior during the stance phase). However, the modulation is less marked than during voluntary movements (see pp. 227–9).

Mechanisms operating at ankle level

Stabilisation of the ankle

The appearance in humans of Ia connections, not matched by equivalent projections of recurrent inhibition, between ankle muscles that are not synergistic in flexion–extension movements (from tibialis anterior to gastrocnemius medialis, and soleus to peroneus brevis [see p. 170]), might help stabilise the ankle during the stance phase of locomotion. As discussed above the modulation of reciprocal Ia inhibition is less marked than during voluntary movements, and this could also reflect the need to stabilise the ankle. However, the main source of stabilisation of the ankle comes from the large stretch responses, spinal or transcortical, produced in both the soleus and tibialis anterior during the stance phase (see pp. 548–9).

Prevention of excessive reflex activity in triceps surae

Because the homonymous group II excitation of the triceps surae contributes to the excitation of soleus motoneurones during the stance phase (see pp. 315–16), less central drive is necessary to activate the motoneurones. The lengthening contraction of triceps surae also evokes a strong Ia discharge, but Ia spinal pathways are not responsible for the decrease in soleus EMG activity when the muscle is unexpectedly unloaded (see above). Actually, the Ia spinal stretch reflex of gastrocnemius-soleus does not contribute greatly to the push-off of the body produced by the triceps surae contraction during the late stance phase (see p. 89). The role of this reflex is to help resist and thereby slow the passive ankle dorsiflexion produced by extrinsic mechanisms, such as kinetic and gravitational forces. However, the calf muscle resistance must be overcome if the body is to be brought forward, and excessive reflex activity in triceps surae should be minimised or a stiff gait would appear, much as may be seen in spastic patients (see p. 575). Several mechanisms help to limit the reflex activation of triceps surae motoneurones: (i) the absence in humans of heteronymous Ia connections from gastrocnemius medialis to soleus, and their weakness from soleus to gastrocnemius medialis or from gastrocnemius medialis to gastrocnemius lateralis, as compared with the cat (see p. 93); (ii) the strong increase in presynaptic inhibition on Ia terminals on triceps surae motoneurones (see above); (iii) the

absence of depression of Ib inhibition to soleus motoneurones by cutaneous afferents from the foot sole (see p. 274); and (iv) the strong propriospinally mediated inhibition of triceps surae motoneurones by group I discharges from intrinsic plantar muscles, which are activated in midstance (see p. 503).

Mechanisms operating at knee level

Quadriceps contraction is important in the early stance phase of human walking

At this time, the weight of the body is shifted to the leg that is about to begin the stance phase (Fig. 11.3), and the quadriceps contraction is required to stabilise the knee joint in order to support the body weight. In this phase of gait, several spinal mechanisms help the quadriceps contraction (see above): (i) transmission to quadriceps motoneurones of the strong group I–group II excitation due to the lengthening contraction of the tibialis anterior is facilitated; (ii) Ib inhibition of quadriceps motoneurones may be suppressed by the cutaneous volley created by the foot contacting the ground (see p. 274); (iii) recurrent inhibition to quadriceps motoneurones is decreased; and (iv) presynaptic inhibition of Ia terminals on quadriceps motoneurones is decreased at heel strike, although it is increased later in order to allow for the yield of the knee and hence the smoothness of the gait.

Reversal of Ib inhibition to biceps femoris

Ib inhibition from pretibial flexors to biceps motoneurones is reversed to facilitation in early stance. Thus, at this time of the gait cycle, the muscle afferent discharge elicited by the lengthening contraction of ankle dorsiflexors facilitates both quadriceps (see above) and biceps motoneurones. Facilitation of the antagonists operating at knee level contributes to their co-contraction, and helps ensure maximal stability of the knee joint when the leg is about to carry the body weight.

Transition

Proprioception might be involved in timing the different phases of locomotion, and both load- and position-dependent triggering of phase transition have been proposed in cat investigations.

(i) Decrease in Ib excitatory input from extensors due to unloading of these muscles appears critical to terminating the stance phase and initiating the swing in the cat but, so far, there is no conclusive evidence for such a mechanism in human walking (see p. 273).

(ii) A specific degree of hip extension must be reached before the leg is lifted (Grillner & Rossignol, 1978), and this position-dependent triggering found in the cat is probably controlled by the length-sensitive Ia afferent input from stretched hip flexors (Andersson & Grillner, 1983). Vibration of the rectus femoris produces an earlier onset time of the swing phase (Verschueren *et al.*, 2003). Although this effect was modest, it suggests the involvement of Ia afferents from thigh muscles in triggering the transition from the stance phase to swing in humans.

Conclusions

In agreement with the different functional role of ankle and knee extensors during human walking, spinal mechanisms are tuned to have opposite effects on these two motoneurone pools. Thus, they provide a safety factor for the quadriceps contraction and contribute to locking the knee in early stance, while they prevent excessive reflex activity from occurring in the triceps surae.

Reactions to external perturbations

Unexpected perturbations may occur during walking: the foot may slip, the ground may give way under the weight of the body, or the swinging leg or foot may hit an obstacle. In all these cases, compensatory reactions signalled by changes in the afferent muscle and/or cutaneous feedback are

required to restore balance (see Nielsen & Sinkjær, 2002a,b).

Stretch-induced responses

Ia spinal stretch reflexes

These responses are consistently observed in triceps surae, provided the velocity of the perturbation is high enough. (The absence of a stretch reflex following acceleration of a treadmill on which the subjects were walking was probably because the perturbation was not of sufficient velocity; see p. 89.) Given the strong presynaptic inhibition of Ia terminals on soleus motoneurones during walking, and the concordant absence of involvement of Ia afferents in the unloading-induced decrease in on-going soleus EMG activity (see above), the existence of a significant stretch reflex may seem surprising. In fact, presynaptic inhibition on Ia terminals does not have the same effect on a reflex response to an abrupt stretch in which Ia afferents may discharge at relatively high frequency as on the Ia afferent feedback evoked by an on-going movement in which discharge rates are lower (see Nielsen & Sinkjær, 2002a; see pp. 354–5). Ia spinal stretch-induced responses appear in the soleus only during the stance phase, and in particular in early stance (10–20% of the step cycle), when the torque resulting from the soleus stretch reflex is greatest. This timing suggests that these responses play a role in the stabilisation of the supporting limb during walking rather than contributing to propulsion during late stance (Zehr & Stein, 1999). Only small variable stretch-induced responses appear at monosynaptic Ia latency in the tibialis anterior, when it is active in the swing phase (see p. 89).

Stumbling over an obstacle

Monosynaptic responses occur simultaneously in ankle and knee flexors and extensors when stumbling over an obstacle during the swing phase of walking. These responses have been attributed to transmission through the limb of the sudden jar created by the collision with the obstacle, causing widespread muscle spindle activation. However, it is possible that the widespread heteronymous monosynaptic Ia connections between ankle and knee muscles also contribute to the diffusion of these monosynaptic responses (see p. 94).

Medium-latency responses

Group II responses are also consistently produced in the soleus by stretch when soleus is active during the stance phase (Grey *et al.*, 2001), in particular in early stance (10–20% of the step cycle, Nielsen & Sinkjær, 2002a). In contrast, M2 stretch-induced responses in tibialis anterior are smaller when it is active during the swing phase than during voluntary contractions (see p. 318). Studies of stretch-induced group II-mediated medium-latency responses in the tibialis anterior during the stance phase have yielded discordant results: the absence of the M2 response to a vertical displacement (Christensen *et al.*, 2001) contrasts with the large group II responses radiating to the quadriceps and contralateral tibialis anterior in response to a horizontal displacement of the whole body, due to deceleration of a treadmill on which the subjects were walking (Berger, Dietz & Quintern, 1984; pp. 316–18). In fact, contrary to a vertical displacement that is limited to the ankle, deceleration of a treadmill results in a large postural disturbance, which favours group II-mediated medium-latency responses to stretch (see p. 541).

Long-latency responses

Long-latency stretch responses (M3) in soleus are elicited rarely during voluntary plantar flexion, but are recorded readily during the stance phase of walking in healthy subjects. The latency of these long-latency responses is compatible with a transcortical pathway, and this is supported by the finding that they are not seen in patients with corticospinal lesions (Sinkjær *et al.*, 1999). During the stance phase of walking, despite the inhibition of tibialis anterior motoneurones due to reciprocal Ia inhibition (see p. 546), long-latency stretch responses mediated

by Ia afferents are much larger than in the swing phase when the muscle is active (Christensen *et al.*, 2001). These long-latency responses to stretch are not present in patients with corticospinal lesions (Christensen *et al.*, 2000), and there is evidence that they result from increased excitability of tibialis anterior-coupled cortical neurones (Capaday *et al.*, 1999; Christensen *et al.*, 2001). They are the only significant responses in tibialis anterior after vertical displacement of the ankle in the stance phase.

Functional implications

In both soleus and tibialis anterior, stretch-induced responses of significant size, whether spinal reflexes mediated by Ia or group II afferents or transcortical responses, are elicited only during the stance phase. Based on this, Christensen *et al.* (2000) proposed that stretch responses play little or no role in the regulation of limb trajectory during the swing phase of gait, but are involved mainly in ensuring the stability of the supporting limb during the stance phase. During the unipedal part of the stance phase, a sudden perturbation would jeopardise balance. The large stretch responses in antagonistic ankle flexors and extensors, as the heteronymous monosynaptic Ia connections linking the different muscles acting around the ankle, may help counteract surface unevenness and prevent a twisted ankle.

Cutaneous reflexes

Cutaneous responses during the swing phase

Reflex responses produced by low-threshold cutaneous afferents occur mainly during the swing phase in flexors of the ankle and knee (see pp. 430–2). The available evidence suggests that they are mediated largely through a supraspinal pathway, possibly transcortical, although this does not exclude a contribution from other supraspinal (spino-bulbospinal) or even spinal pathways (see p. 432). The pattern and timing of the cutaneous responses depend on the skin field stimulated. In early swing, stimuli to the sural and peroneal nerves have opposite effects on the on-going EMG of tibialis anterior: suppression by peroneal but facilitation by sural stimuli. There are also cutaneous responses in the contralateral muscles during walking and running (see p. 432).

Functional implications

The skin field-specific phase-dependent patterns of cutaneous reflexes indicate a dynamic control of cutaneous information from the foot throughout the step cycle (Van Wezel, Ottenhoff & Duysens, 1997). These reflexes appear to be adapted to move the perturbed leg away from the stimulus, with the general constraint of preserving the cadence and balance during the step cycle. For example, when the dorsum of the foot, innervated by the peroneal nerve, meets an obstacle during the swing phase, the suppressive response in the tibialis anterior combined with the excitation of hamstrings is adequate to clear the foot from the obstacle and prepare the leg to step over it, so enabling continuation of the walking pattern. However, when the tip of the foot strikes an obstacle in the transition from stance to swing, a cutaneous reflex originating from the skin field innervated by the sural nerve would provide an automatic mechanism to help dorsiflex the foot (see p. 432). Cutaneous afferent facilitation of reciprocal Ia inhibition of ankle extensors would help produce this ankle dorsiflexion (see pp. 214–15).

Conclusions

Stretch-induced responses ensure the stability of the supporting limb in the stance phase, while cutaneous reflexes allow the foot to clear an unexpected obstacle, in a manner analogous to the ‘stumbling corrective reaction’ observed in chronic spinal cats (see p. 387). An important difference from animal data is that, in humans, the responses evoked by muscle stretch or cutaneous stimulation are also, if not mainly, mediated through transcortical pathways. Because of this particular organisation, it is

possible, after any early spinal reflex compensation to make an 'additional voluntary reaction such as stopping the movement and/or shifting the body weight onto the other leg or – depending on the situation – continue the movement' (Christensen *et al.*, 2000).

Running, hopping, landing

Contrary to walking, during the stance phase of running and hopping and after the impact of landing, the short-latency Ia spinal stretch reflex of the triceps surae is superimposed on pre-programmed activity and contributes to the muscle contraction producing the pushing off of the foot. There is probably also a concomitant short-latency Ia stretch response in the quadriceps (see pp. 87–89). The Ia spinal stretch reflex can produce a mechanically effective contraction and provides a pathway through which rapid automatic load compensation to an unexpected disturbance can be generated. During such motor tasks, all extensors (plantar muscles of the foot, triceps surae, quadriceps and hamstrings [acting as hip extensors]) undergo a lengthening contraction that evokes a strong spindle afferent discharge. It is probable that the extended Ia connections linking muscles across lower limb joints contribute to the readjustment of limb position in the antigravity reaction of the extensors (see pp. 93–4). The load compensation provided by the Ia spinal stretch reflex is effective, despite the increased presynaptic inhibition of Ia terminals, because presynaptic inhibition has little effect on reflexes evoked by abrupt stretch (see pp. 354–5).

REFERENCES

Akazawa, K., Milner, T. E. & Stein, R. B. (1983). Modulation of reflex EMG and stiffness in response to stretch of human finger muscle. *Journal of Neurophysiology*, **49**, 16–27.

Allum, J. H. J., Bloem, B. R., Carpenter, M. G., Hulliger, M. & Halders-Algra, M. (1998). Proprioceptive control of posture: a review of new concepts. *Gait and Posture*, **8**, 214–42.

Alstermark, B., Kümmel, H., Pinter, M. J. & Tantisira, B. (1990). Integration in descending motor pathways controlling the forelimb in the cat. 17. Axonal projection and termination of C3–C4 propriospinal neurones in the C6–Th1 segments. *Experimental Brain Research*, **81**, 447–61.

Andersson, O. & Grillner, S. (1983). Peripheral control of cat's step cycle. II. Entrainment of central pattern generators for locomotion by sinusoidal movements during 'fictive locomotion'. *Acta Physiologica Scandinavica*, **18**, 229–39.

Beevor, C. E. (1904). *The Croonian Lectures on Muscular Movements and their Representation in the Central Nervous System*. London: Adlard.

Berger, W., Dietz, V. & Quintern, J. (1984). Corrective reactions to stumbling in man: neuronal coordination of bilateral leg muscle activity during gait. *Journal of Physiology (London)*, **405**, 1–37.

Bernstein, N. (1967). *The Coordination and Regulation of Movements*, 196 pp. Oxford: Pergamon.

Bonnet, M., Gurfinkel, S., Lipchits, M. J. & Popov, K. E. (1976). Central programming of lower limb muscular activity in the standing man. *Agressologie*, **17**, 35–42.

Brooke, J. D., Cheng, J., Misiaszec, J. E. & Lafferty, K. (1995). Amplitude modulation of the soleus H reflex in the human during active and passive stepping movements. *Journal of Neurophysiology*, **73**, 102–11.

Bussel, B., Katz, R., Pierrot-Deseilligny, E., Bergego, C. & Hayat, A. (1980). Vestibular and proprioceptive influences on the postural reactions to a sudden body displacement in man. In *Spinal and Supraspinal Mechanisms of Voluntary Motor Control and Locomotion*, ed. J. E. Desmedt, pp. 310–22. Basel: Karger.

Capaday, C. (2002). The special nature of human walking and its neural control. *Trends in Neurosciences*, **25**, 370–6.

Capaday, C. & Stein, R. B. (1986). Amplitude modulation of the soleus H-reflex in the human during walking and standing. *Journal of Neuroscience*, **6**, 1308–13.

(1987). Difference in the amplitude of the human soleus H-reflex during walking and running. *Journal of Physiology (London)*, **392**, 513–22.

Capaday, C., Lavoie, B., Barbeau, H., Schneider, C. & Bonnard, M. (1999). Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *Journal of Neurohysiology*, **81**, 129–39.

Carter, R. R., Crago, P. E. & Gorman, P. H. (1993). Nonlinear stretch reflex interaction during cocontractions. *Journal of Neurophysiology*, **69**, 943–52.

Cavagna, G. A., Heglund, N. C. & Taylor, C. R. (1977). Mechanical work in terrestrial locomotion: two basic mechanisms for minimizing energy expenditure. *American Journal of Physiology*, **233**, 243–61.

Cavallari, P., Fournier, E., Katz, R., Pierrot-Deseilligny, E. & Shindo, M. (1984). Changes in reciprocal Ia inhibition from wrist extensors to wrist flexors during voluntary movements in man. *Experimental Brain Research*, **56**, 574–6.

Christensen, L. O. D., Petersen, N., Andersen, J. B., Sinkjær, T. & Nielsen, J. B. (2000). Evidence for transcortical reflex pathways in the lower limb of man. *Progress in Neurobiology*, **62**, 251–72.

Christensen, L. O. D., Andersen, J. B., Sinkjær, T. & Nielsen, J. (2001). Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking. *Journal of Physiology (London)*, **531**, 545–57.

Clemensen, S. (1951). Some studies on muscle tone. *Proceedings of the Royal Society of Medicine*, **44**, 637–46.

Crenna, P. & Frigo, C. (1987). Excitability of the soleus H-reflex arc during walking and stepping in man. *Experimental Brain Research*, **66**, 49–60.

Datta, A. K., Harrison, L. M. & Stephens, J. A. (1989). Task-dependent changes in the size of the response to magnetic brain stimulation in human first dorsal interosseous muscle. *Journal of Physiology (London)*, **418**, 13–23.

Day, B. L., Rothwell, J. C. & Marsden, C. D. (1983). Transmission in the spinal Ia reciprocal inhibitory pathway preceding willed movements of the human wrist. *Neuroscience Letters*, **37**, 245–50.

Day, B. L., Marsden, C. D., Obeso, J. A. & Rothwell, J. C. (1984). Reciprocal inhibition between the muscles of the human forearm. *Journal of Physiology (London)*, **349**, 519–34.

Day, B. L., Steiger, M. J., Thompson, P. D. & Marsden, C. D. (1993). Effect of vision and stance width on human body motion when standing: implications for afferent control of lateral sway. *Journal of Physiology (London)*, **469**, 479–99.

Day, B. L., Severac Cauquil, A., Bartolomei, L., Pastor, M. A. & Lyon, I. N. (1997). Human body-segment tilts induced by galvanic stimulation: a vestibularly driven balance protection mechanism. *Journal of Physiology (London)*, **500**, 661–72.

Desmedt, J. E. (1983). Size principle of motoneuron recruitment and the calibration of muscle force and speed in man. In *Advances in Neurology*, vol. 39, *Motor Control Mechanisms in Health and Disease*, ed. J. E. Desmedt, pp. 253–61. New York: Raven Press.

Deviniskina, N. V. & Levik, Y. S. (2001). Relative contribution of ankle and hip muscles in regulation of the human orthograde posture in frontal plane. *Neuroscience Letters*, **310**, 165–8.

Dichgans, J. & Diener, H. C. (1989). The contribution of vestibulo-spinal mechanisms to the maintenance of human upright posture. *Acta Oto-Laryngologica*, **107**, 338–45.

Dichgans, J., Held, R., Young, L. R. & Brandt, T. (1972). Moving visual scenes influence the apparent direction of gravity. *Science* **178**, 1217–19.

Diener, H. C., Bootz, F., Dichgans, J. & Bruzek, W. (1983). Variability of postural 'reflexes' in humans. *Experimental Brain Research*, **52**, 423–8.

Diener, H. C., Dichgans, J., Bootz, F. & Bacher, M. (1984a). Early stabilization of human posture after a sudden disturbance: influence of rate and amplitude of displacement. *Experimental Brain Research*, **56**, 126–34.

Diener, H. C., Dichgans, J., Guschlbauer, B. & Mau, H. (1984b). The significance of proprioception on postural stabilization as assessed by ischaemia. *Brain Research*, **296**, 103–9.

Diener, H. C., Dichgans, J., Guschlbauer, B. & Bacher, M. (1986). Role of visual and static vestibular influences on dynamic posture control. *Human Neurobiology*, **5**, 105–13.

Dietz, V., Mauritz, K. H. & Dichgans, J. (1980). Body oscillations in balancing due to segmental reflex activity. *Experimental Brain Research*, **40**, 89–95.

Dietz, V., Quintern, J. & Berger, W. (1984). Corrective reactions to stumbling in man: functional significance of spinal and transcortical reflexes. *Neuroscience Letters*, **44**, 131–5.

Dietz, V., Hortsmann, G. & Berger, W. (1988). Involvement of different receptors in the regulation of human posture. *Neuroscience Letters*, **94**, 82–7.

Duysens, J., Clarac, F. & Cruse, H. (2000). Load-regulating mechanisms in gait and posture: comparative aspects. *Physiological Reviews*, **80**, 83–133.

Eklund, G. (1972). General features of vibration-induced effects on balance. *Upsala Journal of Medical Sciences*, **77**, 112–24.

Faist, M., Dietz, V. & Pierrot-Deseilligny, E. (1996). Modulation of presynaptic inhibition of Ia afferents during human gait. *Experimental Brain Research*, **109**, 441–9.

Feldman, A. G. (1980). Superposition of motor programs. I. Rhythmic forearm movements in man. *Neuroscience*, **5**, 81–90.

Ferris, D. P., Aagaard, P., Simonsen, E. B., Farley, C. T. & Dyrhe-Poulsen, P. (2001). Soleus H-reflex gain in humans walking and running under simulated reduced gravity. *Journal of Physiology (London)*, **530**, 167–80.

Fetz, E. E. & Cheney, P. D. (1987). Functional relations between primate motor cortex cells and muscles: fixed and flexible. *CIBA Foundation Symposia*, **132**, 98–117.

Fetz, E. E., Cheney, P. D., Mewes, K. & Palmer, S. (1989). Control of forelimb muscle activity by populations of corticomotoneuronal and rubrospinal cells. *Progress in Brain Research*, **80**, 437–49.

Fetz, E. E., Perlmutter, S. I., Prut, Y., Seki, K. & Votaw, S. (2002). Roles of primate spinal interneurons in preparation and execution of voluntary hand movement. *Brain Research Reviews*, **40**, 53–65.

Fitzpatrick, R., Gorman, R., Burke, D. & Gandevia, S. C. (1992). Postural proprioceptive reflexes in standing human subjects: bandwith of responses and transmission characteristics. *Journal of Physiology (London)*, **458**, 69–83.

Fitzpatrick, R., Burke, D. & Gandevia, S. C. (1994). Task-dependent reflex responses and movement illusions evoked by galvanic vestibular stimulation in standing humans. *Journal of Physiology (London)*, **478**, 363–72.

Fitzpatrick, R., Burke, D. & Gandevia, S. C. (1996). Loop gain of reflexes controlling human standing measured with the use of postural and vestibular reflexes. *Journal of Neurohysiology*, **76**, 3994–4008.

Foster, M. (1879). *Textbook of Physiology* (cited by Liddell, E. G. T. 1960, in the *Discovery of Reflexes*, p. 98 and 101, Clarendon Press, Oxford).

Garrett, M., Kerr, T. & Caulfield, B. (1999). Phase-dependent inhibition of the soleus H-reflexes during walking in humans is independent of reduction in knee angular velocity. *Journal of Neurophysiology*, **82**, 747–53.

Gatev, P., Thomas, S., Kepple, T. & Hallett, M. (1999). Feedforward ankle strategy of balance during quiet stance in adults. *Journal of Physiology (London)*, **514**, 915–28.

Georgopoulos, A. P. & Grillner, S. (1989). Visuomotor coordination in reaching and locomotion. *Science*, **245**, 1209–10.

Grey, M. J., Ladouceur, M., Andersen, J. B., Nielsen, J. B. & Sinkjær, T. (2001). Group II muscle afferents probably contribute to the medium latency soleus stretch reflex during walking in humans. *Journal of Physiology (London)*, **534**, 925–33.

Grillner, S. & Rossignol, S. (1978). On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Research*, **146**, 269–77.

Gurfinkel, V. S. & Osevets, M. (1972). Equilibrium dynamics of human vertical posture. *Biophysics*, **17**, 478–86.

Gurfinkel, V. S., Lipchits, M. J. & Popov, K. E. (1974). Is the stretch reflex the main mechanism in the system of regulation of the vertical posture of man? *Biophysics*, **19**, 761–6.

Hansen, S., Hansen, N. L., Christensen, L. O. D., Petersen, N. T. & Nielsen, J. B. (2002). Coupling of antagonistic muscles during co-contraction in humans. *Experimental Brain Research*, **146**, 282–92.

Hellebrandt, F. (1938). Standing as a geotropic reflex. The mechanism of the asynchronous rotation of motor units. *American Journal of Physiology*, **121**, 471–4.

Horak, F. B. & Macpherson, J. M. (1996). Postural orientation and equilibrium. In *Handbook of Physiology*, section 12, *Exercise: Regulation and Integration of Multiple Systems*, ed. L. B. Rowell & J. T. Shepherd, pp. 255–92. New York: Oxford University Press.

Horak, F. B. & Nashner, L. M. (1986). Central programming of postural movements: adaptation to altered support-surface configurations. *Journal of Neurophysiology*, **55**, 1369–81.

Horak, F. B., Diener, H. C. & Nashner, L. M. (1989). Influence of central set on human postural responses. *Journal of Neurophysiology*, **62**, 841–53.

Horak, F. B., Nashner, L. M. & Diener, H. C. (1990). Postural strategies with somatosensory and vestibular loss. *Experimental Brain Research*, **82**, 167–77.

Hulliger, M. (1984). The mammalian muscle spindle and its central control. *Reviews of Physiology, Biochemistry and Pharmacology*, **101**, 1–110.

Hulliger, M., Dürmüller, N., Prochazka, A. & Trend, P. (1989). Flexible fusimotor control of muscle feedback during a variety of natural movements. *Progress in Brain Research*, **80**, 80–103.

Hultborn, H. (2001). State-dependent modulation of sensory feedback. *Journal of Physiology (London)*, **533**, 5–13.

Hultborn, H. & Illert, M. (1991). How is motor behavior reflected in the organization at spinal systems? In *Motor Control: Concepts and Issues*, ed. D. R. Humphrey & H. J. Freund, pp. 49–73. New York: John Wiley & Sons.

Humphrey, D. R. & Reed, D. J. (1983). Separate cortical systems for control of joint movement and stiffness: reciprocal activation and coactivation of antagonists. *Advances in Neurology*, **39**, 347–72.

Humphrey, D. R. & Tanji, J. (1991). What features of voluntary motor control are encoded in the neuronal discharge of different cortical motor areas? In *Motor Control: Concepts and Issues*, ed. D. R. Humphrey & H. J. Freund, pp. 413–43. New York: John Wiley & Sons.

Iles, J. F., Ali, A. & Pardoe, J. (2000). Task-related changes of transmission in the pathway of heteronymous spinal recurrent inhibition from soleus to quadriceps motor neurones in man. *Brain*, **123**, 2264–72.

Illert, M., Lundberg, A. & Tanaka, R. (1976). Integration in descending motor pathways controlling the forelimb in

the cat. 2. Convergence on neurones mediating disynaptic cortico-motoneuronal excitation. *Experimental Brain Research*, **26**, 521–40.

Jankowska, E. & Lundberg, A. (1981). Interneurones in the spinal cord. *Trends in Neurosciences*, **4**, 230–3.

Johansson, R. S. (2002). Dynamic use of tactile afferent signals in control of dexterous manipulation. *Advances in Experimental Medicine and Biology*, **508**, 397–410.

Joseph, J. (1962). Electromyographic studies of man's posture. *Clinical Orthopedics*, **25**, 92–7.

Kavounoudias, A., Roll, R. & Roll, J. P. (1999). Specific whole-body shifts induced by frequency-modulated vibrations of human plantar soles. *Neuroscience Letters*, **266**, 181–4.

(2001). Foot sole and ankle muscle inputs contribute jointly to human erect posture regulation. *Journal of Physiology (London)*, **532**, 869–78.

Kelton, I. W. & Wright, R. D. (1949). The mechanism of easy standing by man. *Australian Journal of Experimental Biology and Medicine*, **27**, 505–16.

Lemon, R., Sasaki, S., Naito, K. *et al.* (2004). Cortico-motoneuronal system and dexterous finger movements. *Journal of Neurophysiology*, **92**, 3601–3.

Lestienne, F., Soechting, J. & Berthoz, A. (1977). Postural readjustments induced by linear motion of visual scenes. *Experimental Brain Research*, **28**, 363–84.

Livingston, R. B., Paillard, J., Tournay, A. & Fessard, A. (1951). Plasticité d'une synergie musculaire dans l'exécution d'un mouvement volontaire chez l'Homme. *Journal de Physiologie (Paris)*, **43**, 605–19.

Llewellyn, M., Yang, J. F. & Prochazka, A. (1990). Human H-reflexes are smaller in difficult beam walking than in normal treadmill walking. *Experimental Brain Research*, **83**, 22–8.

Loram, I. D. & Lakie, M. (2002a). Human balancing of an inverted pendulum: position control by small, ballistic-like, throw and catch movements. *Journal of Physiology (London)*, **540**, 1111–24.

(2002b). Direct measurement of human ankle stiffness during quiet standing: the intrinsic mechanical stiffness is insufficient for stability. *Journal of Physiology (London)*, **545**, 1041–53.

Loram, I. D., Kelly, S. M. & Lakie, M. (2001). Human balancing of an inverted pendulum: is sway size controlled by ankle impedance? *Journal of Physiology (London)*, **532**, 879–91.

Lund, S. & Broberg, C. (1983). Effects of different head positions on postural sway in man induced by a reproducible error signal. *Acta Physiologica Scandinavica*, **117**, 307–9.

Lundberg, A. (1973). The significance of segmental spinal mechanisms in motor control. In *Symposium 4th International Biophysics Congress, Moscow 1972*, pp. 9–23. Puschino, Moscow.

(1979). Multisensory control of reflex pathways. In *Reflex Control of Posture and Movement, Progress in Brain Research*, vol. 50, ed. R. Grant & O. Pompeiano, pp. 11–28. Amsterdam: Elsevier.

Lundberg, A., Malmgren, K. & Schomburg, E. D. (1987). Reflex pathways from group II muscle afferents. 3. Secondary spindle afferents and the FRA: a new hypothesis. *Experimental Brain Research*, **65**, 294–306.

Macpherson, J. M. (1991). How flexible are motor synergies? In *Motor Control: Concepts and Issues*, ed. D. R. Humphrey & H. J. Freund, pp. 33–47. New York: John Wiley & Sons.

Magnusson, M., Enbom, H., Johansson, R. & Pyykko, I. (1990). Significance of pressor input from the human feet in anterior-posterior postural control. The effect of hypothermia on vibration-induced body-sway. *Acta Oto-Laryngologica*, **110**, 182–8.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and Their Central Action*. 630 pp. London: Arnold.

Mauritz, K. H. & Dietz, V. (1980). Characteristics of postural instability induced by ischemic blocking of leg afferents. *Experimental Brain Research*, **38**, 117–19.

Melvill Jones, G. & Watt, D. G. D. (1971a). Observations on the control of stepping and hopping movements in man. *Journal of Physiology (London)*, **219**, 709–27.

(1971b). Muscular control of landing from unexpected falls in man. *Journal of Physiology (London)*, **219**, 729–37.

Merton, P. A. (1953). Speculations on the servo control of movement. In *The Spinal Cord, Ciba Foundation Symposium*, ed. J. L. Malcolm & J. A. G. Gray, pp. 84–91. Baltimore: University Park Press.

Morasso, P. G. & Sanguineti, V. (2002). Ankle muscle stiffness alone cannot stabilize balance during quiet standing. *Journal of Neurophysiology*, **88**, 2157–62.

Morasso, P. G. & Schieppati, M. (1999). Can muscle stiffness alone stabilize upright standing? *Journal of Neurophysiology*, **83**, 1622–6.

Morin, C., Katz, R., Mazières, L. & Pierrot-Deseilligny, E. (1982). Comparison of soleus H reflex facilitation at the onset of soleus contractions produced voluntarily and during the stance phase of human gait. *Neuroscience Letters*, **33**, 47–53.

Nardone, A., Romanò, C. & Schieppati, M. (1989). Selective recruitment of high-threshold human motor units during voluntary isotonic lengthening contraction of active muscles. *Journal of Physiology (London)*, **409**, 451–76.

Nardone, A., Giordano, A., Corrà, T. & Schieppati, M. (1990). Responses of leg muscles in humans displaced while

standing. Effects of types of perturbation and of postural set. *Brain*, **113**, 65–84.

Nashner, L. M. (1976). Adapting reflexes controlling the human posture. *Experimental Brain Research*, **26**, 59–72.

(1977). Fixed patterns of rapid postural responses during stance. *Experimental Brain Research*, **30**, 13–24.

Nashner, L. M. & McCollum, G. (1985). The organisation of human postural movements: a formal basis and experimental synthesis. *Behavioural Brain Sciences*, **8**, 135–72.

Nashner, L. M., Woollacott, M. & Tuma, G. (1979). Organization of rapid responses to postural and locomotor-like perturbations of standing man. *Experimental Brain Research*, **36**, 463–76.

Nielsen, J. B. (1998). *Co-contraction of Antagonistic Muscles in Man*. 18 pp. Laegeforeningens Forlag, Copenhagen.

Nielsen, J. & Kagamihara, Y. (1992). The regulation of disynaptic reciprocal Ia inhibition during co-contraction of antagonistic muscles in man. *Journal of Physiology (London)*, **456**, 373–91.

Nielsen, J. B. & Sinkjær, T. (2002a). Reflex excitation of muscles during human walking. *Advances in Experimental Medicine and Biology*, **508**, 369–75.

(2002b). Afferent feedback in the control of human gait. *Journal of Electromyography and Kinesiology*, **12**, 213–17.

Nielsen, J., Petersen, N., Deuschl, G. & Ballegaard, M. (1993). Task-related changes in the effect of magnetic brain stimulation on spinal neurones in man. *Journal of Physiology (London)*, **471**, 223–43.

Nielsen, J., Sinkjær, T., Toft, E. & Kagamihara, Y. (1994). Segmental reflexes and ankle joint stiffness during co-contraction of antagonistic ankle muscles in man. *Experimental Brain Research*, **102**, 350–8.

Petersen, N., Morita, H., Christensen, L. O. D., Sinkjær, T. & Nielsen, J. (1998). Evidence that a transcortical pathway contributes to stretch reflexes in the tibialis anterior in man. *Journal of Physiology (London)*, **512**, 267–76.

Rack, P. M. H. (1981). A critique of the papers by Houk, Crago and Rymer; Hoffer and Andreassen; Allum and Dietz. In *Muscle Receptors and Movement*, ed. A. Taylor & A. Prochazka, pp. 347–54. London: Macmillan.

Raoul, S., Aymard, C., Katz, R., Lafitte, C., Lo., E. & Pénicaud, A. (1999). Differential changes in Ia reciprocal inhibition at wrist level during voluntary contractions of flexor and extensor muscles in healthy subjects and hemiplegic patients. *Clinical Neurophysiology*, **110 Suppl.1**, S.138, PS-11.2.

Rothwell, J. C., Day, B. L., Berardelli, A. & Marsden, C. D. (1984). Effect of motor cortex stimulation on spinal interneurones in intact man. *Experimental Brain Research*, **54**, 382–4.

Runge, C. F., Schupert, C. L., Horak, F. B. & Zajac, F. E. (1999). Ankle and hip postural strategies defined by joint torques. *Gait and Posture*, **10**, 161–70.

Schieppati, M. & Nardone, A. (1995). Time course of 'set'-related changes in muscle response to stance perturbation in humans. *Journal of Physiology (London)*, **487**, 787–96.

Schieppati, M., Nardone, A., Siliotto, R. & Grasso, M. (1995). Early and late stretch responses of human foot muscles induced by perturbation of stance. *Experimental Brain Research*, **105**, 411–22.

Schneider, C., Lavoie, B. & Capaday, C. (2000). On the origin of the soleus H-reflex modulation pattern during human walking and its task-dependent differences. *Journal of Neurophysiology*, **83**, 2630–3.

Schomburg, E. D. (1990). Spinal sensorimotor systems and their supraspinal control. *Neuroscience Research*, **7**, 265–340.

Simonsen, E. B. & Dyhre-Poulsen, P. (1999). Amplitude of the human soleus H reflex during walking and running. *Journal of Physiology (London)*, **515**, 929–39.

Sherrington, C. S. (1906). *The Integrative Action of the Nervous System*. New Haven: Yale University Press.

Sinkjær, T., Andersen, J. B., Nielsen, J. B. & Hansen, H. J. (1999). Soleus long-latency stretch reflexes during walking in healthy and spastic humans. *Clinical Neurophysiology*, **110**, 951–9.

Smith, A. M. (1981). The coactivation of antagonist muscles. *Canadian Journal of Physiology and Pharmacology*, **59**, 733–747.

Soames, R. W. & Atha, J. (1981). The role of antigravity musculature during quiet standing in man. *Experimental Brain Research*, **47**, 159–67.

Stein, R. B. & Capaday, C. (1988). The modulation of human reflexes during functional tasks. *Trends in Neurosciences*, **11**, 326–32.

Tyler, A. E. & Hutton, R. S. (1986). Was Sherrington right about co-contractions? *Brain Research*, **370**, 171–5.

Van Wezel, B. M. H., Ottenhoff, F. A. M. & Duysens, J. (1997). Dynamic control of location-specific information in tactile cutaneous reflexes from the foot during human walking. *Journal of Neuroscience*, **17**, 3804–14.

Verschueren, S. M. P., Swinnen, S. P., Desloovere, K. & Duysens, J. (2003). Vibration-induced changes in EMG during human locomotion. *Journal of Neurophysiology*, **89**, 1299–307.

De Vries, H. A. (1965). Muscle tonus in postural muscles. *American Journal of Physical Medicine*, **44**, 275–91.

Windhorst, U. (Group report: Burke, R. E., Dieringer, N., Evinges, C. *et al.*) (1991). What are the output units of motor behavior and how are they controlled? In *Motor Control: Concepts and Issues*, ed. D. R. Humphrey & H. J. Freund, pp. 101–19. New York: John Wiley & Sons.

Winter, D. A., Patla, A. E., Prince, F. & Ishac, M. (1998). Stiffness control of balance in quiet standing. *Journal of Neurophysiology*, **80**, 1211–21.

Winter, D. A., Patla, A. E., Rietdyk, S. & Ishac, M. (2001). Ankle muscle stiffness in the control of balance during quiet standing. *Journal of Neurophysiology*, **85**, 2630–3.

Yang, J. F. & Whelan, P. J. (1993). Neural mechanisms that contribute to cyclical modulation of the soleus H-reflex in walking in humans. *Experimental Brain Research*, **95**, 547–56.

Zehr, E. P. & Stein, R. B. (1999). What function do reflexes have during human locomotion? *Progress in Neurobiology*, **58**, 185–205.

12

The pathophysiology of spasticity and parkinsonian rigidity

As discussed in Chapters 3–10, transmission in spinal pathways is controlled from descending tracts. This descending control is exerted on all interneurones, whether they mediate presynaptic inhibition of primary afferent terminals or postsynaptic effects. Transmission in multiple spinal pathways may be altered after a lesion of the central nervous system. These alterations contribute to the pathophysiological mechanisms underlying movement disorders following upper motor neurone lesions and basal ganglia diseases. A tonic imbalance between descending excitatory and inhibitory inputs on various spinal pathways accounts for the changes in muscle tone of spasticity and parkinsonian rigidity at rest. On the other hand, the loss of the normal descending modulation of these pathways during motor tasks, together with the abnormal descending command to motoneurones, contributes to the motor impairment of the patients. Methods used in clinical neurophysiology help determine the extent to which spinal pathways malfunction after a lesion of the central nervous system. Only spasticity following upper motor neurone lesions and Parkinson's disease are considered in the overview given in this chapter. The involvement of spinal pathways in the pathophysiology of other motor disorders, such as dystonia, has been discussed in previous chapters.

Spasticity

Spasticity is one of the components of the upper motor neurone syndrome, and occurs in a variety of diseases and disorders of the central nervous system, such as spinal cord injuries and diseases, multiple sclerosis, brain injuries, stroke and cerebral palsy. These conditions deserve special consideration because they are common (e.g. annually ~750 000 new stroke cases in USA, see Smith *et al.*, 1999), and they may cause a persistent handicap. Even though its contribution to the motor disability of patients needs to be revisited (see pp. 558–60), spasticity has given rise to much attention for two reasons: (i) it is the component of the upper motor neurone (or corticofugal, see below) syndrome most accessible to therapy; and (ii) it remains a key dividing point among major schools of physiotherapy, with some aiming at inhibiting spasticity (see Bobath, 1990) and other at encouraging it (see Brunnström, 1970).

It is generally assumed (e.g. Delwaide, 1985a), but so far not demonstrated, that analyses of the pathophysiological mechanisms underlying spasticity provided by clinical neurophysiological studies may be important, because therapeutic interventions might be more effective if targeted to the underlying pathophysiology. If this were so, accurate evaluation of the mechanisms underlying spasticity in individual patients would become increasingly important as appropriate treatment modalities were developed to reduce spasticity. These therapies include: botulinum toxin injection, blockade of peripheral nerves by alcohol or phenol, intrathecal and oral medication, and physical/occupational therapy (for review, see Satkunam, 2003). Moreover, clinical neurophysiological techniques may provide

the objective and quantitative data necessary for clinical trials and longitudinal studies and to follow the progress of individual patients.

What is spasticity? What is it not?

The title of this section has been borrowed from a paper by Landau (1980) who pointed out the careless use of the word spasticity, emphasising that it is only a facet of the upper motor neurone syndrome, not necessarily the one that causes the greatest disability. In the upper motor neurone syndrome, Jackson (1958) made the distinction between (i) negative symptoms due to loss of function such as weakness and loss of dexterity, and (ii) positive symptoms, due to exaggeration and/or distortion of normal behavioural responses to stimuli. Reflex release phenomena involving both stretch and flexor reflexes fall into this grouping. The differentiation into 'minus' and 'plus' symptoms may have outlived its usefulness.

(i) A 'minus' symptom may be due to a 'plus' symptom in the antagonistic muscle (Thilmann, 1993). This leads to a discussion of the motor impairment produced by spasticity (see below).

(ii) The loss of dexterity after stroke is not just a 'minus' symptom, because associated involuntary contractions (synkinesia) due to the transmission of the descending command by pathways other than the corticospinal tract (see p. 579) may impair co-ordination.

Definition

Spasticity and stretch reflex exaggeration

The most commonly used definition of spastic hypertonia, or spasticity, has been given by Lance (1980): 'spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes ('muscle tone') with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as a component of the upper motor neuron syndrome'. The tonic stretch reflex has been shown to have a low correlation with the briskness of the tendon jerks (Fellows, Ross & Thilmann, 1993), and this definition is far from perfect, but it remains the lowest common denominator on which most neurologists and physiologists may agree. Accordingly, in a subsequent workshop held in Essen in 1992, substantial discussion failed to formulate a better definition. Either the description was too simplistic, and therefore unhelpful, or the participants could not agree on the detailed quantitative features of the exaggerated stretch reflex in spastic hypertonia. Conflicting views were presented concerning the dominant abnormality of the increased resistance to passive stretch in spastic muscles: lowering of the stretch reflex threshold (Katz & Rymer, 1989), increase in the stretch reflex gain ('stiffness', Thilmann, Fellows & Garms, 1991), or mainly changes in the intrinsic properties of the muscle ('contracture', Dietz, Trippel & Berger, 1991).

Corticofugal syndrome

In the same workshop, it was proposed to rename the upper motor neurone syndrome the 'corticofugal syndrome' to reflect the fact that other descending pathways are involved, not solely the corticospinal projection. The alternative definition proposed of the corticofugal syndrome is 'a disorder of motor control due in part to reduction in cortical influences on the spinal cord, characterised by weakness, impaired coordination, spasticity, increased tendon jerks, and release of cutaneomuscular reflexes such as the Babinski response' (see Thilmann, 1993). However, attractive as it may be, it must be recognised that this proposition has not echoed as much, and the term upper motor neurone syndrome continues to be used in the literature.

Pathophysiology of spasticity varies with the causative lesion

Whatever the lesion of the central nervous system responsible for spasticity, the corticospinal tract is damaged. However, because the other descending pathways involved by the lesion are different after

cerebral and spinal lesions, it is not surprising that the pathophysiology of spasticity is different after stroke and spinal cord injury (pp. 575–82).

Clinical features of spasticity

Muscle tone and exaggerated tendon jerks

According to Lance's definition (see above), the clinical features required for spasticity are increased muscle tone and tendon jerk hyperreflexia, the increase in tone being more apparent the faster the stretching movement, often undetectable if extremely slow movements are used. There are other features of spasticity, such as clonus and the clasp-knife phenomenon, but these are not invariably demonstrable.

Clonus

Clonus is an oscillating reflex contraction of muscle, most easily produced for triceps surae, and now believed to be due to repetitive elicitation of the tendon jerk by the stretch-evoked muscle spindle volley triggered by the relaxation of the preceding reflex contraction (Szumski *et al.*, 1974; Hagbarth *et al.*, 1975). Thus, the relaxation of a vigorous reflex contraction stretches muscle spindle endings and can produce a volley that, given the hyperactivity of the reflex arc, is sufficient to trigger another reflex contraction. The presence of clonus is directly related to the tendon jerk hyperreflexia, and whether it can be elicited depends on the skill of the examiner who may need to adjust the stretch put on the contracting muscle to be optimal. As clonus subsides, the spindle discharge produced by relaxation of the twitch contraction gradually becomes dispersed. The rate of clonus is thus determined by the mechanical properties of muscle and the conduction time for the reflex arc.

Clasp-knife phenomenon

The clasp-knife phenomenon consists of the collapse in reflex tension during stretch of a reflexly contracting muscle, and is only demonstrable clinically for the quadriceps muscles, where the range of possible movement is large, allowing a relatively high velocity of passive movement. This produces a 'catch-and-give' sensation – the 'catch' due to the build-up of the resistance to stretch, the 'give' due to its subsequent suppression. This suppression is due to an autogenetic inhibitory process caused not by the activation of Ib afferents but by the convergent actions of FRA, particularly non-spindle group II and smaller muscle afferents, and cutaneous and joint afferents (see p. 326). It should be distinguished from the decrease in the resistance to stretch that occurs when a dynamic reflex response subsides as movement slows or ceases. This latter process underlies the feeling of the 'catch' when passively stretching muscles such as biceps and triceps brachii and, unlike the 'true' clasp-knife phenomenon at the knee, there is no true 'give' and it is not associated with an autogenetic inhibitory process (Ashby & Burke, 1971).

To what extent does spasticity contribute to motor impairment?

In neurological practice, the crucial question about spasticity is the extent to which it contributes to the motor impairment and limitation of activity in patients with a corticofugal syndrome. It is often assumed that a voluntary movement that stretches a spastic muscle might be expected to produce reflex activity that would oppose the movement. However, stretch reflex activity during movement depends both on the exaggeration of the stretch reflex and changes in the transmission in spinal pathways during active motor tasks (see pp. 573–5). Accordingly, it has been demonstrated repeatedly that neither the exaggeration of tendon jerks nor the increased resistance to passive stretch in the relaxed state can predict the contribution of spasticity to the disorders of voluntary movement or gait (e.g. see McLellan, 1977; Dietz, Quintern & Berger, 1981; Fellows *et al.*, 1993; Yelnik *et al.*, 1999).

Spastic restraint – a debated proposition

The contribution of spasticity to motor impairment has been the subject of vigorous discussion, and some divergences exist about whether stretch reflexes in an antagonistic muscle impede movement due to agonist contraction, by either limiting the amplitude of the movement and/or slowing it down. Several reports suggest that voluntary movements in spastic patients may be disrupted by exaggerated stretch reflexes (Dimitrijević & Nathan, 1967; Mizrahi & Angel, 1979; Benecke *et al.*, 1983; Corcos *et al.*, 1986; Knutsson, Mårtensson & Gransberg, 1997). In contrast, Dietz & Berger (1983) found no evidence for a significant contribution of exaggerated stretch reflexes in the gastrocnemius to the 'spastic gait' of post-stroke hemiparetic patients, and concluded that the increased resistance to stretch of spastic muscles mainly results from changes in non-neural factors (see pp. 572–3). These apparently conflicting views are actually due to the fact that different results may be obtained in patients with different lesions of the central nervous system, and/or in different muscle groups, in subjects performing different tasks.

Stroke patients

In stroke patients, there is evidence that the increased resistance to stretch in the triceps surae is due to mechanical rather than reflex causes (Perry *et al.*, 1978; Berger & Dietz, 1993; Ada *et al.*, 1998; Dietz, 2003; Sommerfeld *et al.*, 2004). Spasticity of the quadriceps and the resulting inability to flex the knee during the swing phase does not seem to affect the patient's speed of gait (Bohannon & Andrews, 1990), and is only disabling on stairs (Yelnik *et al.*, 1999). That reduction of spasticity will improve gait remains to be firmly established (Landau, 2003; Cramer, 2004) and, on the contrary, its reduction might be counterproductive as spasticity often helps support the body during locomotion (see Dietz, 2003). Conflicting results have been obtained concerning the resistance opposed by the biceps brachii to voluntary elbow extension: decreased stretch reflex threshold (Powers, Marder-Meyer & Rymer, 1988), increased stretch reflex gain (Thilmann, Fellows & Garms, 1991), but no evidence for abnormal stretch reflex (Dietz *et al.*, 1993; O'Dwyer, Ada & Neilson, 1996). Recently, Rymer's group have demonstrated that exaggerated stretch reflexes in the finger flexors contribute to the impairment of finger extension in stroke survivors (Kamper *et al.*, 2003).

Patients with cerebral palsy

In patients with cerebral palsy, the role of spasticity in the impairment of voluntary movement or gait has also been challenged (see Vaughan, Neilson & O'Dwyer, 1988; Neilson, O'Dwyer & Nash, 1990; Berger & Dietz, 1993). However, the prevailing view is that the exaggeration of stretch reflexes in *some* of these patients may give rise to crucial restraint to gait movements (e.g. Perry *et al.*, 1974; Knutsson, 1985; Tuzson, Granata & Abel, 2003). Accordingly, the usefulness of reducing spasticity is now generally accepted (using, e.g. botulinum toxin injections, for review, see Davis & Barnes, 2000).

Patients with spinal cord lesions

In patients with spinal cord lesions, in particular in spinal cord compression, chronic myelopathies or hereditary spastic paraparesis, there is evidence that exaggerated stretch reflexes can disrupt movement (Dimitrijević & Nathan, 1967; Mizrahi & Angel, 1979; Corcos *et al.*, 1986). Thus, abnormalities found in paraspastic patients investigated during the locomotor-like tasks of bicycling (Benecke *et al.*, 1983) and treadmill walking (Conrad, Benecke & Meinck, 1985) were more in favour of a neural origin of spastic hypertonia than of changes in the muscle itself. More recently, unwanted stretch reflex activity in the antagonist triggered by the dynamic concentric contraction of the agonist has been shown to limit the amplitude and/or to slow down the movement of knee muscles (Knutsson, Mårtensson & Gransberg, 1997).

Conclusions

Spasticity is characterised by an exaggeration of the stretch reflex. However, the exaggeration of the tonic stretch reflex has only a low correlation with the briskness of the tendon jerks. Moreover, the increased resistance to stretch is also, and perhaps mainly in some cases, due to changes in the intrinsic properties of muscle fibres. The contribution of exaggerated stretch reflexes to motor disability of patients with corticofugal lesions has been overestimated, and varies with the underlying cause, being more important in patients with spinal cord lesions than in stroke patients.

Spasticity and animal decerebrate rigidity are unrelated

If one admits, with most authors, that spasticity is characterised by an exaggeration of the stretch reflex (see above), two questions arise concerning its pathophysiology.

(i) What are the spinal mechanisms underlying this exaggeration?

(ii) Why do spinal pathways malfunction?

At first sight, human spasticity and animal decerebrate rigidity following intercollicular transection of the brainstem have some characteristics in common: the main feature of both is the increased reactivity to a stretch stimulus which is (i) more pronounced the faster the stretch is applied, and (ii) preferentially distributed to antigravity muscles. It was therefore presumed that the same spinal mechanisms might be responsible for the stretch reflex exaggeration characterising the two conditions. In decerebrate rigidity of the cat, the mechanisms include α hyperexcitability, γ over-activity, suppression of Ib inhibition, closure of pathways mediating FRA inhibition to extensor motoneurones, and possibly opening of pathways mediating oligosynaptic Ia and group II excitations (for review, see Matthews, 1972). The existence of an appropriate animal model of spasticity would have allowed the effects of pharmacological substances acting on specific spinal mechanisms to be tested in the preclinical phase. However, there are important differences between spasticity and animal decerebrate rigidity (Burke *et al.*, 1972; Denny-Brown, 1980). In particular, decerebrate rigidity immediately follows the causal lesion, while spasticity takes days, often weeks to develop. This gives time for rearrangements to occur at spinal level (see pp. 571–2).

Possible spinal mechanisms underlying the pathophysiology of spasticity at rest

As indicated in Fig. 12.1, many spinal mechanisms control the excitability of the stretch reflex, and an abnormality in any one of them might, theoretically at least, produce stretch reflex exaggeration. The functional derangements that could theoretically give rise to an exaggerated stretch reflex are listed below, with for each: (i) how it could produce spasticity; (ii) the method(s) currently used to investigate the mechanism, given that, in patients the methodology should be simple and rapid; and (iii) whether it actually contributes to spasticity.

Reduction of spasticity accompanies selective blockade of specific pathways (e.g. γ axons), and this has often been taken as an argument that overactivity of that pathway was a primary factor in the pathophysiology of spasticity. In fact, the excitability of the stretch reflex depends on an intact reflex arc and on several excitatory and inhibitory mechanisms. Blockade of any excitatory mechanism and/or facilitation of an inhibitory one will reduce the stretch reflex, even though its exaggeration (spasticity) is caused by other mechanisms.

Hyperexcitability of α motoneurones

Here, a normal stretch-induced reflex volley would produce an exaggerated response because motoneurones are closer to their discharge threshold. Landau & Clare (1964) did not find evidence for fusimotor hyperactivity, and assumed, in accordance with 'the law of parsimony', that hyperexcitability of α motoneurones was sufficient to account for spasticity. Hyperexcitability of α motoneurones may result

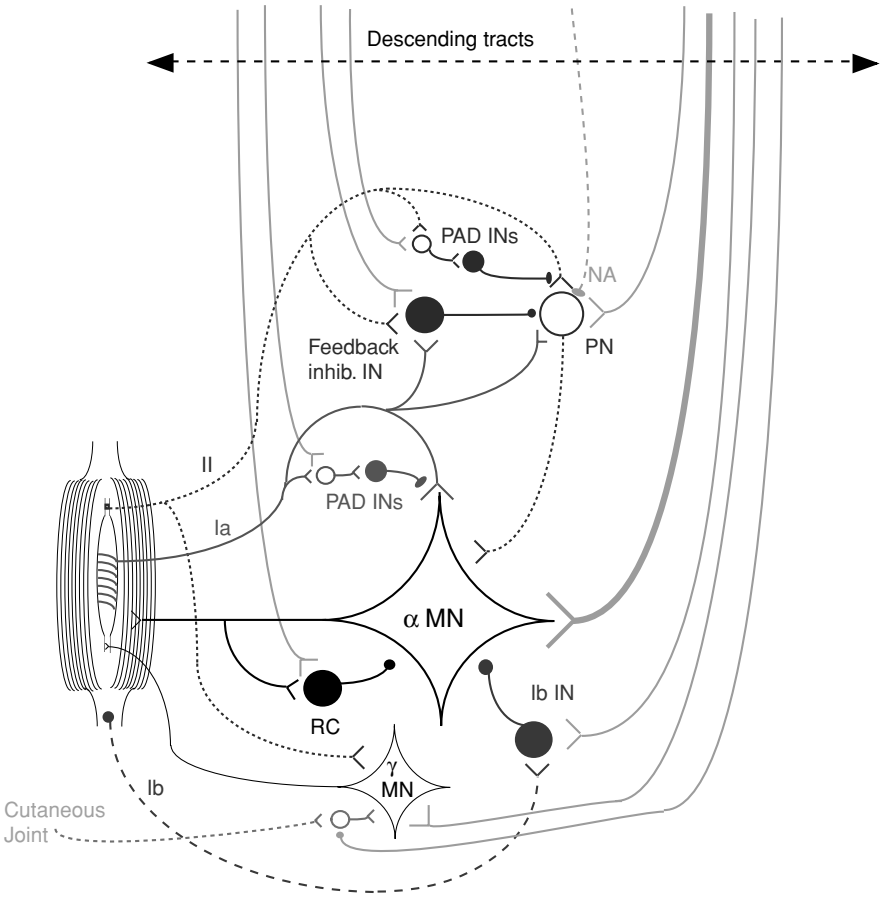


Fig. 12.1. Sketch of some spinal pathways that underlie the stretch reflex exaggeration in spasticity. Excitatory synapses are represented by Y-shaped bars and inhibitory synapses by small filled circles, excitatory interneurones by open circles and inhibitory interneurones by large filled circles. α and γ motoneurones (MN) of a muscle, and Renshaw cells (RC) sketched in black. Ia afferents with their presynaptic inhibition (PAD INs) sketched in continuous red. Group II afferents with their presynaptic inhibition (PAD INs) sketched in dotted blue. Ia and group II afferents converge onto propriospinal neurones (PN) and feedback inhibitory interneurones (inhib. IN) inhibiting PNs. Group II afferents also have monosynaptic projections on γ MNs (projections of PNs on γ MNs have been omitted). Ib afferents (dashed) and Ib inhibitory INs sketched in brown. Cutaneous and joint afferent exciting γ MNs sketched in dotted pink (with a normal tonic descending inhibitory control in green). Descending tracts controlling transmission in spinal pathways sketched in green. Noradrenergic (NA) gating from the brainstem of the transmission of group II excitation (exerted pre- or post-synaptically) sketched in dashed green. The double-headed horizontal dashed arrow indicates the lesion interrupting the descending projections.

from changes in the intrinsic properties of motoneurones associated with loss of activity due to interruption of the motor command (see p. 572), and/or imbalance between excitatory and inhibitory inputs from descending tracts. In animal experiments, such an imbalance occurs following anaemic decerebration (producing so-called 'α rigidity', which persists despite section of the posterior roots; see Pollock & Davis, 1931). There is currently no method that allows the selective assessment of α motoneurone

excitability in humans, and a change in the baseline excitability of α motoneurones can only be inferred by elimination of other possibilities by appropriate control studies.

Increased H reflex

Increased excitability of α motoneurones can be inferred when an increase in the H reflex cannot be explained by a change in transmission of the afferent volley of the reflex. To do this requires elimination of: (i) mechanisms acting on the Ia volley (presynaptic inhibition of Ia terminals with PAD, post-activation depression, oligosynaptic propriospinal transmission); (ii) mechanisms that help limit the size of the H reflex (Ib inhibition, pp. 14–16); and (iii) changes in motoneurone excitability due to alterations in tonically transmitted effects (e.g. group II excitatory effects produced by the posture in which the reflex is explored, release of Ib excitation, suppression of reciprocal Ia inhibition). Hence, an increase in the H_{max}/M_{max} ratio by itself does not establish increased α motoneurone excitability. Several methods have been proposed to assess the extent to which H reflexes are increased.

(i) The H_{max}/M_{max} ratio in the soleus is consistently increased with respect to healthy subjects (e.g. Angel & Hoffmann, 1963; Landau & Clare, 1964; Sommerville & Ashby, 1978; Delwaide, 1985a, 1993; Yanagisawa *et al.*, 1993; Ongerboer de Visser *et al.*, 1993; Faist *et al.*, 1994; Aymard *et al.*, 2000). Because of the large interindividual variability due in part to the decrease in the ratio with age, there is a poor correlation between this ratio and clinical spasticity.

(ii) The threshold of the H reflex is decreased with respect to that of the M wave. However, this factor is correlated even less well with spasticity than the H_{max}/M_{max} ratio (Angel & Hoffmann, 1963; Yanagisawa *et al.*, 1993).

(iii) The ratio of the developmental slope of the H reflex to the slope of the M wave (Hslp/ Mslp) has been recently proposed. This ratio is increased in stroke patients and may be better correlated to spasticity (Higashi *et al.*, 2001).

(iv) When investigating the recovery cycle of the H reflex (pp. 10–11), it has been claimed that spastic patients have a quicker and higher initial peak of recovery (the 'secondary facilitation' at ISIs >150 ms) than normal subjects. This abnormality of the recovery cycle was taken as a sign of increased α motoneurone excitability (e.g. Magladery *et al.*, 1952; Olsen & Diamantopoulos, 1967; Garcia-Mullin & Mayer, 1972). However, it has been recently suggested that this apparent abnormality was simply due to the fact that larger reflexes were used in the studies on spastic patients (Kagamihara *et al.*, 1998).

Increased F waves

An increased mean F wave amplitude has been described in spasticity, with values above 10% of M_{max}, instead of below 5% as in normal subjects (Schiller & Stålberg, 1978; Eisen & Fisher, 1999). The duration and persistence was of the F wave are also increased in patients with stroke (Milanov, 1992) and spinal cord injury (Dressnandt, Auer & Conrad, 1995). However, these findings are not constant since, in other studies in spastic patients, the amplitude of the F wave was not altered and its persistence was either increased (Eisen & Odusote, 1979) or unchanged (Tsai, Chen & Chang, 2003). It has been claimed that the F wave would provide a better measure of motoneurone excitability than the H reflex, because its amplitude, *a priori*, does not depend on the transmission of the afferent volley (Delwaide, 1985a, 1993; Milanov & Georgiev, 1994). However, several factors limit the size of the F wave in spastic patients and probably account for the inconsistency of the increased amplitude and duration: (i) the sensitivity of the F response to changes in motoneurone excitability is ten times less than that of the H reflex (see p. 23); (ii) an H reflex discharge protects motoneurones from antidromic invasion, so that the increased H reflex occurring with higher motoneuronal excitability would decrease the number of motoneurones that could produce an F response (see pp. 23–4); and (iii) the antidromic motor discharge which evokes the F wave activates Renshaw cells,

and the increased recurrent inhibition observed in most spastic patients (see p. 569) could oppose the increased motoneurone excitability. (Note, however, that this last point cannot be a factor with distal muscles because their motor axons do not have recurrent collaterals.)

Plateau potentials

Motoneurones in reduced animal preparations can develop plateau potentials which amplify their response to synaptic drive and can lead to periods of sustained motor output. Plateau potentials have been documented in motoneurones of chronic spinal rats and may be an important factor in the associated spasticity. There is mounting evidence that plateau potentials can be induced in humans (see p. 20). Plateau-like behaviour can be recorded in spinal cord-injured patients, where it could contribute to a patient's clinical manifestations, and in particular spasticity (Gorassini *et al.*, 2004; Nickolls *et al.*, 2004). In this respect, it is of interest that the depression by baclofen of both spasticity and the H reflex has been ascribed to direct depression of motoneuronal excitability (Azouvi *et al.*, 1993; Ørsnes *et al.*, 2000), and this drug has been shown to inhibit plateau potentials in animals (Russo, Nagy & Hounsgaard, 1998). One group reports that, if anything, plateau-like behaviours are less easy to record in spinal cord-injured patients than in normal subjects (Nickolls *et al.*, 2004). However, this could have been due to a limitation of the technique of inducing such behaviour, and the role of plateau potentials in spasticity remains to be clarified. Certainly in the chronic spinal rat, plateau potentials seem to play a significant role in spasticity (Bennett *et al.*, 2001, 2004) and this may also be so in patients (Gorassini *et al.*, 2004).

Changes in axonal excitability

Chronic changes in the excitability and activity of the motoneurone will lead to changes in the expression of conductances and pumps on the motoneurone, and it is a reasonable assumption that there might be changes in the excitability of motor axons reflecting these changes. Accordingly, in patients with amyotrophic lateral sclerosis, evidence has been presented suggesting a decrease in voltaged-gated K^+ conductances (Bostock *et al.*, 1995) and an increase in persistent Na^+ conductances (Mogyoros *et al.*, 1998). However, whether these changes reflect the upper motoneurone abnormality or the lower motoneurone abnormality has not been clarified. In patients hemiparetic following a hemispheric stroke there is evidence of a decrease in inward rectification due to diminished activity of the hyperpolarisation-activated cation conductance, I_H (Jankelowitz *et al.*, 2004). These changes occured in motor axons on the paretic side only. They were significant when the findings for the two sides were compared and when the pathological side was compared with control data for healthy age-matched volunteers. There were no such changes in cutaneous afferents in the same nerve.

Conclusions

There are no methods to allow the assessment of hyperexcitability of α motoneurones in human experiments. Most experiments using the H reflex have neglected to ensure that there were no associated changes in transmission in spinal pathways. Because it is probable that the excitability of α motoneurones as assessed by the F wave is underestimated, an increase in amplitude, duration and persistence of the F wave in spastic patients might be a better argument in favour of α motoneurone hyperexcitability. To sum up, hyperexcitability of α motoneurones has never been demonstrated unequivocally, although it is likely.

Increased fusimotor activity

If there were heightened fusimotor drive, particularly γ_d, the response of primary endings to stretch would be increased. As a result, the enhanced Ia discharge would produce an increased stretch reflex and exaggerated tendon jerks. As with the hyperexcitability of α motoneurones (see above), that of

γ_d motoneurones might result from changes in their intrinsic properties following their inactivation due to the impairment of the motor command and/or an imbalance between excitatory and inhibitory inputs from descending tracts.

Fusimotor overactivity as a cause of spasticity was a popular hypothesis in the 1960s

This was primarily because of the superficial resemblance of human spasticity to decerebrate rigidity in the cat, in which heightened fusimotor tonus contributes to the exaggeration of the stretch reflex (see above). Arguments from human experiments were then presented to support this view:

(i) The tendon jerk was found to be more enhanced than the H reflex in the soleus of spastic patients, a finding that was attributed, not unreasonably at the time, to the fact the H reflex bypasses the muscle spindle while the tendon jerk does not (Dietrichson, 1973). However, we now know that the two reflexes differ in so many other respects that comparison of them as a measure of fusimotor function is invalid (see pp. 117–18).

(ii) Spasticity can be reduced by a block of small fibres using local anaesthetics (Dietrichson, 1973), but, in human subjects, local anaesthetic nerve blocks cannot produce selective de-efferentation of muscle spindles (see pp. 118–19), and the reduction of spasticity might have been due to a reduction in the afferent traffic entering spinal cord circuits.

(iii) The failure of the Jendrassik manoeuvre to potentiate the tendon jerk of spastic patients was attributed to an inability to increase further an already high level of background fusimotor activity (Buller, 1957; Dietrichson, 1971); however, the view that the Jendrassik manoeuvre potentiates tendon jerks through activation of γ_d motoneurones is seriously flawed (see pp. 131–3).

When examining fusimotor drive in spastic patients, it is pertinent to ask two questions:

(i) Is increased fusimotor drive sufficient to cause spasticity?

(ii) Does increased fusimotor drive occur in spastic patients?

The answer to the first question is no: without other changes in the nervous system, increased fusimotor drive cannot cause spasticity. Vibration can produce a more intense spindle discharge than is ever seen in human subjects, be they normal or spastic. At most, the vibration will produce a TVR but that can be readily controlled by normal subjects. Typically spastic patients cannot control the TVR, and this points to a defect in the control of spinal pathways in these patients. These arguments have been presented elsewhere (Burke, 1980, 1983). The answer to the second question is probably yes, at least in some patients, and the question is then the extent to which fusimotor overactivity can contribute to the patient's deficit.

Animal models

Evidence for fusimotor overactivity has not been found in animal models designed to reproduce the deficits seen in patients, e.g. ablation of areas 4 and 6 in monkeys (Gilman, Lieberman & Marco, 1974), medullary pyramidotomy in monkeys (Gilman, Marco & Ebel, 1971), various spinal and cerebral lesions in monkeys (Meltzer, Hunt & Landau, 1963), chronic spinal transection in cats (Bailey, Lieberman & Kitchell, 1980), and chronic spinal hemisection with terminal transection in monkeys and cats (Fujimori *et al.*, 1966; Aoki, Mori & Fujimori, 1976).

Recordings from spindle afferents

Evidence for fusimotor overactivity has not been found in recordings made from spindle afferents in triceps surae and forearm extensor muscles of hemiplegic patients (see p. 139). In neither muscle were the background discharge and the response to stretch for spindle endings in relaxed muscles greater than those in control subjects. These results argue against a contribution of γ_d overactivity to spasticity, but it would be imprudent to discard completely heightened fusimotor excitability as a possible contributing factor to spasticity: (i) only in two patients

were triceps surae afferents so explored; (ii) in the upper limb, spasticity is preferentially distributed on forearm flexors, not extensors; (iii) recordings have only been made in stroke patients, and not in patients with cerebral palsy or spinal cord injury in whom the contribution of exaggerated stretch reflexes to motor disability of patients is more likely; (iv) results obtained with monoamines in paraspastic patients suggest that the activation of γ motoneurones by the stretch-induced group II volley could be a factor in the exaggeration of the stretch reflex of such patients (see Chapter 7, p. 325, and p. 581).

Conclusions

The arguments in favour of fusimotor overactivity are seriously flawed. On the other hand, the absence of evidence for this mechanism in recordings from muscle spindles needs confirmation from a greater number of patients, in particular, from patients with spinal cord injury. Fusimotor overactivity is not the primary abnormality driving spasticity; the extent to which it contributes to the deficit of patients remains an open question (see p. 140).

Decreased presynaptic inhibition of Ia terminals with PAD

A decrease in presynaptic inhibition of Ia terminals would increase the efficacy of the stretch-induced Ia volley in firing motoneurones, and might therefore be one of the spinal mechanisms underlying the stretch reflex exaggeration. Because presynaptic inhibition of Ia terminals with primary afferent depolarisation (PAD) is subject to potent control from higher centres (p. 339; Fig. 12.1), it is conceivable that a corticofugal lesion would alter the level of presynaptic inhibition. It should be pointed out, however, that (i) decreased presynaptic inhibition of Ia terminals with PAD would have only a small effect on the reflex responses to abrupt stretch (see pp. 354–5); and (ii) no decrease in presynaptic inhibition of Ia terminals has been found in the chronic spinal cat (Hultborn & Malmsten, 1983b).

Inhibition of the H reflex produced by prolonged vibration of the homonymous tendon does not assess presynaptic inhibition selectively

It was postulated, not unreasonably at the time (Delwaide, 1973), and for long accepted that the degree of reflex suppression so produced faithfully reflected the excitability of PAD interneurones mediating presynaptic inhibition of Ia terminals. Accordingly, the decreased reflex suppression seen in most spastic patients was thought to reflect a decrease in presynaptic inhibition of Ia terminals with PAD (Chapter 8, p. 368). In fact, when the conditioning and test volleys are both mediated by the same afferents, post-activation depression of transmission at the Ia-motoneurone synapse will depress the H reflex (Chapter 8, p. 341). The finding that diazepam increases the vibration-induced suppression of the reflex (Delwaide, 1985a) simply suggests that presynaptic inhibition of Ia terminals with PAD contributes to the reflex suppression, not that it is the only mechanism underlying it. The problem is accentuated by the fact that post-activation depression is decreased in spastic patients (see below). The vibration-induced depression of the H reflex cannot therefore be used to estimate presynaptic inhibition of Ia terminals with PAD.

Suppression of the H reflex by a heteronymous group I volley

The conditioning volley involves different afferents to the test Ia volley, and activates PAD interneurones mediating presynaptic inhibition of the terminals of the test volley so reducing the test H reflex (see pp. 341–5). The lower the excitability of PAD interneurones in patients, the smaller the reflex depression with respect to controls. For clinical studies, electrically induced D1 inhibition is a suitable method, at least at rest (Chapter 8, pp. 343–4). In the lower limb, the soleus H reflex is conditioned by a peroneal volley (train of three shocks, 300 Hz, 1.2 × MT, 21 ms ISI between the first shock of the train and the test stimulus). In the upper limb, the

FCR H reflex is conditioned by a single shock to the radial nerve (0.95 × MT, 13 ms ISI). Suppression of the H reflex by a tap to the tendon of a heteronymous muscle (40–60 ms ISI) is also a convenient method. In order to eliminate the possibility of a change in recruitment gain of the reflex, the more demanding method of the heteronymous monosynaptic Ia facilitation of the H reflex may be used in parallel (the larger the facilitation, the smaller the presynaptic inhibition, cf. Chapter 8, pp. 345–7).

Conclusions

Investigations using homonymous vibratory inhibition of the H reflex largely have overestimated the role of decreased presynaptic inhibition of Ia terminals in the exaggerated stretch reflex of spastic patients. As discussed below, the changes in presynaptic inhibition of Ia terminals with PAD are not uniform in spastic patients, and vary with the level of the lesion (e.g. they are absent in the lower limb of stroke patients, see p. 576). Moreover, several findings suggest that the changes in presynaptic inhibition of Ia terminals observed in spastic patients could be an epiphenomenon that plays a limited, or no, pathophysiological role in spasticity as assessed under resting conditions (Chapter 8, p. 370).

Decreased post-activation depression at the Ia-motoneurone synapse

When an impulse train is conducted, there is, at the Ia-motoneurone synapse, an early transient facilitation, superimposed on a dominant depression ('post-activation depression') lasting several seconds (see pp. 96–9). Post-activation depression helps to keep the efficacy of the Ia fibre-motoneurone synapse at a relatively low level. Decreased post-activation depression would increase the efficacy of the stretch-induced Ia volley in firing motoneurones, and thereby would enhance the stretch reflex.

Methodology

The best method to assess the amount of post-activation depression is to measure the depressive effect of stimulus rate on the size of the test reflex: i.e. in practice, to compare the size of the H reflex when elicited repeatedly at rest at 0.1 and 0.5 Hz. The dramatic decrease observed at 0.5 Hz in normal subjects is much less in the lower and upper limbs of all tested spastic patients, regardless of the causative lesion (Chapter 2, pp. 97–9).

Conclusions

Although the phenomenon of post-activation depression has been known from the early 1950s, it has been neglected as a factor in spasticity. Instead, attention was focused on decreased presynaptic inhibition of Ia terminals, without realising that much of the depression of the H reflex following vibration to the homonymous tendon is actually due to post-activation depression, that post-activation depression is reduced in spasticity, and that this abnormality may be a major spinal mechanism underlying spasticity (Hultborn & Nielsen, 1998). If homonymous vibratory inhibition of the H reflex results mainly from post-activation depression, the hypothesis that decreased post-activation depression could be an important factor in spasticity is supported by the observation that this form of vibratory inhibition decreases in parallel with the development of reflex exaggeration after the causative lesion (Ashby, Verrier & Carleton, 1980).

Increased oligosynaptic propriospinally mediated group I excitation

Facilitation of transmission in oligosynaptic pathways mediating group I excitation to motoneurones would assist in the development of the stretch reflex. Cervical propriospinal neurones mediate an important part of the corticospinal command to upper limb motoneurones and also receive some excitation from group I afferents in the upper limb (see p. 460). Lumbar propriospinal neurones receive their

main excitatory input from group I and group II muscle afferents (see p. 494). A number of different mechanisms could increase propriospinally mediated group I excitation: (i) Decreased post-activation depression at the synapses of peripheral afferents with lumbar propriospinal neurones is unlikely, because post-activation depression is only marginal at this synapse in normal subjects (see p. 310). (ii) A decrease in presynaptic inhibition of Ia terminals is possible. (iii) A decrease in the noradrenergic gating of group II excitation could indirectly be responsible (Chapter 7, see p. 324). (iv) Changes in the corticospinal control of propriospinal neurones are likely (Fig. 12.1; p. 503).

Methodology

The best method to assess the excitability of lumbar propriospinal neurones by group I volleys is to measure the peak of early facilitation (10 ms ISI) of the quadriceps H reflex produced by low-intensity common peroneal nerve stimulation (1 × MT). The peroneal propriospinally mediated group I excitation of quadriceps motoneurones is increased in spastic patients, regardless of the causative lesion. Given the convergence of group I afferents from quadriceps and the pretibial flexors onto common lumbar propriospinal neurones projecting to quadriceps motoneurones (see p. 496), it has been suggested that the exaggeration of the homonymous stretch reflex, including the tendon jerk, in the quadriceps involved facilitation of these interneurones (see p. 324). Disruption of the strong corticospinal control on feedback inhibitory interneurones inhibiting propriospinal neurones (Fig. 12.1) would explain the facilitation of the transmission of group I propriospinally mediated excitation in spastic patients (see, pp. 322–4, 503).

Propriospinal relay for upper limb motoneurones

A greater part of the descending command to upper limb motoneurones is relayed through cervical propriospinal neurones in hemiplegic patients with poor recovery (see pp. 483–4). The easiest method to assess this increased descending excitation of cervical propriospinal neurones is to measure the suppression of the on-going EMG activity of ECR by a brief train of stimuli to the superficial radial nerve (three shocks at 300 Hz at 0.5 × MT, window of analysis 32–41 ms after the onset of the train, see pp. 458–9). If there were increased excitability of these neurones at rest, this might contribute to the stretch reflex exaggeration.

Conclusions

The contribution of heightened propriospinally mediated group I excitation to spasticity has been revealed only recently. This contribution is probably important regardless of the causative lesion, at least in the lower limb.

Increased group II excitation

Muscle stretch also activates spindle secondary endings. The stretch-induced homonymous and heteronymous group II discharges from leg muscles play a major role in the control of perturbations to normal upright stance (see pp. 312–14). Facilitation of the transmission of this group II excitation could produce exaggeration of the stretch reflex, and thereby contribute to spasticity. Facilitation of the transmission may result from a change in the corticospinal control of the relevant propriospinal neurones, and/or disruption of the normal noradrenergic gating from the brainstem of transmission of group II excitation (Fig. 12.1).

Methodology

The best method to assess the transmission of group II excitation is to measure the peak of late facilitation (15–20 ms ISI) of the quadriceps H reflex produced by high-intensity common peroneal nerve stimulation (2–3 × MT). Peroneal-induced early group I and late group II excitations of quadriceps motoneurones are both increased in spastic patients, regardless of the causative lesion (see p. 322). In patients with spinal cord lesions, the contribution of increased group II

excitation to spasticity could be amplified by the projections of lumbar group II interneurones to γ motoneurones, which would produce positive feedback from spindle afferents to α motoneurones (see below). This latter factor is not taken into account when group II excitation is assessed electrically, and this might explain the weak correlation between increased peroneal-induced group II excitation of the H reflex and the stretch reflex exaggeration (see see p. 325).

Effects of monoaminergic agonists

If an increase in the late peroneal-induced facilitation of the quadriceps H reflex reflected increased group II excitation, it should be suppressed by monoamine agonists, which selectively gate the transmission of this action. Note, however, that monoaminergic suppression is a condition necessary but insufficient by itself to attribute an increased late facilitation of the reflex to increased group II excitation. A normal group II input reaching hyperexcitable α motoneurones would produce an increased reflex facilitation, which would be similarly suppressed by monoamines. It is therefore important that changes produced by monoamine agonists in the group II excitation have been observed without changes in α motoneurone excitability (see pp. 321–2). The concomitant monoaminergic depression of the group I facilitation probably results from the suppression of the background group II discharge from pretibial flexors due to static stretch (Chapter 7, p. 324).

Conclusions

Despite the reservations expressed above about pathophysiological conclusions based on selective blockade of particular pathways, the reduction of spasticity produced by monoaminergic agonists is so complete that a contribution of group II excitation to spasticity is likely to be significant. This contribution could be particularly important in patients with spinal cord lesions, because the lesion would disrupt the normal noradrenergic gating of group II excitation from the brainstem. Importantly, this component of spasticity can be treated selectively using monoaminergic drugs, such as tizanidine.

Decreased non-reciprocal group I inhibition

The adequate stimulus for Golgi tendon organs is not muscle stretch, to which they have a high threshold and rapid adaptation. However, (i) once a stretch reflex contraction occurs, autogenetic Ib inhibition of motoneurones may help limit the reflex, and (ii) interneurones mediating non-reciprocal group I inhibition are also excited from Ia afferents (see pp. 260–1). Interneurones mediating non-reciprocal group I inhibition are subjected to potent descending control (Fig. 12.1), and a change in this control (inhibition or disfacilitation) would make the non-reciprocal group I inhibition less effective in opposing spindle excitation when a muscle is stretched, again favouring the stretch reflex.

Methodology

The best method to assess the transmission of non-reciprocal group I inhibition is to assess the suppression of the soleus H reflex produced by stimulation of the gastrocnemius medialis nerve (0.95 × MT, 5 ms ISI). However, the reflex suppression so determined is inconstant and, when present, is modest in normal subjects. This makes it difficult to determine the significance of a reduction of the suppression in patients (see p. 256).

Change in Ib inhibition or in group I excitation?

A decrease in Ib inhibition of the soleus H reflex has been reported in spastic patients, but this does not obligatorily imply decreased transmission across the Ib inhibitory pathway. The inhibition tends to be replaced by facilitation, and this could indicate that facilitated group I excitation (e.g. through propriospinal neurones, see above) overwhelms the Ib inhibition, whether or not there is decreased Ib inhibition (see p. 277).

Conclusions

A decrease in non-reciprocal group I inhibition might contribute to spasticity, but is probably not a major factor.

Increased reciprocal Ib facilitation

Oligosynaptic group I ('Ib') excitation between antagonists operating at the same joint is rare and weak in normal subjects (at least in the lower limb), possibly because the activity in the relevant pathway is normally subjected to strong tonic supraspinal inhibition (see p. 278). Disruption of this inhibitory control could result in facilitation of motoneurones and exaggeration of the stretch reflex.

Methodology

The best method to assess transmission in the pathway of Ib facilitation is to condition the soleus H reflex by a volley to the common peroneal nerve ($1 \times$ MT, 2–4 ms ISIs). In spastic patients the reciprocal Ia inhibition is replaced by facilitation. Several lines of evidence suggest that this facilitation involves not only decreased reciprocal Ia inhibition (see below), but also increased Ib excitation (see pp. 277–8). The Ib facilitation appeared in parallel with the development of hyperactive Achilles tendon reflexes, the only clinical finding that could be correlated with the facilitation. Such a correlation suggests that Ib facilitation could contribute to the development of spasticity (see p. 279).

Mechanism of the facilitation

Ib facilitation may be regarded as a 'release phenomenon' due to suppression of either a descending tonic inhibitory control on Ib excitatory interneurones or of a facilitatory control on PAD interneurones mediating presynaptic inhibition of Ib afferents (see p. 278). However, here also, an alternative possibility would be facilitated oligosynaptic group I excitation transmitted through lumbar propriospinal neurones (see above).

Conclusions

There is no experimental evidence that increased Ib excitation contributes to spasticity, but this mechanism cannot be disregarded.

Alterations in recurrent inhibition

Renshaw cells are subject to potent descending controls, both excitatory and inhibitory (see p. 153). Theoretically, decreased recurrent inhibition could contribute to the stretch reflex exaggeration that characterises spasticity: activity of the motoneurone pool would then be less effectively opposed by recurrent inhibition, and a greater discharge would ensue.

Methodology

The best method to assess homonymous recurrent inhibition of soleus motoneurones is the paired H reflex technique (pp. 184–7).

Increased recurrent inhibition

Recurrent inhibition is commonly increased after corticospinal lesions, whether cerebral or spinal. In chronic spinal cats, there is similarly increased recurrent inhibition on the hemisected side (Hultborn & Malmsten, 1983b). The increased recurrent inhibition implies that Renshaw cells are released from a descending tonic inhibitory control (see p. 186). This change is the opposite of that required for abnormal recurrent inhibition to play a role in the stretch reflex exaggeration of spasticity. Decreased recurrent inhibition has been claimed in spastic stroke patients, but this was due to a technique that tested not transmission in the recurrent pathway but the excitability of the monosynaptic reflex arc (pp. 154–5).

Conclusions

Decreased recurrent inhibition at rest has been observed only in relatively rare patients with slowly progressive paraparesis (Chapter 4, pp. 184–6) and, in most cases, does not contribute to spasticity.

Changes in reciprocal Ia inhibition

Ia interneurones to ankle extensors probably receive tonic descending facilitation. The disfacilitation of these interneurones by the corticospinal lesion would remove a tonic inhibition on ankle extensor α motoneurones, and thereby contribute to spasticity (see p. 232).

Methodology

The best method to assess reciprocal Ia inhibition is to condition the soleus H reflex by a volley to the common peroneal nerve (1 × MT, 2 ms ISI).

Reciprocal Ia inhibition at rest

At rest, reciprocal Ia inhibition of soleus is reduced and that to the pretibial flexors is increased. Thus, corticospinal lesions release reciprocal Ia inhibition from ankle extensors to flexors and reduce the reciprocal Ia inhibition of ankle extensors, probably through mutual inhibition of opposite Ia interneurones (cf. Fig. 11.1(*c*)). This could contribute to the hyperexcitability of triceps surae α motoneurones.

Conclusions

There is no experimental evidence that decreased reciprocal Ia inhibition of lower limb extensor motoneurones contributes to spasticity, but this mechanism cannot be disregarded.

Reflex irradiation

Reflex irradiation is common in spastic patients. It is associated with the transmission through skeletal structures of a vibration wave set up by percussion of bone or tendon, so that spindles are activated in muscles throughout the limb (Lance & de Gail, 1965). However, the widespread heteronymous Ia connections present in the upper and lower limbs also contribute to reflex irradiation and could be a more important mechanism (see p. 96).

Conclusions concerning spinal mechanisms underlying spasticity

Much of the evidence on which spinal mechanisms have been implicated or not in spasticity was collected when techniques available to investigate transmission in spinal pathways in man were in their infancy. This has led to many fallacious interpretations, concerning, e.g. the role of the fusimotor system, presynaptic inhibition of Ia terminals and recurrent inhibition. The contribution of the different pathways to spasticity assessed under resting conditions, as it appears from the more recent data, may be summarised as follows.

Several spinal mechanisms probably contribute to spasticity

(i) Decreased post-activation depression is present whatever the causative lesion, and seems to be a major mechanism underlying spasticity. It may be the result of lack of use of the circuitry following the impairment of the descending command.

(ii) Increased propriospinally mediated group I excitation is often found, and could contribute to spasticity.

(iii) Increased transmission of group II excitation could be a major cause of spasticity in spinal cord lesions. Decreased monoaminergic gating of the transmission of group II excitation would produce hyperexcitability of propriospinal neurones, and this could be accentuated by the projection of lumbar propriospinal neurones to γ motoneurones.

(iv) Changes in transmission in Ib pathways (decreased Ib inhibition, increased Ib excitation) have been reported, but their importance remains to be determined.

(v) Decreased reciprocal Ia inhibition to extensor motoneurones may play a role, but its importance also remains to be determined.

(vi) Decreased presynaptic inhibition of Ia terminals can occur but depends on the level of the lesion and, in any event, probably plays little role in the spasticity as assessed under resting conditions.

(vii) Hyperexcitability of α motoneurones has never been demonstrated unequivocally, although it appears probable.

Other spinal mechanisms unlikely to contribute to spasticity

(i) Fusimotor hyperactivity has been eliminated as a consistent pathophysiological mechanism, but it remains possible that reflex excitation of γ motoneurones plays a significant role in spasticity of patients with spinal cord lesions.

(ii) Recurrent inhibition is, if anything, increased and does not contribute to spasticity, except in patients with slowly progressive paraparesis, where it is decreased.

Whatever the spinal mechanism tested, no statistically significant relationship has been found between the degree of abnormality and the intensity of the spasticity

This is often taken as an argument to refute the contribution of a given mechanism to the exaggeration of the stretch reflex. However, a number of reasons make a significant correlation unlikely.

(i) Several pathophysiological mechanisms can contribute to spasticity, and they do not necessarily co-vary.

(ii) Changes in one mechanism may act on motoneurones through different pathways (e.g. changes in presynaptic inhibition on Ia terminals may modify monosynaptic and oligosynaptic propriospinally mediated excitations and reciprocal Ia and non-reciprocal group I inhibitions).

(iii) Different fibres, with different presynaptic controls, converge onto common interneurones (e.g. group I and group II afferents on lumbar propriospinal neurones, Ia and Ib afferents on the interneurones of non-reciprocal group I inhibition).

(iv) Conflicting results concerning some mechanisms have been found with different causative lesions and, in many studies, spastic patients with different lesions were mixed together.

(v) The number of patients tested in each investigation is often small.

(vi) Changes in the stiffness of muscle must affect clinical assessments of spasticity as the resistance to passive stretch. The contribution of muscle stiffness may be significant (see pp. 572–3).

Why do spinal pathways malfunction?

Abnormal descending control

Because spinal pathways are under powerful control by descending tracts, it has long been thought that their dysfunction in spasticity, much as in the animal decerebrate rigidity, resulted directly from an abnormal descending control due to the interruption of the tonic activity of descending tracts. Thus, there would be inhibition or disfacilitation of the transmission in inhibitory pathways, and facilitation or disinhibition of the transmission in excitatory pathways. As discussed above, interruption of various descending tracts are likely to be responsible for the changes observed in many spinal pathways: PAD interneurones mediating presynaptic inhibition of Ia terminals, propriospinal neurones, group II pathways, Ib pathways, recurrent pathway, pathway of reciprocal Ia inhibition.

Plastic changes

Contrary to animal decerebrate rigidity, which is present as soon as anaesthesia wears off, spasticity takes weeks or months to develop. This gives time for synaptic rearrangements to occur at the spinal level. Thus, it is highly probable that, in addition to the 'direct' effects of the interruption of descending tracts, lack of activity due to impairment of the descending motor command contributes to the increased resistance to stretch characterising spasticity. Several arguments support this view.

Experimental support for 'plastic' changes

After hemisection of the spinal cord in the rat and cat, Hultborn & Malmsten (1983a,b) observed below the lesion the expected increase in monosynaptic and polysynaptic reflexes with respect to the unaffected side, starting no later than 2 days after the lesion and lasting for at least 1 year. The important point is that the *asymmetry persisted after acute spinal transection* below the initial hemisection, demonstrating that it was not a direct effect of disturbed descending control of spinal pathways, but the result of adaptive changes resulting from the loss of that control. They hypothesised that the partial denervation following the initial cord hemisection would lead to supersensitivity of the postsynaptic membrane and a stronger response to the – still unchanged – presynaptic activity in the remaining fibres. Later, the supersensitivity would subside as intact fibres sprouted to form new synapses at vacant sites. The new synapses would, in turn, give permanently enhanced input from the remaining fibres.

Hyperexcitability of α motoneurones

The above changes could result in hyperexcitability of α motoneurones after chronic lesions of the central nervous system, though they have not been demonstrated unequivocally yet (see pp. 560–3). Similar plastic changes could also affect the excitability of γ motoneurones and various interneurones.

Decreased post-activation depression at the Ia-motoneurone synapse

Several lines of evidence, including the time course of the development of spasticity after the causative lesion, suggest that the development of adaptive changes in the efficacy of the Ia-motoneurone synapse follows the changes in activity of motoneurones and Ia fibres associated with the impaired motor command (see pp. 99–100).

Prevention of plastic changes

In spastic patients receiving frequent peroneal nerve stimulation ('functional electrical stimulation' using an external peroneal stimulator to assist walking), peroneal reciprocal Ia inhibition of the soleus H reflex, which is markedly reduced in such patients (see p. 570), was as pronounced as in normal subjects. The patients did not differ from the other patients in their degree of spasticity or other clinical features. This suggests that regular peroneal nerve activation is important for the maintenance of activity in the spinal pathway of reciprocal Ia inhibition. It may be assumed that decreased transmission in other pathways mediating inhibitory effects, whether acting presynaptically (PAD interneurones) or postsynaptically (e.g. Ib inhibitory interneurones), can also result from non-utilisation following the motor impairment.

Conclusions

The loss of the normal tonic descending (in particular corticospinal) control of various spinal pathways plays a role in the abnormal transmission observed in these pathways after a corticospinal lesion. However, there is some evidence that lack of activity of these pathways results in denervation supersensitivity and collateral sprouting and contributes further to the malfunction. This evidence is important because it has implications for the rehabilitation of spastic patients.

Changes in the intrinsic properties of muscle fibres (contracture)

Another type of plastic change concerns the muscle itself and is often referred to as 'contracture'. Alterations in muscle fibres are probably not related only to inactivity of the muscle, but could also result from inactivity of motoneurones (see Dietz, 1992). As postulated from animal experiments (Buller, Eccles & Eccles, 1960), it is possible that, in motoneurones deprived of their supraspinal control, changes in

trophic influences from the motoneurone transform muscle fibres.

Arguments against a significant contribution of the stretch reflex to the passive resistance to stretch

Dietz and colleagues investigated triceps surae of stroke patients during the stance phase of gait (for reviews, see Dietz, 1992, 2003). In the 1980s, they found that, in normal subjects and on the unaffected side of stroke patients, the tension developed by triceps surae correlated with the modulation of ongoing EMG activity. However, on the spastic side, it was associated with a tonically low-amplitude activation of the triceps surae due to passive stretching. On this side, the spinal stretch reflex generated only a small part of the overall muscle activity, and this was reduced compared to healthy subjects, and underwent reduced modulation during the gait cycle.

Mechanical properties of muscle

The above changes were taken as suggestive of alterations in the mechanical properties of muscle fibres on the spastic side, and several lines of evidence supported this hypothesis: (i) investigations of single motor units revealed prolonged twitch contraction times; (ii) experiments using stretches applied by a torque motor suggested a peripheral contribution to increased muscle tone; and (iii) morphometric and histochemical investigations of spastic leg muscles revealed changes in muscle fibres that were specific to the spastic muscle (for review, see Dietz, 1992). A number of authors have emphasised that the increased resistance to passive stretch of contracting upper and lower limb muscles in stroke patients cannot be explained by increased EMG activity in the relevant muscle, and that increased spinal stretch reflex activity played a minor role in the genesis of the 'spasticity' in these patients (e.g. Davies, Mayston & Newham, 1996; O'Dwyer, Ada & Neilson, 1996; Sommerfeld *et al.*, 2004). In relaxed muscles, the increase in tone is associated with an exaggerated reflex EMG response, but it is likely that this is insufficient by itself to produce the increase in tone, i.e. that the passive stiffness of non-contracting muscle is also increased.

Clinical assessments of spasticity

The Ashworth score is not the ideal tool to assess spasticity, because the resulting measure involves both the neural stretch reflex activity which is velocity-dependent and the contracture which is not (Vattanasilp, Ada & Crosbie, 2000). The Tardieu scale may be better at identifying a neural component to stiffness because the test involves moving the limb at different velocities and comparing the difference in the response (Tardieu, Shentoub & Delarue, 1954). An English translation of this work is now available (Boyd *et al.*, 1998).

Changes in muscle properties must be distinguished from fibrosis contracture

Fibrosis contracture is the common form of muscle shortening, that inevitably follows prolonged fixation and complete inactivity of a normally innervated muscle (as in broken limb immobilised by cast). This fibrosis contracture complicates both weakness and spasticity, and must be prevented by appropriate physiotherapy with passive stretching of the affected muscles.

Conclusions

Dietz's view of 'spasticity located in the muscle' has long been an isolated view that was eccentric and was expressed perhaps a little dogmatically. However, there is growing evidence that, in stroke patients at least, increased resistance to passive stretch is due not only to increased reflex activity but also to changes in the intrinsic properties of muscle.

Changes in spinal pathways during movements in spasticity

Often, discussions about the pathophysiology of spasticity have been centred on the stretch reflex

exaggeration passively produced at rest. However, as discussed above (see pp. 558–60), the important question for the patient (and the neurologist) is the extent to which stretch reflexes in an antagonistic muscle prevent the agonist from moving the limb during an intended movement. Because the mechanisms involved in gait or performing a voluntary movement alter the gain of the stretch responses (see Chapter 11), the amplitude of the response to passive stretch is a poor indicator of the amount of restraint imposed by spastic antagonists during an intended movement. Thus, for example: (i) even when there is abnormal stretch reflex activity under relaxed conditions in stroke patients, stretch reflexes evoked in voluntarily active muscles under conditions simulating walking are of similar magnitude as in normal subjects (Ada *et al.*, 1998); (ii) in patients with multiple sclerosis or focal spinal cord injury, baclofen was found to suppress passive stretch responses in the quadriceps without appreciably changing the amount of inappropriate activity during voluntary flexion of the knee at the same angular velocity (McLellan, 1977). The contribution of spasticity to motor impairment depends not only on the hyperexcitability of the stretch reflex but also, and perhaps more, on alterations in the many mechanisms that normally control the relaxation of antagonists (see Chapter 11, pp. 519–20, 524–6) and ensure the smoothness of the movement. Thus, several mechanisms, which are of little importance under resting conditions, may restrain intended movements because they are deprived of their normal descending control during voluntary contraction.

Evidence for abnormal reciprocal inhibition

Evidence for abnormal relaxation of the antagonist during voluntary contraction of knee muscles has been sought in patients with multiple sclerosis and focal spinal cord injury. Responses to stretch in quadriceps and hamstrings were present at rest, suppressed by voluntary effort in patients with mild spasticity, but enhanced in severe spasticity (McLellan, 1977). This finding was confirmed by Knutsson, Mårtensson & Gransberg (1997), who showed that concentric contractions of knee muscles at high velocity were disrupted by a stretch reflex in the antagonistic muscle. The appearance of this stretch reflex attests that reciprocal inhibition from agonist to antagonist motoneurones is reduced during dynamic actions involving strong effort. In contrast, increased reciprocal inhibition in the opposite direction, i.e. from stretched antagonists to voluntarily activated agonist motoneurones, may accentuate the weakness of paretic muscles (Knutsson, Mårtensson & Gransberg, 1997; see also Yanagisawa, Tanaka & Ito, 1976). Changes in transmission in several spinal pathways may contribute to this abnormal reciprocal inhibition. They have been investigated mainly at ankle level and are discussed below.

Alteration in transmission in spinal pathways during attempted movements

Reciprocal inhibition

The absence of a contraction-associated increase in reciprocal inhibition directed to motoneurones of the antagonistic muscle, whether reciprocal Ia and/or propriospinally mediated inhibition (see below), could be a major factor in the unwanted stretch reflex activity triggered by contraction of the agonists in spastic patients (see above). Such unwanted stretch reflexes might explain some of the functional disabilities of patients with spasticity, in particular in patients with spinal cord injury or cerebral palsy.

An increase in peroneal reciprocal Ia inhibition of the soleus H reflex occurs consistently at the onset of voluntary dorsiflexion in healthy subjects, but not in spastic patients with multiple sclerosis (Morita *et al.*, 2001; see pp. 231–2). The absence of the normal increase in reciprocal Ia inhibition may be due to several mechanisms (see Fig. 11.1(*c*)).

(i) Ia interneurones do not receive their corticospinal drive.

(ii) They do not receive their Ia input because of a loss of the descending drive to γ motoneurones and/or of the descending suppression of presynaptic inhibition on Ia terminals on tibialis anterior-coupled Ia interneurones (see below).

(iii) Recurrent inhibition of Ia interneurones activated by the natural motor discharge is no longer disinhibited (see below).

(iv) Inhibition from opposite Ia interneurones activated by the Ia discharge from the antagonistic soleus can manifest itself because this Ia input is no longer gated by increased presynaptic inhibition.

On the other hand, propriospinally mediated inhibition is a major mechanism in the relaxation of the antagonists (Chapter 11, pp. 519–20). There are, so far, no experimental data on this pathway in spastic patients, but it is likely that the suppression of the descending drive to the relevant interneurones (as on Ia inhibitory interneurones) also helps prevent relaxation of the antagonists in these patients.

Presynaptic inhibition of Ia terminals

Changes in presynaptic inhibition may contribute to restraining voluntary movements and gait in spastic patients, even though presynaptic inhibition of Ia terminals is not or is only slightly altered at rest (see p. 566). Normally during movement the descending modulation of PAD interneurones enhances presynaptic inhibition on Ia terminals on motoneurones antagonist to the contracting muscle (p. 361). This modulation is lost in spastic patients (see p. 370), and this could contribute to the occurrence of a stretch reflex in the antagonistic muscle during voluntary movement. Moreover, the absence of gating of the Ia discharge from the antagonist allows activation of antagonist-coupled Ia interneurones and, through mutual inhibition of Ia interneurones (see Fig. 11.1(*c*)), this could contribute to reducing reciprocal Ia inhibition of antagonistic motoneurones. Abnormalities in the modulation of reflexes during gait, in particular in patients with spinal cord injury, probably result from a lack of modulation of presynaptic inhibition of Ia terminals (see pp. 370–1).

Ib facilitation

Increased Ib facilitation (p. 569) might also contribute to adverse co-contraction of antagonistic muscles during voluntary movement: the Ib discharge from Golgi tendon organs produced by the agonist contraction would produce Ib facilitation of antagonistic motoneurones.

Recurrent inhibition

Recurrent inhibition is increased or not modified in most spastic patients (see above). However, here again, the modulation of recurrent inhibition seen in normal subjects during movements is lost (see p. 187): (i) there is no facilitation of antagonist-coupled Renshaw cells, a process that normally helps curtail the stretch reflex in the antagonist; and (ii) recurrent inhibition of Ia interneurones activated by the natural motor discharge is not suppressed.

Conclusions

The corticofugal lesion disrupts the command not only for the activation of the agonists, but also for the relaxation of the antagonists. Thus, the loss of the descending controls on spinal pathways that normally contribute to the relaxation of the antagonist during voluntary movement or gait can explain the unwanted stretch reflex activity triggered during intended movements, even though transmission in these pathways may not be altered at rest.

Pathophysiology of spasticity after cerebral lesions

Exaggeration of stretch reflexes in stroke patients

The incidence of spasticity in stroke patients has been questioned recently. In a study of 95 stroke patients (Sommerfeld *et al.*, 2004), only 19% of these patients had increased tendon jerks after 3 months, considerably less than in most other investigations. On the other hand, in accordance with classical data, the study of Thilmann, Fellows, & Ross (1993) on 63 stroke patients reported that Achilles and biceps brachii tendon jerks were increased significantly in most patients, and that the tonic stretch

reflex generally was increased in these muscles, even though there was a low correlation between this increase and the briskness of the tendon jerks.

Changes in transmission in spinal pathways on the affected side of stroke patients

The methods described on pp. 560–70 have shown that many spinal pathways malfunction in stroke patients.

Hyperexcitability of the monosynaptic reflex arc

(i) The H_{max}/M_{max} ratio in the soleus is consistently increased on the affected side of stroke patients (e.g. Angel & Hoffmann, 1963; Landau & Clare, 1964; Sommerville & Ashby, 1978; Delwaide, 1985a, 1993; Yanagisawa *et al.*, 1993; Ongerboer de Visser *et al.*, 1993; Faist *et al.*, 1994; Aymard *et al.*, 2000). However, as mentioned on p. 562, changes in many spinal pathways can alter this ratio, and an increase cannot be taken by itself as evidence of hyperexcitability of α motoneurones.

(ii) The H reflex of FCR is not increased significantly on the affected side of stroke patients (Aymard *et al.*, 2000). This suggests that the mechanisms tending to increase the FCR H reflex (decrease in presynaptic inhibition of Ia terminals and in post-activation depression, see below) must be counteracted by an inhibitory mechanism limiting the size of the FCR H reflex. It has been shown that, because of the rise time of the compound Ia EPSP, there is ample time for a disynaptic IPSP to suppress the spike in the last motoneurones contributing to the test reflex discharge (see pp. 9–10). Recurrent inhibition could be a good candidate to do this, since recurrent inhibition may be increased in stroke patients (see p. 569) and, in FCR more than in soleus, the H_{max} response is generally obtained with stimulation that also evokes a direct M response. Thus recurrent inhibition elicited by both the discharge of early orthodromically recruited motoneurones and by the antidromic volley due to direct stimulation of motor axons could prevent the recruitment of high-threshold motoneurones, so limiting the size of the H_{max}.

(iii) The increase in F-wave amplitude, duration and persistence (Milanov, 1992; Fierro, Raimondo & Modica, 1990) could provide an index of hyperexcitability of α motoneurones, but inconsistent results have been reported (Eisen & Odusote, 1979).

(iv) Plateau-like behaviours have so far not been investigated in stroke patients.

Fusimotor over-activity

Evidence for γ over-activity was absent in recordings made from spindle afferents in triceps surae and forearm extensor muscles of hemiplegic patients (see p. 139).

Presynaptic inhibition on Ia terminals

(i) In the lower limb on the affected side, presynaptic inhibition of Ia terminals, as assessed with two independent and reliable methods (heteronymous Ia facilitation and D1 inhibition), is unchanged at rest (see pp. 368–9; Faist *et al.*, 1994; Aymard *et al.*, 2000). The decreased suppression of the soleus H reflex produced by vibration of the homonymous Achilles tendon (e.g. Delwaide, 1973, 1993; Delwaide & Pennisi, 1994; Ongerboer de Visser *et al.*, 1993; Stein, 1995) does not reflect a change in presynaptic inhibition of Ia terminals and is probably due to decreased post-activation depression at the Ia-motoneurone synapse (see p. 368).

(ii) In contrast, in the upper limb on the affected side, presynaptic inhibition on FCR Ia terminals, as assessed with the D1 inhibition of the FCR H reflex, is significantly decreased (Chapter 8, p. 369; Nakashima *et al.*, 1989; Artieda, Queseda & Obeso, 1991; Aymard *et al.*, 2000). The normal corticospinal control of PAD interneurones mediating presynaptic inhibition on Ia terminals on FCR motoneurones is facilitatory, and the decrease in presynaptic inhibition of Ia terminals on FCR motoneurones observed after corticospinal lesions therefore suggests that the corticospinal control is exerted tonically (see pp. 369–70).

Post-activation depression

Post-activation depression is consistently reduced in both the lower (soleus) and upper (FCR) limbs on the affected side of stroke patients (p. 99; Aymard *et al.*, 2000). As discussed above, the reduced depression may be a consequence of the lack of activity of the synapse due to the motor impairment.

Lumbar propriospinal pathways

Group I and group II excitations mediated through lumbar propriospinal neurones are increased on the affected side of stroke patients (p. 322; Marque *et al.*, 2001; Maupas *et al.*, 2004). Given the normally strong corticospinal control on feedback inhibitory interneurones inhibiting lumbar propriospinal neurones, disruption of this control by the corticospinal lesion could explain the facilitation of group I and group II propriospinally mediated excitations.

Non-reciprocal group I (Ib) inhibition

Ib inhibition is decreased (p. 276; Delwaide & Oliver, 1988). It is possible that the decreased inhibition results from an increased facilitation overwhelming the inhibition rather than a reduction in disynaptic inhibition (see p. 568). Alternatively, the suppression of the inhibition in patients with corticospinal lesions would suggest that there is normally tonic corticospinal facilitation of Ib interneurones. In the upper limb, the early phase of disynaptic radial-induced non-reciprocal group I inhibition of the FCR H reflex is consistently decreased in patients with spasticity (Nakashima *et al.*, 1989; Artieda, Quesada & Obeso, 1991), but not in patients with normal muscle tone or flaccid hemiplegia (Nakashima *et al.*, 1989).

Reciprocal Ib facilitation

Ib facilitation is increased (p. 277; Crone *et al.*, 2003). The enhanced facilitation has been regarded a 'release phenomenon' (cf. Yanagisawa, 1980), due to either suppression of a descending tonic inhibitory control on Ib excitatory interneurones or alternatively of a facilitatory control on PAD interneurones mediating presynaptic inhibition of Ib afferents.

Reciprocal Ia inhibition

Corticospinal lesions release reciprocal Ia inhibition from ankle extensors to flexors and reduce the reciprocal Ia inhibition of ankle extensors (Yanagisawa, Tanaka & Ito, 1976; Yanagisawa & Tanaka, 1978; Crone *et al.*, 2003), probably through mutual inhibition of opposite Ia interneurones. The better the recovery, the greater the reciprocal Ia inhibition of the soleus H reflex (p. 230).

Recurrent inhibition

Recurrent inhibition is, if anything, increased (Katz & Pierrot-Deseilligny, 1982; p. 184).

Conclusions

In stroke patients, there is no evidence that hyperexcitability of γ motoneurones, decreased presynaptic inhibition on Ia terminals or decreased recurrent inhibition contribute to the exaggeration of the stretch reflex in the lower limb. Transmission is modified in the other spinal pathways that can be tested, in the direction that would produce increased excitability of the reflex arc (see Table 12.1).

Changes in transmission in spinal pathways on the unaffected side of stroke patients

Abnormal transmission in some pathways

Abnormal transmission in some spinal pathways has been described on the 'unaffected' side of patients with a unilateral focal lesion.

(i) In contrast with normal subjects, the H_{max}/M_{max} ratio in the soleus may increase along with the static stretch of the triceps surae (Castaigne *et al.*, 1966).

(ii) The response of the soleus to imposed dynamic stretch is increased on the affected spastic side, but

Table 12.1. Spinal mechanisms underlying spasticity in the lower limb of patients with stroke and spinal cord injury

	Stroke	Spinal cord injury
Alpha motoneurone hyperexcitability	Probable	Probable
Fusimotor activity	Normal	Possible via afferent projections
Presynaptic inhibition of Ia terminals	Normal	Decreased **
Post-activation depression	Decreased ***	Decreased ***
Propriospinally-mediated group I excitation	Facilitated *	Facilitated **
Group II excitation	Facilitated *	Facilitated ****
Autogenetic Ib inhibition	Decreased **	Decreased ?
Reciprocal Ib facilitation	Facilitated *	Facilitated *
Recurrent inhibition	Normal or increased	Decreased ***
Reciprocal Ia inhibition	Decreased *	Decreased *

Exaggeration of facilitatory mechanisms: grey cells ('facilitated'). Decrease of inhibitory mechanisms: grey cells ('decreased'). Changes in recurrent inhibition in spinal cord injury are those observed during progressive paraparesis. The number of asterisks indicates the presumed importance of the mechanisms in the genesis of the stretch reflex exaggeration. Although there is no direct evidence, hyperexcitability of α motoneurones appears probable. There is also no direct evidence for hyperexcitability of γ motoneurones, but this remains a possibility in spinal cord injury, due to reflex activation from afferents (group II, cutaneous, joint) projecting to γ motoneurones. The decrease in Ib inhibition in patients with spinal cord injury is not significant.

is decreased on the apparently unaffected side. This depression diminishes over time, but is still present 1 year after stroke (Thilmann, Fellows & Ross, 1993).

(iii) On the affected side the response to stretch in biceps brachii is enhanced and that in triceps reduced with respect to normal subjects, but opposite results (decreased response in biceps and increased response in triceps) are found on the unaffected side (Thilmann, Fellows & Garms, 1990).

(iv) D1 inhibition of the FCR H reflex, reflecting presynaptic inhibition of Ia terminals, is decreased on the unaffected side, though to a lesser extent than on the affected side (Aymard *et al.*, 2000).

(v) Reciprocal Ia inhibition from ankle flexors to extensors is suppressed (Crone *et al.*, 2003).

Origin of the abnormalities on the unaffected side

Slight weakness has also been reported in the unaffected upper limb, possibly reflecting ipsilateral corticofugal projections (see Gandevia, 1993). It is similarly tempting to attribute abnormalities in transmission in reflex pathways on the unaffected side to ipsilateral corticofugal projections. However, the alterations of transmission on the unaffected side do not involve all spinal pathways. Thus, transmission is unchanged on the unaffected side in several pathways in which it is altered on the affected side: (i) post-activation depression at the Ia-motoneurone synapse (Aymard *et al.*, 2000); (ii) propriospinally mediated group I and group II excitations (Maupas *et al.*, 2004); (iii) Ib inhibition (Delwaide & Oliver, 1988); and (iv) reciprocal Ib facilitation (Crone *et al.*, 2003). The lack of change in these circuits might indicate that there is a strictly unilateral control from the contralateral hemisphere of the relevant interneurones (as is probably the case for propriospinal neurones). Alternatively, the abnormality on the affected side might be related to the lack of normal activity (as is likely to be the case with post-activation depression).

Increased excitability of cervical propriospinal neurones

There is evidence that the component of the descending command for movement relayed through cervical propriospinal neurones is greater on the affected side of stroke patients with poor recovery than in normal subjects (Mazevet *et al.*, 2003; pp. 481–4). Reticulospinal pathways project to propriospinal neurones in the cat, and it is likely that analogous projections mediate the greater propriospinal contribution to movement in patients with a damaged corticospinal system. Unmasking and/or reorganisation of connections from the ipsilateral undamaged hemisphere to the reticular formation, resulting in increased efficacy of reticulospinal projections to propriospinal neurones could account for the greater excitability of these neurones. The greater reliance on the propriospinal system for the movement repertoire of the upper limb would be accompanied by synkinetic movements in patients with poor recovery from stroke (see p. 484). Increased excitability of cervical propriospinal neurones activated by antagonistic group I volleys could also be a cause of disruption of the movement by an exaggerated stretch reflex in the antagonist.

Spasticity in cerebral palsy

In most patients with cerebral palsy, spasticity and athetosis are mixed. In these patients, there have been few investigations of transmission in specific spinal pathways, other than reciprocal Ia inhibition. The first evidence for reciprocal Ia inhibition from ankle flexors to soleus in humans was provided in patients with athetosis (Mizuno, Tanaka & Yanagisawa, 1971), in whom the inhibition was profound. Using PSTHs, Berbrayer & Ashby (1990) showed that reciprocal Ia inhibition from ankle extensors to tibialis anterior is also increased in patients with cerebral palsy, whether they have mainly athetosis or spasticity. This contrasts with the reciprocal Ia excitation elicited in similar patients, at the latency of the monosynaptic reflex, by a tap to the antagonistic tendon described by Gottlieb & Myklebust (1993). However, spread of the mechanical stimulus to excite receptors in the agonist and/or field-spread of the EMG response from the agonist could also account for the latter finding (cf. Chapter 2, p. 86).

Pathophysiology of spasticity after spinal lesions

In many patients with spinal cord lesions the dominant reflex dysfunction is the exaggeration of flexor reflexes, whose pathophysiology is discussed in Chapter 9. Such reflexes fall outside the definition of spasticity (see pp. 557–8), and are not considered here.

Exaggeration of stretch reflexes in patients with spinal lesions

There is no doubt that the exaggeration of stretch reflexes characterising spasticity may be a major cause of restraint to movement in patients with spinal cord lesions, such as hereditary spastic paraparesis (Strümpell–Lorrain disease), progressive spinal cord compression, cervical spondylitic myelopathy and multiple sclerosis (which behaves like spinal spasticity, presumably because of the diffuse nature of the lesions). Such spinal cord lesions represent the best indications for a specific treatment of spasticity.

Changes in transmission in spinal pathways in patients with spinal lesions

Transmission is altered in all spinal pathways that have been investigated in these patients, always in the direction that would exaggerate the stretch reflex (see Table 12.1).

Hyperexcitability of the soleus monosynaptic reflex arc

Hyperexcitability has been found consistently, as evidenced by an increase in the H_{max}/M_{max} ratio (e.g. see Delwaide, 1993; Ongerboer de Visser *et al.*, 1993) or in the F wave amplitude (Dressnandt, Konstanzer & Conrad, 1993). Plateau-like behaviours can be recorded in spinal cord-injured patients (Gorassini *et al.*, 2004; Nickolls *et al.*, 2004) but may be less easy to obtain than in normal subjects (Nickolls *et al.*, 2004), at least with that paradigm.

Fusimotor activity

There are, as yet, no published recordings from spindle endings in patients with spinal spasticity. Intuitively, one might expect there to be disinhibition of reflex pathways acting on γ and β motoneurones, such that normally innocuous stimuli such as stroking the skin would cause a heightened spindle discharge (cf. Fig. 12.1). If this proved to be the case, it is possible that the skin, bladder and bowel complications of paraplegia would result in a steady afferent input to γ motoneurones in such patients, producing widespread γ activity even in the absence of EMG activity. Similarly, stretch-induced group II volleys, released from the monoaminergic gating from the brainstem, could play a major role in the spasticity of patients with spinal cord lesions by reflexly activating γ motoneurones (see below).

Presynaptic inhibition on Ia terminals in the lower limbs

Presynaptic inhibition is decreased in patients with focal spinal cord lesions (Faist *et al.*, 1994), amyotrophic lateral sclerosis (Pierrot-Deseilligny, 1990), and multiple sclerosis (Nielsen, Petersen & Crone, 1995). This cannot be due to the interruption of the corticospinal tract (which, if anything, would produce increased presynaptic inhibition of Ia terminals, given the normal inhibitory corticospinal control on PAD interneurones in the lumbar enlargement). It therefore probably results from interruption of other descending pathways which help maintain a tonic level of presynaptic inhibition of Ia terminals in normal subjects under resting conditions (e.g. descending suppression of inhibitory interneurones transmitting cutaneous inhibition of first-order PAD interneurones, pathway [2] in Fig. 8.1. p. 338).

Post-activation depression

Post-activation depression at the Ia-motoneurone synapse is decreased in patients with spinal cord lesions due to traumatic injury and multiple sclerosis (Hultborn & Nielsen, 1998; see p. 99).

Propriospinally mediated group I excitation

Oligosynaptic group I excitation is increased (Remy-Néris *et al.* 2003; p. 503), probably because of disruption of the normal corticospinal control on feedback inhibitory interneurones inhibiting lumbar propriospinal neurones.

Group II excitation

The finding that the increase in the late peroneal group II excitation of the quadriceps generally is much greater than the increase in the early group I excitation, suggests interruption of the normal monoaminergic gating of group II excitation from the brainstem (Remy-Néris *et al.*, 2003; p. 324). Because the increase in peroneal excitation of quadriceps motoneurones is not correlated with spasticity, facilitation of the transmission in lumbar propriospinal pathways to α motoneurones is likely to be accompanied by changes in other mechanisms, such as a parallel excitation of γ motoneurones by group II afferents (see p. 325).

Ib inhibition

Ib inhibition has been found to be only slightly decreased with respect to normal subjects (Downes, Ashby & Bugaresti, 1995; p. 276).

Reciprocal Ib facilitation

Ib facilitation is increased (Crone *et al.*, 2003), probably the result of a 'release phenomenon' (pp. 277–9).

Recurrent inhibition

Variable results have been obtained, according to the nature of the causative lesion.

(i) In patients with complete or partial spinal cord injury, recurrent inhibition is increased (Shefner *et al.*, 1992).

(ii) In patients with progressive paraparesis, either amyotrophic lateral sclerosis (Raynor & Shefner, 1994) or hereditary spastic paraplegia (Mazzocchio & Rossi, 1997), recurrent inhibition is decreased and contributes to the stretch reflex exaggeration. In such cases, it is likely that the spinal lesion involves the descending inhibitory pathways less than the descending facilitatory pathways to Renshaw cells, so shifting the balance in favour of the former (see p. 186).

Reciprocal Ia inhibition

Reciprocal Ia inhibition is decreased from ankle flexors to extensors in patients with multiple sclerosis. However, this is not a major factor in spasticity at rest, because repeated high-frequency stimulation of the peroneal nerve can lead to a normalisation of reciprocal inhibition, though this is not accompanied by significant changes in spasticity (Crone *et al.*, 1994; p. 233). In patients with focal lesions, reciprocal Ia inhibition of the soleus H reflex is also decreased (Okuma, Mizuno & Lee, 2002), while it is increased to ankle dorsiflexors (Ashby & Wiens, 1989) (see pp. 230–2).

Conclusions

Not surprisingly, there are alterations in all spinal pathways in patients with spinal cord lesions. The dominant abnormalities are probably the decrease in post-activation depression and the decreased gating of group II excitation.

From spinal shock to spasticity

Adaptive changes in excitability of spinal neural circuits below the level of a lesion have been investigated from spinal shock to spasticity in patients with acute spinal cord injury (Hiersmenzel, Curt & Dietz, 2000). During spinal shock, the loss of tendon jerks was associated with a low persistence of F waves, but H reflexes could still be elicited in soleus. During the transition to spasticity, the reappearance of tendon jerks was associated with the recovery of F waves, but

the H_{max}/M_{max} ratio remained stable over months. A longitudinal study of one patient with spinal cord injury found that the reduction of post-activation depression developed with the transition from flaccid to spastic paralysis (Chapter 2, p. 100). Further studies are required of the evolution of the changes in transmission in specific spinal circuits, preferably longitudinal studies on individual patients.

Conclusions

Table 12.1 compares the spinal mechanisms underlying spasticity in the lower limb of stroke and spinal cord injury patients (data in the upper limb are more sparse and have been omitted). Post-activation depression at the Ia-motoneurone synapse is similarly reduced in the two groups of patients but, otherwise, abnormalities in spinal cord injury patients involve more spinal pathways and are more prominent. This is consistent with a greater contribution of spasticity to motor disability in patients with spinal cord lesions than in stroke patients.

Parkinson's disease

Transmission in spinal pathways has been investigated in patients with Parkinson's disease less extensively and less thoroughly than in spastic patients. It would not be surprising if there were abnormalities due to defective supraspinal control of spinal circuits. Whether spinal mechanisms contribute to the disorder of parkinsonian patients at rest is not yet resolved, and the issue is complicated by inconsistencies in the published findings.

Possible mechanisms underlying Parkinsonian rigidity

Rigidity is a cardinal symptom of Parkinson's disease, and is characterised clinically by a sustained increase in resistance to passive stretch of flexor and extensor muscles throughout the full range of motion. Increased muscle stiffness due to altered viscoelastic properties of muscle (cf. below) and inability of these patients to 'relax' and to eliminate entirely voluntary activation of the muscles are likely to be important variables in different studies (see below). Rigidity depends on the muscle afferent inflow, as demonstrated many years ago by the observation that it is abolished or markedly reduced by interruption of the inflow by section of the dorsal roots (Foerster, 1921) and by anaesthetic block of intramuscular nerve terminals, sufficient to abolish the tendon jerk, while leaving power intact (Walshe, 1924). The question then arises which afferents and which central pathways are involved in the production of the rigidity.

Changes in viscoelastic properties of muscle fibres

Changes in mechanical properties of Parkinsonian muscles have been postulated because the decreased ankle dorsiflexion during the stance phase of gait was not explained by increased EMG activity of the triceps surae (Dietz, Quintern & Berger, 1981). Observations made after altering the temperature of the leg led these authors to postulate that the increased muscle tone resulted from alterations in the properties of the muscle fibres themselves rather than of connective tissues. Alterations in triceps surae muscle fibres were considered responsible for the slower ankle rotation following brisk backward translation of the body, whereas no similar alterations were found in the tibialis anterior after forward translation (Dietz, Berger & Horstmann, 1988). In parkinsonian patients, even in those with relatively mild symptoms, there is greater stiffness in EMG-silent totally relaxed elbow muscles than in normals. This greater passive stiffness has been considered due to a change in the intrinsic properties of muscle fibres (Watts, Wiegner & Young, 1986). However, Rothwell *et al.*, (1983) showed that changes in the intrinsic muscle stiffness, at least in the early part of a stretch, cannot be responsible for parkinsonian rigidity, and Dietz (1992) conceded that changes in muscle fibre properties

are less pronounced in parkinsonian patients than in spastic patients (see above). Watts, Wiegner & Young (1986) proposed that 'additional physiological studies, ideally in anaesthetised Parkinson's disease patients treated with neuromuscular blocking agents in preparation for surgery, are needed to elucidate further the role played by changes in passive mechanical and neural-mediated active processes in the production of parkinsonian rigidity'. So far, such investigations have not been performed and the question remains open.

Short-latency stretch reflexes

Tendon jerks usually are not accentuated in parkinsonian patients (e.g. Dietrichson, 1971; Lee, 1989). Similarly, short-latency Ia spinal stretch reflexes (the 'M1' responses, see Chapter 2, p. 87) evoked at wrist, elbow, knee or ankle are not enhanced in comparison with normal subjects (Lee & Tatton, 1978; Berardelli, Sabra & Hallett, 1983; Rothwell *et al.*, 1983; Cody *et al.*, 1986; Bergui *et al.*, 1992). Unlike spasticity, rigidity cannot be explained by hyperexcitability of short-latency spinal stretch reflexes.

Long-latency responses to stretch

Increased long-latency responses

Long-latency responses to stretch (the 'M2' responses, Lee & Tatton, 1975) have been found to be increased in all investigated muscles: wrist muscles, flexor pollicis longus, triceps brachii, ankle muscles, quadriceps (Lee & Tatton, 1975, 1978; Cody *et al.*, 1986; Rothwell *et al.*, 1983; Berardelli, Sabra & Hallett, 1983; Bergui *et al.*, 1992). The increase in the M2 response in parkinsonian patients contrasts with the normality of the M1 response discussed above. Thus, in the flexor carpi radialis (FCR), which has been the muscle most extensively investigated, the M1 response, occurring at a latency of ~25 ms and mediated through mono- or oligo-synaptic Ia pathways, is of similar amplitude to that in normal subjects, while the M2 response occurring at a latency of ~50 ms is significantly enhanced in parkinsonian patients. The increase involves predominantly the later part (70–90 ms) of the long-latency response (see below).

Origin of the increased long-latency stretch reflex response

While the M2 response is increased consistently in parkinsonian patients, the origin of the response is still a matter of debate, even though there is growing evidence for a group II contribution in proximal muscles.

(i) Because of the inability of these patients to relax, Evarts *et al.* (1979) suggested that the enlarged M2 response might merely result from an increased pre-existing level of muscle contraction in parkinsonian patients (see also Burke, Hagbarth & Wallin, 1977). However, experiments performed on top of an identical pre-existing voluntary contraction in normal subjects and patients have confirmed the increase in the M2 responses in the patients (e.g. Rothwell *et al.*, 1983; Bedingham & Tatton, 1984; Tatton *et al.*, 1984; Cody *et al.*, 1986).

(ii) Because the long-latency stretch reflex in hand muscles is mediated through Ia afferents and a transcortical pathway (Chapter 2, pp. 90–2), the increased M2 response in the flexor pollicis longus of parkinsonian patients is probably due to enhanced transmission through this transcortical loop (Rothwell *et al.*, 1983).

(iii) In wrist muscles of both normal subjects and parkinsonian patients, ramp stretch elicits well-defined M1 and M2 responses, but the abrupt onset of vibration produces only an M1 response (Cody *et al.*, 1986). Vibration is a less effective stimulus for muscle spindle secondary endings (Chapter 3, p. 130), and this finding provides indirect evidence for a group II contribution to the transmission of the M2 response in wrist muscles, the longer latency of the response being explained by the slower conduction velocity of the afferents. Cody *et al.* (1986) therefore concluded that the increased long-latency response to stretch in wrist muscles of parkinsonian patients results from a change in the tonic descending control of transmission of group II excitation.

At least in the lower limb of parkinsonian patients, there is now evidence for a decrease in the normal gating from the brainstem of group II excitation to motoneurones (Chapter 7, p. 326 and pp. 588–9).

(iv) This does not eliminate the possibility that the increased M2 response in wrist and other proximal muscles results from overactivity in two parallel pathways (Limousin *et al.*, 1999): one involving group I afferents and a transcortical pathway, the other group II afferents and a shorter spinal pathway (cf. Chapter 2, pp. 91–2).

Later part of the M2 reponse

The later part of the M2 response is more enhanced and prolonged than its earlier part in the different proximal muscles investigated in parkinsonian patients (Berardelli, Sabra & Hallett, 1983; Cody *et al.*, 1986; Bergui *et al.*, 1992). 'This change in the waveform and duration of the M2 response suggests that the derangement in the reflexes in Parkinson's disease consists of more than a simple increase in gain of one or other direct excitatory pathway' (Cody *et al.*, 1986). Several mechanisms could be responsible: (i) weakening of an inhibitory mechanism, whether activated by afferent input or motor discharge (Cody *et al.*, 1986); (ii) increase in a transcortical group II response (Lee, 1989), superimposed on the increase in spinal group II excitation of α motoneurones; and (iii) an excitatory action of group II afferents on γ motoneurones, as in spastic patients (see Chapter 7, p. 325). The last possibility would require the conduction time through the γ loop before any excitation was manifest in α motoneurones.

Correlation between rigidity and the increase in the M2 response

This correlation was found to be good by Lee & Tatton (1975) and Mortimer & Webster (1979), but poor in later investigations (Rothwell *et al.*, 1983; Cody *et al.*, 1986), in which the most severely affected patients sometimes had M2 responses within the normal range. However, pallidotomy decreases both the rigidity and the amplitude of the M2 response in the contralateral arm of parkinsonian patients without altering the early Ia spinal stretch reflex (Limousin *et al.*, 1999; Hayashi *et al.*, 2001). These findings do not clarify the pathway of M2 because pallidotomy could have affected the pallidal output to brainstem nuclei gating the transmission of group II excitation or a transcortical pathway through pallidothalamocortical projections.

Conclusions

In parkinsonian patients, there is enhancement of long-latency (M2) responses produced by stretch, but not the short-latency (M1) responses. The mechanisms underlying this increase are likely to differ for proximal and distal muscles: (i) alteration of the transmission in a transcortical loop in hand muscles, and/or (ii) decreased gating of the transmission of group II excitation to α and, possibly, γ motoneurones in wrist and proximal muscles. However, the correlation between rigidity and increased M2 response to stretch is only weak, probably because the changes in transmission affect many other spinal pathways (see below).

Transmission in spinal pathways at rest

Transmission in all spinal pathways that can be investigated using the methods described in earlier chapters have been explored in parkinsonian patients. However, the data are sparse, and conflicting results have been reported.

Excitability of α motoneurones

H_{max}/M_{max} ratio

The H_{max}/M_{max} ratio in the soleus of parkinsonian patients in the early and late stages of the disease is not significantly different from that of normal subjects (Angel & Hoffmann, 1963; Dietrichson, 1971; Kushnir, Klein & Rabey, 2001; Sabbahi *et al.*, 2002). However, in the FCR, Obeso *et al.* (1985) reported that the H reflex was absent in 11 of 13 patients. This difficulty in eliciting the FCR H reflex in

parkinsonian patients was also encountered in some patients by Meunier *et al.* (2000), but has not been mentioned by other authors (Lelli, Panizza & Hallett, 1991; Nakashima *et al.*, 1994; Tsai, Chen & Lu, 1997).

H reflex threshold

Recent investigations have shown that the threshold for the soleus H reflex is increased in parkinsonian patients (Kushnir, Klein & Rabey, 2001; Kushnir *et al.*, 2002). In most normal subjects, H reflex threshold is lower than M wave threshold, but it was similar to, or higher than, M wave threshold in most patients. In patients with severe rigidity, the increased threshold was observed even with stimuli of 1 ms duration, which favours the recruitment of Ia fibres over α motor axons (cf. p. 6). The increased threshold was only seen with brief stimuli of 0.2 ms duration in patients with mild and moderate rigidity. The use of stimuli of duration 0.6–1 ms in less severely affected patients (and the wide range of normal values) could account for the absence of a difference in the threshold for the H reflex in normal subjects and parkinsonian patients in previous investigations (Angel & Hoffmann, 1963; Dietrichson, 1971).

H reflex recovery cycle

The secondary facilitation of the recovery cycle, occurring at ISIs >150 ms is increased and the following period of relative inhibition at 300–700 ms is decreased in parkinsonian patients (Olsen & Diamantopoulos, 1967; Takamori, 1967; Yap, 1967), even in the early stages of the disease (Sabbahi *et al.*, 2002). The increased facilitation of the H reflex recovery cycle disappears after successful thalamotomy (Yap, 1967) and treatment by L-dopa (McLeod & Walsh, 1972). As discussed in Chapter 1 (pp. 10–11), the recovery cycle results from too many phenomena to allow an easy pathophysiological interpretation of these findings. However, the increased facilitation at 150–700 ms could result from decreased post-activation depression at the Ia-motoneurone synapse, due to adaptive changes following akinesia. Post-activation depression is reduced in the elderly (Robertson & Koceja, 2003), and its reduction in these patients could be partly the result of the relatively old mean age of the parkinsonian patients.

F waves

F waves recorded in distal upper limb muscles (first dorsal interosseus, abductor pollicis brevis) occur more frequently and have a longer duration and a larger amplitude in parkinsonian patients than in normal subjects. These findings have been observed by many investigators (Abbruzzese *et al.*, 1985; Naito *et al.*, 1988; Cantello *et al.*, 1991; Ikoma, Mano & Takayanagi, 1994; Milanov, 2001), and have been interpreted as evidence of hyperexcitability of α motoneurones.

MEP

At rest, a decrease in the threshold of the MEP produced by TMS in the first dorsal interosseus (Cantello *et al.*, 1991) and an increase in its amplitude (Valls-Solé *et al.*, 1994) have been interpreted as further evidence for hyperexcitability of α motoneurones. However, changes in the threshold and the amplitude of the MEP at rest reported in the literature have been inconsistent, possibly due to differences in methods for threshold determination, differences in the tested patients and differences in their degree of relaxation (for review see Cantello, Tarletti & Civardi, 2002). In addition, the MEP produced by TMS activates cortical neurones trans-synaptically, and is therefore affected by the excitability of corticospinal neurones (see Chapter 1, p. 43).

Conclusions

In patients with Parkinson's disease, the amplitude of the H reflex is not increased in soleus and is, if anything, reduced in FCR, and the threshold for the soleus H reflex is increased. However, there is a concomitant decrease in the on-going presynaptic inhibition of Ia terminals (see below) and possibly in the post-activation depression at the Ia-motoneurone synapse (see above), and these

changes should enhance Ia-mediated reflexes (see below). Decreased excitability of α motoneurones in parkinsonian patients is also inconsistent with the increase in the F wave. However, the F wave was recorded in distal upper limb muscles, which are the muscles most involved in the tremor. The increased excitability of α motoneurones of these muscles could simply be due to the fact that they were not truly at rest. Alternatively, the decreased excitability of α motoneurones of more proximal muscles tested with the H reflex could be due to tonic reciprocal inhibition from the antagonists (see below).

Fusimotor activity

Absence of evidence for increased γ drive in microneurographic recordings

There are few recordings of spindle activity using microneurography in Parkinson's disease. However, in the limited data base, there was no evidence for selective or disproportionate γ drive to spindle endings in parkinsonian patients, and no evidence that the rigidity was driven by enhanced fusimotor drive (cf. Chapter 3, pp. 140–1). The apparent increase in spindle activity mentioned by Wallin, Hongell & Hagbarth (1973) was probably due to the inability of parkinsonian patients to relax completely (Burke, Hagbarth & Wallin, 1977).

Stretch- vs. electrically induced responses

Indirect evidence for increased γ_s drive was, however, claimed by Noth *et al.* (1988), based on comparisons of the responses evoked in the first dorsal interosseus by small amplitude stretches with those evoked by electrical stimulation of the median nerve, in parkinsonian patients and normal subjects. While the electrically induced responses were similar in the two groups, the responses to stretch were markedly reduced in parkinsonian patients. Given that γ_s stimulation in the cat reduces the sensitivity of primary endings to small-amplitude stretches, the authors suggested that this finding could result from heightened γ_s drive or a change in the balance between γ_s and γ_d activity. They argued that this disorder might not necessarily be detected by microneurographic recordings. However, this conclusion was based on a comparison of electrically and mechanically evoked reflexes as a measure of fusimotor drive, and the problems with this time-honoured but now discredited practice are addressed elsewhere (Chapter 3, pp. 117–18).

Conclusions

As in the case of spasticity, it would be imprudent to discard completely the possibility that enhanced γ drive plays a role in parkinsonian rigidity. Any enhanced γ motoneurone discharge need not result from enhanced descending drive onto fusimotor neurones: it could also result from a disruption of the normal gating of the transmission of group II excitation to γ motoneurones (see above). Clarification of this issue requires detailed studies under identical conditions of the responses of single spindle afferents in patients and control subjects.

Presynaptic inhibition of Ia terminals

Ia terminals to soleus motoneurones

Evidence for decreased presynaptic inhibition of Ia terminals to soleus motoneurones has been found consistently using techniques studying specifically presynaptic inhibition of Ia terminals with PAD. Thus, in parkinsonian patients, the suppression of the soleus H reflex caused by a heteronymous tendon tap to the biceps femoris is reduced (Roberts *et al.*, 1994), and the femoral-induced heteronymous monosynptic facilitation of the reflex is increased (Morita *et al.*, 2000). No significant relationship was found between the reduction of presynaptic inhibition assessed with either method and the rigidity in the limb studied. However, the increased femoral-induced facilitation was significantly correlated with the degree of bradykinesia, before and after treatment with L-dopa (see p. 371).

Homonymous vibratory inhibition

Homonymous vibratory inhibition of the soleus H reflex is not modified in these patients (Delwaide, Pepin & Maertens de Noordhout, 1993; Sabbahi *et al.*, 2002). Vibratory depression of a homonymous reflex involves post-activation depression at the Ia-motoneurone synapse (cf. p. 341) as well as presynaptic inhibition, but both mechanisms are probably decreased in parkinsonian patients (see above). It is possible that prolonged vibration of the homonymous tendon activated reciprocal Ia inhibition from pretibial flexors, because vibration applied to the Achilles tendon spreads to these muscles (Ashby, Verrier & Carleton, 1980). The absence of a change in homonymous vibratory inhibition in parkinsonian patients might then be explained by the increased reciprocal Ia inhibition that has been reported in these patients (see below), a change that could offset the decrease in presynaptic inhibition of Ia terminals.

D1 inhibition of the FCR H reflex

Radial-induced D1 inhibition of the FCR H reflex is decreased in patients with Parkinson's disease (Lelli, Panizza & Hallett, 1991). The results were similar for the two sides of asymmetrical patients, and this indicates that the abnormality does not correlate with the degree of rigidity. However, here again, inconsistent results have been reported. Nakashima *et al.* (1994) found no reduction of the radial-induced D1 inhibition of the FCR H reflex at ISIs around 20 ms. Only the late inhibition at ISIs of 70–100 ms, which is not due to presynaptic inhibition (see Chapter 8, pp. 344, 372), was found to be reduced in the patients explored by Tsai, Chen & Lu (1997).

Conclusions

There are congruent arguments in favour of a decrease in presynaptic inhibition of soleus Ia terminals but this abnormality contributes only marginally to the rigidity of ankle muscles. Inconsistent results have been reported at wrist level.

Reciprocal inhibition

Lower limb

Peroneal-induced reciprocal Ia inhibition of the soleus H reflex is increased in parkinsonian patients with respect to normal subjects (Obeso *et al.*, 1985; Delwaide, Pepin & Maertens de Noordhout, 1993). The effects of anaesthetic blockade of the peroneal nerve using lidocaine on the soleus H reflex were compared in parkinsonian patients and normal subjects. After the blockade, the soleus H reflex was increased significantly, thus revealing an exaggerated tonic inhibitory action from flexor to extensor muscles (Bathien & Rondot, 1977; Obeso *et al.*, 1985). Interestingly, abnormal tonic reciprocal inhibition was also decreased by L-dopa treatment, suggesting that a disorder of peripheral reciprocal inhibition might be involved in the pathophysiology of parkinsonian rigidity.

Upper limb

Reports of radial-induced early, 'reciprocal', inhibition of the FCR H reflex at rest have been particularly inconsistent. The inhibition has been found either to be decreased (Lelli, Panizza & Hallett, 1991), unchanged (Nakashima *et al.*, 1994; Tsai, Chen & Lu, 1997; Meunier *et al.*, 2000), or even probably increased (Obeso *et al.*, 1985). The FCR H reflex could not been obtained in 11 of 13 parkinsonian patients explored in the last study, but it appeared in 4 of 5 patients after anaesthetic blockade of the radial nerve, a finding that suggests a tonic level of inhibition.

Conclusions

Transmission of reciprocal Ia inhibition to ankle extensors is tonically increased and the resulting decreased excitability of soleus motoneurones might explain why the soleus H reflex is not increased despite the decreased presynaptic inhibition of Ia terminals. The increased reciprocal Ia inhibition could be due to increased γ drive to ankle flexors associated with the incomplete relaxation of those

muscles. Alternatively, abnormal reticulospinal activation has been proposed (Delwaide, Pepin & Maertens de Noordhout, 1993, see below). Particularly inconsistent findings have been reported at wrist level for what was probably non-reciprocal group I inhibition.

Ib inhibition (and/or oligosynaptic propriospinally mediated group I excitation)

Decreased Ib inhibition

In patients with Parkinson's disease, gastrocnemius medialis-induced inhibition of the soleus H reflex may be reduced or even replaced by facilitation (Delwaide, Pepin & Maertens de Noordhout, 1991). The departures from normal values correlated with the intensity of rigidity assessed by the Webster scale: increased rigidity was associated, first, with a reduction of inhibition and, in the more rigid patients, with facilitation replacing the normal inhibition. Because of the strong correlation between the decreased Ib inhibition and the increased reciprocal Ia inhibition, a common mechanism for these two abnormalities has been advanced (increased reticulospinal activation, Delwaide, Pepin & Maertens de Noordhout, 1993).

Increased oligosynaptic facilitation?

Inhibition tends to be replaced by facilitation, possibly because facilitated group I excitation overwhelms the Ib inhibition, with or without decreased Ib inhibition (cf. p. 277). Facilitation of transmission of group I excitation in lumbar propriospinal neurones would explain the facilitation. The increased amplitude and decreased threshold of the MEP elicited by TMS in the quadriceps of patients with Parkinson's disease has been attributed to hyperexcitability of the relevant lumbar propriospinal neurones (Trembley & Trembley, 2002). The absence of increased peroneal-induced propriospinally mediated group I facilitation of the quadriceps H reflex (Simonetta-Moreau *et al.*, 2002) does not eliminate this possibility, because the latter investigation focused on patients in the early stages of the disease, whereas the replacement of Ib inhibition by facilitation was observed in the most severely affected patients.

Correlation with treatment

In *de novo* patients treated with L-dopa, the decrease in facilitation paralleled the reduction of the rigidity (Delwaide, Pepin & Maertens de Noordhout, 1991). High-frequency stimulation in the subthalamic nucleus (Pötter *et al.*, 2004) has recently also been shown to restore the inhibition, paralleling the reduction of the axial symptoms and gait disorders.

Conclusions

There is little doubt that gastrocnemius medialis-induced group I inhibition of soleus motoneurones is reduced in parkinsonian patients, and that it is restored by clinically effective treatments. However, interesting as this latter finding may be, it remains an open question whether the disorder affects primarily Ib inhibition or propriospinally mediated group I facilitation.

Group II excitation

Evidence for increased group II excitation

The late group II, but not the early group I, deep peroneal facilitation of the quadriceps H reflex is larger in parkinsonian patients than in normal subjects (Simonetta-Moreau *et al.*, 2002; Chapter 7, see p. 326). The finding that only the group II excitation is increased suggests a decrease in gating from the brainstem of transmission specifically of the group II excitation to motoneurones, possibly due to loss of the monoaminergic control arising from locus coeruleus. In accordance with this speculation, there is a significant cell loss in the locus coeruleus, even in the early stages of the disease (German *et al.*, 1992). This failure might also explain the absence of the changes in group II excitation during postural adjustments (see below).

Correlation with clinical state

Increased group II excitation has been found only on the affected side of hemiparkinsonian patients, where it was correlated with the rigidity score. However, in contrast with mildly affected unilateral patients, the group II excitation of severely affected bilateral patients was not increased with respect to normal subjects. Other dysfunctions could mask the increased peroneal-induced group II excitation in the severely affected patients, much as has been suggested to explain the absence of an increase in the M2 response to stretch in such patients (Rothwell *et al.*, 1983; Cody *et al.*, 1986).

Conclusions

Peroneal-induced group II excitation of quadriceps motoneurones is increased. Such a finding in the upper limb would support a group II contribution to the enhanced M2 responses to stretch in wrist muscles.

Recurrent inhibition

Homonymous recurrent inhibition of soleus assessed with the paired H reflex technique is not modified (Delwaide, 1985b; Lelli, Panizza & Hallett, 1991).

Cutaneomuscular responses

Reduction of transcortical inhibitory cutaneomuscular responses

In parkinsonian patients, the early inhibitory (I1) component of the cutaneomuscular response in the first dorsal interosseus is decreased (Fuhr, Zeffiro & Hallett, 1992). So too is the cutaneous inhibition of the MEP in the abductor pollicis brevis, though this can be reversed to facilitation (Delwaide & Olivier, 1990). These two cutaneous inhibitory effects act through transcortical loops (cf. Chapter 9, p. 437). Thus, in Parkinson's disease, transmission may be altered in both excitatory proprioceptive (cf. pp. 583–4) and inhibitory exteroceptive transcortical pathways to hand muscles. The depression of the transmission in inhibitory cutaneous pathways is partially reversed with dopaminergic treatments, and could be a factor contributing to parkinsonian rigidity.

Withdrawal reflexes

Withdrawal reflexes in the lower limb of patients with Parkinson's disease differ from those in normal subjects in four respects: (i) lower threshold; (ii) 'co-contractions' with absence of the normal reciprocal relationships in antagonistic motoneurones; (iii) brevity of cutaneous silent periods; and (iv) greater habituation than in normals (Delwaide, Schwab & Young, 1974). These abnormalities are reversed largely, though not completely, by the administration of L-dopa (see pp. 436–7).

Conclusions

In contrast with spasticity, studies of the transmission in many spinal pathways have provided inconsistent findings. This could be because Parkinson's disease is a complex motor syndrome with variable degrees of akinesia, rigidity and tremor, which do not involve all muscles equally. However, inconsistent results for the same pathway at the same joint have been reported (e.g. early "reciprocal" inhibition of the FCR H reflex, see p. 587). The different ability of the patients to relax is often advanced to explain the difficulty in interpreting results in Parkinson's disease, and could account for some of the inconsistencies. A further factor could be that the disease process is not homogeneous in different patients.

Alterations of transmission in spinal pathways during motor tasks

Decreased modulation of stretch-induced group II excitation during upright stance

Responses produced by tilt of the platform

The amplitude of the stretch-induced group II-mediated medium-latency responses produced by tilting the platform during active upright stance is

normal or slightly increased in the soleus and tibialis anterior of patients with Parkinson's disease (Schieppati & Nardone, 1991), and slightly increased in the gastrocnemius lateralis (Scholtz *et al.*, 1987). The main abnormality is the absence of an influence of 'postural set' on medium-latency responses, with inability of patients to decrease the amplitude of these responses, particularly in the tibialis anterior, when standing and holding onto a stable frame. This decreased depression of the medium-latency response when stance is stabilised correlates significantly with the severity of the disease (Schieppati & Nardone, 1991; Chapter 7, p. 326).

Responses produced by backward translation

The amplitude of group II-mediated medium-latency responses in the gastrocnemius medialis produced by backward translation of the body is decreased in parkinsonian patients. This reduction may partially be attributed to the slower perturbation-induced ankle rotation velocity resulting from the greater stiffness of the muscle (cf. pp. 582–3), but there is also evidence for a lower stretch reflex sensitivity (Dietz, Berger & Horstmann, 1988).

Interpretation

In normal subjects, the gating of transmission of group II excitation to motoneurones is regulated according to the requirements of the upright posture: (i) When holding onto a stable frame, the medium-latency responses are not required to ensure stable stance, and the gating is increased (Chapter 7, pp. 312–14). (ii) In contrast, large medium-latency responses are required after a translation to prevent the subject from falling (Chapter 11, p. 541), and the gating is then decreased. In parkinsonian patients, there is failure of this modulation of the gating of group II excitation (Nardone, Corna & Schieppati, 2001). From animal experiments, it is likely that the gating is monoaminergic and arises from the locus coeruleus. A role for the locus coeruleus in the control of posture has been proposed by Pompeiano (2001), and it is relevant that there is a significant cell loss in this structure, early in the disease (cf. p. 588).

Conclusions

Increased group II excitation probably contributes to parkinsonian rigidity (see pp. 583–4, 588–9). However, in functional terms, the major abnormality involving group II excitation is the loss of the modulation of group II excitation during postural adjustments. This abnormality would contribute to the loss of appropriate postural reflexes of these patients and thereby to their enhanced risk of falling (as also does the forward shift of the centre of gravity in stooped patients).

Abnormal modulation of reciprocal inhibition during voluntary movement

It has been suggested that the basal ganglia inhibit muscle contractions that are inappropriate for accurate voluntary movement, and that a failure of this inhibitory function contributes to Parkinsonism (Mink, 1996). This hypothesis has prompted experiments investigating changes in reciprocal inhibition during voluntary movement.

Reciprocal Ia inhibition at ankle level

At the onset of voluntary ankle dorsiflexion, the inhibition of the soleus H reflex observed in normal subjects ('natural reciprocal inhibition', Chapter 5, p. 217) is reversed to facilitation in parkinsonian patients, suggesting an inappropriate central control of reciprocal inhibition of ankle extensors during the initiation of voluntary contraction of the antagonist (Hayashi *et al.*, 1988). Conversely, at the onset of voluntary plantar flexion, the normal facilitation of the soleus H reflex produced by TMS was reduced and, in some cases, reversed to inhibition. This finding suggests that the motor cortical process that generates the excitatory command to ankle extensors also reaches the antagonist dorsiflexors and, through excitation of tibialis anterior-coupled Ia inhibitory interneurones, produces inhibition of

soleus motoneurones (Morita *et al.*, 2002). This abnormal effect of TMS is correlated with the motor component of the unified Parkinson's disease rating scale, and is improved by pallidotomy. These findings suggest that control of reciprocal Ia inhibition mediated through the corticospinal system is abnormal in parkinsonian patients (see below).

'Reciprocal' inhibition at wrist level

In normal subjects, the disynaptic radial-induced early group I inhibition of the FCR H reflex is suppressed at the onset of voluntary wrist flexion (Chapter 11, p. 524). This modulation is almost completely absent on the more affected side of parkinsonian patients and is reduced on the less affected side (Meunier *et al.*, 2000). This abnormality in the control of non-reciprocal group I inhibition was correlated weakly with the axial signs score, but not with akinesia or rigidity. The normal suppression of the non-reciprocal group I inhibition of FCR motoneurones at the onset of wrist flexion is thought to be due to corticospinal facilitation of FCR-coupled group I inhibitory interneurones, and is mediated through mutual inhibition of opposite group I inhibitory interneurones (cf. Chapter 11, pp. 525–6; Fig. 11.2). Thus, the suppression of this effect in parkinsonian patients might result, here also, from abnormal descending control of group I inhibition between antagonists mediated through the corticospinal system.

Interpretation

The cortical control of movement of a selected target muscle is disturbed in Parkinson's disease, but can be restored by removing the inappropriate subcortical modulation of cortical function by pallidotomy. Experiments using transcranial electrical stimulation (Dick *et al.*, 1984) suggest that corticospinal projections are not abnormal in Parkinson's disease. The site of the abnormal cortical control of reciprocal inhibition at ankle and wrist level should therefore be upstream of the origin of the corticospinal tract. In this respect, intracortical inhibitory systems are dysfunctional in parkinsonian patients (e.g. see Ridding, Inzelberg & Rothwell, 1995). The dysfunction might also involve the reciprocal inhibition by muscle afferents of cortical neurones driving antagonistic muscles seen in normal subjects (Bertolasi *et al.*, 1988).

Conclusions

While the transmission in the pathway of early reciprocal inhibition at rest is either enhanced (ankle) or normal (wrist), reciprocal inhibition, whether mediated through Ia inhibitory interneurones (ankle) or group I inhibitory interneurones (wrist), does not undergo normal modulation during voluntary contractions. This is due to a loss of the corticospinal control of the relevant spinal interneurones caused by an abnormality upstream of the origin of corticospinal tract. The resulting disorder of the agonist–antagonist activation pattern probably underlies some of the difficulty that parkinsonian patients have in performing discrete movements.

Propriospinally mediated excitation of upper limb motoneurones

Increased propriospinal transmission

The component of the descending command for movement relayed through cervical propriospinal neurones is greater in parkinsonian patients than in normal subjects, at least in the early stages of the disease (Pol *et al.*, 1998; Chapter 10, pp. 484–5). In this study, the increased excitation of propriospinal neurones was not directly related to the motor disturbance (e.g. to afferent discharges resulting from tremor and/or rigidity), because the increased EMG suppression: (i) was not correlated with the severity of symptoms; (ii) was symmetrical whereas the symptoms were clearly asymmetrical; (iii) returned to the control level in the more severe patients; and (iv) was not modified by levodopa treatment, which improved the patients' clinical status.

Possible compensatory mechanism

Increased transmission of the descending command through propriospinal neurones might result from a compensatory mechanism aimed at modifying the defective command: e.g. the strong inhibitory input from muscle and cutaneous afferents to propriospinal neurones could be an adaptation designed to smooth movement execution and/or to overcome the difficulty of these patients in relaxing. This adaptive response was not detectable in the more advanced patients, and this suggests that the compensation occurs and/or is relayed through basal ganglia, so that it can no longer manifest itself when there is extreme dopaminergic denervation.

Conclusions

There is, as yet, no unifying picture of the changes in spinal reflex pathways in patients with Parkinson's disease when they are, or are attempting to be, at rest. This is not surprising given that the primary pathology is not in the spinal cord. On the other hand, there is strong evidence that abnormal descending control of activity in spinal cord circuits contributes significantly to abnormalities of postural control and movement in parkinsonian patients. Not only do these abnormalities shed light on the parkinsonian movement disorder, but they also point to the importance of reflex feedback in shaping the motor drive to muscle. In the Preface, it was stated: *'It is a thesis of this book that the final movement is only that part of the supraspinally derived programme that the spinal cord circuitry deems appropriate*'. This view is illustrated well by the movement abnormalities in patients suffering from Parkinson's disease.

REFERENCES

Abbruzzese, G., Vische, M., Ratto, S., Abbruzzese, M. & Favale, E. (1985). Assessment of motor neuron excitability in parkinsonian rigidity by the F wave. *Journal of Neurology*, **232**, 246–9.

Ada, L., Vattanasilp, W., O'Dywer, N. J. & Crosbie, J. (1998). Does spasticity contribute to walking dysfunction after stroke? *Journal of Neurology, Neurosurgery and Psychiatry*, **64**, 628–35.

Angel, R. W. & Hofmann, W. W. (1963). The H-reflex in normal, spastic and rigid subjects. *Archives of Neurology*, **8**, 591–6.

Aoki, M., Mori, S. & Fujimori, B. (1976). Exaggeration of knee-jerk following spinal hemisection in monkeys. *Brain Research*, **107**, 471–85.

Artieda, J., Queseda, P. & Obeso, J. A. (1991). Reciprocal inhibition between forearm muscles in spastic hemiplegia. *Neurology*, **41**, 286–9.

Ashby, P. & Burke, D. (1971). Stretch reflexes in the upper limb of spastic man. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 765–71.

Ashby, P. & Wiens, M. (1989). Reciprocal inhibition following lesions of the spinal cord in man. *Journal of Physiology (London)*, **414**, 145–57.

Ashby, P., Verrier, M. & Carleton, S. (1980). Vibratory inhibition of the monosynaptic reflex. In *Progress in Clinical Neurophysiology*, vol. 8, ed. J. E. Desmedt, pp. 254–62. Basel: Karger.

Aymard, C., Katz, R., Lafitte, C., *et al.* (2000). Presynaptic inhibition and homosynaptic depression: A comparison between lower and upper limbs in normal subjects and patients with hemiplegia. *Brain*, **123**, 1688–702.

Azouvi, P., Roby-Brami, A., Biraben, A., Thiebaut, J. B., Thurel, C. & Bussel, B. (1993). Effect of intrathecal baclofen on the monosynaptic reflex in humans: evidence for a postsynaptic action. *Journal of Neurology, Neurosurgery and Psychiatry*, **56**, 515–19.

Bailey, C. S., Lieberman, J. S. & Kitchell, R. L. (1980). Response of muscle spindle primary endings to static stretch in acute and chronic spinal cats. *American Journal of Veterinary Research*, **41**, 2030–6.

Bathien, N. & Rondot, P. (1977). Reciprocal continuous inhibition in rigidity in Parkinsonism. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 20–4.

Bedingham, W. & Tatton, W. G. (1984). Dependence of EMG responses evoked by imposed wrist displacements on pre-existing activity in the stretched muscles. *Canadian Journal of the Neurological Sciences*, **11**, 272–80.

Benecke, R., Conrad, B., Meinck, H. M. & Hohne, J. (1983). Electromyographic analysis of bicycling on an ergometer for evaluation of spasticity of lower limbs in man. *Advances in Neurology*, **39**, 1035–46.

Bennett, D. J., Li, Y., Harvey, P. J. & Gorassini, M. (2001). Evidence for plateau potentials in tail motoneurons of awake chronic

spinal rats with spasticity. *Journal of Neurophysiology*, **86**, 1972–82.

Bennett, D. J., Sanelli, L., Cooke, C. L., Harvey, P. J. & Gorassini, M. A. (2004). Spastic long-lasting reflexes in the awake rat after sacral spinal cord injury. *Journal of Neurophysiology*, **91**, 2247–58.

Berardelli, A., Sabra, A. F. & Hallett, M. (1983). Physiological mechanisms of rigidity in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **46**, 45–53.

Berbrayer, D. & Ashby, P. (1990). Reciprocal inhibition in cerebral palsy. *Neurology*, **40**, 653–6.

Berger, W. & Dietz, V. (1993). Spastic movement disorder: similarities and differences in children and adults. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 150–4. Heidelberg: Springer-Verlag.

Bergui, M., Lopiano, L., Paglia, G., Quattrocolo, G., Scarzella, L. & Bergamasco, B. (1992). Stretch reflex of quadriceps femoris and its relation to rigidity in Parkinson's disease. *Acta Neurologica Scandinavica*, **86**, 226–9.

Bertolasi, L., Priori, A., Tinazzi, M., Bertasi, V. & Rothwell, J. C. (1988). Inhibitory action of forearm flexor muscle afferents on corticospinal outputs to antagonist muscles in humans. *Journal of Physiology (London)*, **511**, 947–56.

Bobath, B. (1990). *Adult Hemiplegia: Evaluation and Treatment*. Oxford: Butterworth-Heinemann.

Bohannon, R. W. & Andrews, A. W. (1990). Correlation of knee extensor muscle torque and spasticity with gait speed in patients with stroke. *Archives of Physical Medicine and Rehabilitation*, **71**, 330–3.

Bostock, H., Sharief, M. K., Reid, G. & Murray, N. M. (1995). Axonal ion channel dysfunction in amyotrophic lateral sclerosis. *Brain*, **118**, 217–25.

Boyd, S. G., Barwood, S. A., Ballieu, C. *et al.* (1998). Validity of a clinical measure of spasticity in children with cerebral palsy in a double blinded randomised controlled clinical trial. *Developmental Medicine and Child Neurology*, **40**, 7.

Brunnström, S. (1970). *Motor Behavior of Adult Patients with Hemiplegia: Movement Therapy in Hemiplegia*. New York: Harper & Row.

Buller, A. J. (1957). The ankle-jerk in early hemiplegia. *Lancet*, **2**, 1262–3.

Buller, A. J., Eccles, J. C. & Eccles, R. M. (1960). Interactions between motoneurones and muscles in respect of the characteristic speeds of their responses. *Journal of Physiology (London)*, **150**, 417–36.

Burke, D. (1980). A reassessment of the muscle spindle contribution to muscle tone in normal and spastic man. In *Spasticity: Disordered Motor Control*, ed. R. G. Feldman, R. R. Young & W. P. Koella, pp. 261–78. Chicago: Year Book Publishers.

(1983). Critical examination of the case for or against fusimotor involvement in disorders of muscle tone. In *Motor Control Mechanisms in Health and Disease, Advances in Neurology*, vol. 39, ed. J. E. Desmedt, pp. 133–50. New York: Raven Press.

Burke, D., Knowles, L., Andrews, C. J. & Ashby, P. (1972). Spasticity and decerebrate rigidity: An experimental study in the cat. *Brain*, **95**, 31–48.

Burke, D., Hagbarth, K.-E. & Wallin, B. G. (1977). Reflex mechanisms in Parkinsonian rigidity. *Scandinavian Journal of Rehabilitation Medicine*, **9**, 15–23.

Cantello, R., Giannelli, M., Bettucci, D., Civardi, C., De Angelis, M. S. & Mutani, R. (1991). Parkinson's disease rigidity: magnetic motor evoked potentials in small hand muscle. *Neurology*, **41**, 1449–56.

Cantello, R., Tarletti, R. & Civardi, C. (2002). Transcranial magnetic stimulation and Parkinson's disease. *Brain Research Reviews*, **38**, 309–27.

Castaigne, P., Cathala, H. P., Lacert, P. & Pierrot-Deseilligny, E. (1966). Contribution à l'étude des troubles du tonus par le réflexe monosynaptique de Hoffmann. *Revue Neurologique*, **115**, 943–54.

Cody, F. W., MacDermott, P. B., Matthews, P. B. C. & Richardson, H. C. (1986). Observations on the genesis of the stretch reflex in Parkinson's disease. *Brain*, **109**, 229–49.

Conrad, B., Benecke, R. & Meinck, H. M. (1985). Gait disturbances in paraspastic patients. In *Clinical Neurophysiology in Spasticity. Contribution to Assessment & Pathophysiology*, ed. P. J. Delwaide & R. R. Young, pp. 155–74. Amsterdam: Elsevier.

Corcos, D. M., Gottlieb, G. L., Penn, R. D., Myklebust, B. & Agarwal, G. C. (1986). Movement deficits caused by hyperexcitable stretch reflexes in spastic humans. *Brain*, **109**, 1043–58.

Cramer, S. C. (2004). Editorial comment – spasticity after stroke: what's the catch? *Stroke*, **35**, 139–40.

Crone, C., Nielsen, J., Petersen, N., Ballegaard, M. & Hultborn, H. (1994). Disynaptic reciprocal inhibition of ankle extensors in spastic patients. *Brain*, **117**, 1161–8.

Crone, C., Johnsen, L. L., Biering-Sørensen, F. & Nielsen, J. B. (2003). Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury. *Brain*, **126**, 495–507.

Davies, J. M., Mayston, M. J. & Newham, D. J. (1996). Electrical and mechanical output of the knee muscles during isometric and isokinetic activity in stroke and healthy adults. *Disability Rehabilitation*, **18**, 83–90.

Davis, E. C. & Barnes, M. P. (2000). Botulinum toxin and spasticity. *Journal of Neurology, Neurosurgery and Psychiatry*, **69**, 143–7.

Delwaide, P. J. (1973). Human monosynaptic reflexes and presynaptic inhibition. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 508–22. Basel: Karger.

(1985a). Electrophysiological testing of spastic patients: its potential usefulness and limitation. In *Clinical Neurophysiology in Spasticity*, ed. J. E. Delwaide & R. R. Young, pp. 185–203. Amsterdam: Elsevier.

(1985b). Are there modifications in spinal cord functions of parkinsonian patients? In *Clinical Neurophysiology in Parkinsonism*, ed. P. J. Delwaide & E. Agnoli, pp. 19–32. Amsterdam: Elsevier.

(1993). Pathophysiological mechanisms of spasticity at the spinal cord level. In *Spasticity: Mechanisms & Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 296–308. Heidelberg: Springer Verlag.

Delwaide, P. J. & Olivier, E. (1988). Short-latency autogenic inhibition (Ib inhibition) in human spasticity. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 1546–50.

(1990). Conditioning transcranial cortical stimulation (TCCS) by exteroceptive stimulation in parkinsonian patients. *Advances in Neurology*, **53**, 175–81.

Delwaide, P. J. & Pennisi, G. (1994). Tizanidine and electrophysiologic analysis of spinal control mechanisms in humans with spasticity. *Neurology*, **44**, S21–7; S27–8.

Delwaide, P. J., Schwab, R. S. & Young, R. R. (1974). Polysynaptic spinal reflexes in Parkinson's disease. *Neurology*, **24**, 820–7.

Delwaide, P. J., Pepin, J. L. & Maertens de Noordhout, A. (1991). Short-latency autogenic inhibition in patients with Parkinsonian rigidity. *Annals of Neurology*, **30**, 83–9.

(1993). The audiospinal reaction in Parkinsonian patients reflects functional changes in reticular nuclei. *Annals of Neurology*, **33**, 63–9.

Denny-Brown, D. (1980). Historical aspects of the relation of spasticity to movement. In *Spasticity: Disordered Motor Control*, ed. R. G. Feldman, R. R. Young & W. P. Koella, pp. 1–6. Chicago: Year Book Medical Publishers.

Dick, J. P., Cowan, J. M., Day, B. L. *et al.* (1984). The corticomotoneurone connection is normal in Parkinson's disease. *Nature*, **310**, 407–9.

Dietrichson, P. (1971). Phasic ankle reflex in spasticity and parkinsonian rigidity. *Acta Neurologica Scandinavica*, **47**, 22–51.

(1973). The role of the fusimotor system in spasticity and parkinsonian rigidity. In *New Developments in Electromyography and Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 496–507. Basel: Karger.

Dietz, V. (1992). Human neuronal control of automatic functional movements : interaction between central programs and afferent input. *Physiological Reviews*, **72**, 33–9.

(2003). Spastic movement disorder: what is the impact of research on clinical practice? *Journal of Neurology, Neurosurgery and Psychiatry*, **74**, 820–6.

Dietz, V. & Berger, W. (1983). Normal and impaired regulation of muscle stiffness in gait. A new hypothesis about muscle hypertonia. *Experimental Neurology*, **79**, 680–7.

Dietz, V., Quintern, J. & Berger, W. (1981). Electrophysiological studies of gait in spasticity and rigidity: evidence that altered mechanical properties of muscle contribute to hypertonia. *Brain*, **104**, 431–49.

Dietz, V., Berger, W. & Horstmann, G. A. (1988). Posture in Parkinson's disease: impairment of reflexes and programming. *Annals of Neurology*, **24**, 660–9.

Dietz, V., Trippel, M. & Berger, W. (1991). Reflex activity and muscle tone during elbow movements in patients with spastic paresis. *Annals of Neurology*, **30**, 767–78.

Dietz, V., Ibrahim, I. K., Trippel, M. & Berger, W. (1993). Spastic paresis: reflex activity and muscle tone in elbow muscles during passive and active motor tasks. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 251–65. Heidelberg: Springer Verlag.

Dimitrijević, M. R. & Nathan, P. W. (1967). Studies of spasticity in man. 2. Analysis of stretch reflexes in spasticity. *Brain*, **90**, 333–58.

Downes, L., Ashby, P. & Bugaresti, J. (1995). Reflex effects from Golgi tendon organ (Ib) afferents are unchanged after spinal cord lesion in humans. *Neurology*, **45**, 1720–4.

Dressnandt, J., Konstanzer, A. & Conrad, B. (1993). Dynamics of reflex excitability following intrathecal baclofen administration in patients with severe spastic syndromes. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 309–18. Heidelberg: Springer Verlag.

Dressnandt, J., Auer, C. & Conrad, B. (1995). Influence of baclofen upon the alpha-motoneuron in spasticity by means of F-wave analysis. *Muscle and Nerve*, **18**, 103–7.

Eisen, A. & Fisher, M. (1999). The F wave. In *Recommendations for the Practice of Clinical Neurophysiology : Guidelines of the International Federation of Clinical Neurophysiology*, ed. G. Deutschl & A. Eisen, pp. 255–7. Amsterdam: Elsevier.

Eisen, A. & Odusote, K. (1979). Amplitude of the F-wave : a potential means of documenting spasticity. *Neurology*, **29**, 1306–9.

Evarts, E. V., Teräväinen, H. T., Beuchert, D. E. & Calne, D. B. (1979). Pathophysiology of motor performance in Parkinson's disease. In *Dopaminergic Ergot Derivatives and Motor Function*, ed. K. Fuxe & D. B. Calne, pp. 45–59. Oxford: Pergamon Press.

Faist, M., Mazevet, D., Dietz, V. & Pierrot-Deseilligny, E. (1994). A quantitative assessment of presynaptic inhibition of Ia afferents in spastics. Differences in hemiplegics and paraplegics. *Brain*, **117**, 1449–55.

Fellows, S. J., Kaus, C., Ross, H. F. & Thilmann, A. F. (1993a). Disturbances of voluntary arm movement in human spasticity: the relative importance of paresis and muscle hypertonia. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 139–49. Heidelberg: Springer-Verlag.

Fellows, S. J., Ross, H. F. & Thilmann, A. F. (1993b). The limitation of the tendon jerk as a marker of pathological stretch reflex activity in human spasticity. *Journal of Neurology, Neurosurgery and Psychiatry*, **56**, 531–7.

Fierro, B., Raimondo, D. & Modica, A. (1990). Analysis of F response in upper motoneurone lesions. *Acta Neurologica Scandinavica*, **82**, 329–34.

Foerster, O. (1921). Zur Analyse und Pathophysiologie der striären Bewegungsstörungen. *Zeischrift für die Gesamte Neurologie und Psychiatrie*, **73**, 1–169.

Fuhr, P., Zeffiro, T. & Hallett, M. (1992). Cutaneous reflexes in Parkinson's disease. *Muscle and Nerve*, **15**, 733–9.

Fujimori, B., Kato, M., Matsushima, S., Mori, S. & Shimamura, M. (1966). Studies on the mechanisms of spasticity following spinal hemisection in the cat. In *Muscular Afferents & Motor Control*, ed. Granit, R., pp. 397–413. Stockholm: Almqvist and Wiksell.

Gandevia, S. C. (1993). Strength changes in hemiparesis: measurements and mechanisms. In *Spasticity : Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 111–22. Heidelberg: Springer Verlag.

Garcia-Mullin, R. & Mayer, R. F. (1972). H reflexes in acute and chronic hemiplegia. *Brain*, **95**, 559–72.

German, D. C., Manaye, K. F., White, C. L. *et al.* (1992). Disease-specific patterns of locus coeruleus cell loss. *Annals of Neurology*, **32**, 667–76.

Gilman, S., Marco, L. A. & Ebel, H. C. (1971). Effects of medullary pyramidotomy in the monkey. II. Abnormalities of spindle afferent responses. *Brain*, **94**, 515–30.

Gilman, S., Lieberman, J. S. & Marco, L. A. (1974). Spinal mechanisms underlying the effects of unilateral ablation of areas 4 and 6 in monkeys. *Brain*, **97**, 49–64.

Gorassini, M. A., Knash, M., Harvey, P. J., Bennett, D. J. & Yang, J. F. (2004). Role of motoneurons in the generation of muscle spasms after spinal cord injury. *Brain*, **127**, 2247–58.

Gottlieb, G. L. & Myklebust, B. M. (1993). Hyper-reflexia and disordered voluntary movement. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 155–66. Heidelberg: Springer-Verlag.

Hagbarth, K.-E., Wallin, G., Löfstedt, L. & Aquilonius, S. M. (1975). Muscle spindle activity in alternating tremor of Parkinsonism and in clonus. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 636–41.

Hayashi, A., Kagamihara, Y., Nakajima, Y., Narabayahi, H., Okuma, Y. & Tanaka, R. (1988). Disorder in reciprocal Ia inhibition upon initiation of voluntary movements in patients with Parkinson's disease. *Experimental Brain Research*, **70**, 437–40.

Hayashi, R., Hashimoto, T., Tada, T. & Ikeda, S. (2001). Relation between changes in long-latency stretch reflexes and muscle stiffness in Parkinson's disease – comparison before and after unilateral pallidotomy. *Clinical Neurophysiology*, **112**, 1814–21.

Hiersmenzel, L. P., Curt, A. & Dietz, V. (2000). From spinal shock to spasticity. Neuronal adaptations to a spinal cord injury. *Neurology*, **54**, 1574–82.

Higashi, T., Funase, K., Kusano, K. *et al.* (2001). Motoneuron pool excitability of hemiplegic patients: Assessing recovery stages by using H-reflex and M response. *Archives of Physical Medicine and Rehabilitation*, **82**, 1604–10.

Hultborn, H. & Malmsten, J. (1983a). Changes in segmental reflexes following chronic spinal cord hemisection in the cat. I. Increased monosynaptic and polysynaptic ventral root discharges. *Acta Physiologica Scandinavica*, **119**, 405–22.

(1983b). Changes in segmental reflexes following chronic spinal cord hemisection in the cat. II. Conditioned monosynaptic test reflexes. *Acta Physiologica Scandinavica*, **119**, 423–33.

Hultborn, H. & Nielsen, J. B. (1998). Modulation of transmitter release from Ia afferents by their preceding activity – a 'postactivation depression'. In *Presynaptic Inhibition and Neural Control*, ed. P. Rudomin, R. Romo & L. Mendell, pp. 178–91. New York: Oxford University Press.

Ikoma, K., Mano, Y. & Takayanagi, T. (1994). Pulsed magnetic stimulation and F waves in Parkinson's disease. *Internal Medicine*, **33**, 77–81.

Jackson, J. H. (1958). *Selected Writings of John Hughlings Jackson*, ed. J. Taylor, New York: Basic Books.

Jankelowitz, S. K., Trevillion, L., Howells, J. & Burke, D. (2004). Changes in excitability of motor axons in stroke. *Clinical Neurophysiology*, **115**, 92.

Kagamihara, U., Hayashi, A., Okuma, Y., Nagaoka, M., Nakajima, Y. & Tanaka, R. (1998). Reassessment of H-reflex recovery curve using the double stimulation procedure. *Muscle and Nerve*, **21**, 352–60.

Kamper, D. G., Harvey, R. L., Suresh, S. & Rymer, W. Z. (2003). Relative contributions of neural mechanisms versus muscle mechanics in promoting finger extension deficits following stroke. *Muscle and Nerve*, **28**, 309–18.

Katz, R. & Pierrot-Deseilligny, E. (1982). Recurrent inhibition of motoneurones in patients with upper motor neuron lesions. *Brain*, **105**, 103–24.

Katz, R. T. & Rymer, W. Z. (1989). Spastic hypertonia: mechanisms and measurement. *Archives of Physical Medicine and Rehabilitation*, **70**, 144–55.

Knutsson, E. (1985). Studies of gait control in patients with spastic paresis. In *Clinical Neurophysiology in Spasticity. Contribution to Assessment and Pathophysiology*, ed. P. J. Delwaide & R. R. Young, pp. 175–83. Amsterdam: Elsevier.

Knutsson, E., Mårtensson, A. & Gransberg, L. (1997). Influences of muscle stretch reflexes on voluntary, velocity-controlled movements in spastic paraparesis. *Brain*, **120**, 1626–33.

Kushnir, M., Klein, C. & Rabey, J. M. (2001). H reflex behavior in Parkinson's disease patients and patients with extrapyramidal and pyramidal signs combined. *Journal of the Neurological Sciences*, **186**, 101–5.

Kushnir, M., Klein, C., Pollack, L. & Rabey, J. M. (2002). H reflex threshold in Parkinson's disease patients for different stimulus duration. *Parkinsonism and Related Disorders*, **9**, 85–7.

Lance, J. W. (1980). Symposium synopsis. In *Spasticity: Disordered Motor Control*, ed. R. G. Feldman, R. R. Young & W. P. Koella, pp. 485–94. Chicago: Year Book Medical Publishers.

Lance, J. W. & DeGail, P. (1965). Spread of phasic muscle reflexes in normal and spastic subjects. *Journal of Neurology, Neurosurgery and Psychiatry*, **28**, 328–334.

Landau, W. M. (1980). What is it? What is it not? In *Spasticity: Disordered Motor Control*, ed. R. G. Feldman, R. R. Young & W. P. Koella, pp. 17–24. Chicago: Year Book Medical Publishers.

(2003). Botulinum toxin for spasticity after stroke. *New England Journal of Medicine*, **348**, 258–9.

Landau, W. M. & Clare, M. H. (1964). Fusimotor function. VI. H reflex tendon jerk and reinforcement in hemiplegia. *Archives of Neurology and Psychiatry (Chicago)*, **10**, 128–34.

Lee, R. G. (1989). Pathophysiology of rigidity and akinesia in Parkinson's disease. *European Neurology*, **29**, 13–18.

Lee, R. G. & Tatton, W. G. (1975). Motor responses to sudden limb displacement in primates with specific CNS lesions and in human patients with motor system disorders. *Canadian Journal of Neurological Sciences*, **2**, 285–93.

(1978). Long loop reflexes in man: clinical applications. In *Cerebral Motor Control in Man: Long Loop Mechanisms. Progress in Clinical Neurophysiology*, vol. 4, ed. J. E. Desmedt, pp. 320–33. Basel: Karger.

Lelli, S., Panizza, M. & Hallett, M. (1991). Spinal inhibitory mechanisms in Parkinson's disease. *Neurology*, **41**, 553–6.

Limousin, P., Brown, R. G., Jahanshahi, M. *et al.* (1999). The effects of posteroventral pallidotomy on the preparation and execution of voluntary hand and arm movements in Parkinson's disease. *Brain*, **122**, 315–27.

McLellan, D. L. (1977). Co-contraction and stretch reflexes in spasticity during treatment with baclofen. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 30–8.

McLeod, J. & Walsh, J. (1972). H-reflex studies in patients with Parkinson's disease *Journal of Neurology, Neurosurgery and Psychiatry*, **35**, 77–80.

Magladery, J. W., Teasdall, R. D., Park, A. M. & Languth, H. W. (1952). Electrophysiological studies of reflex activity in patients with lesions of the nervous system. I. A comparison of spinal motoneurone excitability following afferent nerve volleys in normal persons and patients with upper motor neurone lesions. *Bulletin of the Johns Hopkins Hospital*, **91**, 219–43.

Marque, P., Simonetta-Moreau, M., Maupas, E. & Roques, C. F. (2001). Facilitation of transmission in heteronymous group II pathways in spastic hemiplegic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **70**, 36–42.

Matthews, P. B. C. (1972). *Mammalian Muscle Spindles and their Central Action*, 630 pp. London: Arnold.

Maupas, E., Marque, P., Roques, C. F. & Simonetta-Moreau, M. (2004). Modulation of the transmission in group II heteronymous pathways by tizanidine in spastic hemiplegic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **75**, 130–5.

Mazevet, D., Meunier, S., Pradat-Diehl, P., Marchand-Pauvert, V. & Pierrot-Deseilligny, E. (2003). Changes in propriospinally-mediated excitation of upper limb motoneurones in stroke patients. *Brain*, **126**, 988–1000.

Mazzocchio, R. & Rossi, A. (1997). Involvement of spinal recurrent inhibition in spasticity. Further insight into the regulation of Renshaw cell activity. *Brain*, **120**, 991–1003.

Meltzer, G. E., Hunt, R. S. & Landau, W. M. (1963). Fusimotor function. III. The spastic monkey. *Archives of Neurology*, **168**, 133–6.

Meunier, S., Pol, S., Houeto, J. L. & Vidailhet, M. (2000). Abnormal reciprocal inhibition between antagonist muscles in Parkinson's disease. *Brain*, **123**, 1017–26.

Milanov, I. (1992). A comparison of methods to assess the excitability of lower motor neurones. *Canadian Journal of Neurological Sciences*, **19**, 64–8.

(2001). Motoneuron activity in patients with different types of tremor. *Electromyography and Clinical Neurophysiology*, **41**, 479–84.

Milanov, I. & Georgiev, D. (1994). Mechanisms of tizanidine action on spasticity. *Acta Neurologica Scandinavica*, **89**, 274–9.

Mink, J. W. (1996). The basal ganglia: focused selection and inhibition of competing motor programs. *Progress in Neurobiology*, **50**, 381–425.

Mizrahi, E. M. & Angel, R. W. (1979). Impairment of voluntary movement by spasticity. *Annals of Neurology*, **5**, 594–5.

Mizuno, Y., Tanaka, R. & Yanagisawa, N. (1971). Reciprocal group I inhibition of triceps surae motoneurones in man. *Journal of Neurophysiology*, **34**, 1010–17.

Mogyoros, I., Kiernan, M. C., Burke, D. & Bostock, H. (1998). Strength-duration properties of sensory and motor axons in amyotrophic lateral sclerosis. *Brain*, **121**, 851–9.

Morita, H., Shindo, M., Ikeda, S. & Yanagisawa, N. (2000). Decrease in presynaptic inhibition on heteronymous monosynaptic Ia terminals in patients with Parkinson's disease. *Movement Disorders*, **15**, 830–4.

Morita, H., Crone, C., Christenhuis, D., Petersen, N. T. & Nielsen, J. B. (2001). Modulation of presynaptic inhibition and disynaptic reciprocal Ia inhibition during voluntary movement in spasticity. *Brain*, **124**, 826–37.

Morita, H., Shindo, M., Morita, S., Hashimoto, T., Tada, T. & Ikeda, S. (2002). Abnormal conditioning effect of transcranial magnetic stimulation on soleus H-reflex during voluntary movement in Parkinson's disease. *Clinical Neurophysiology*, **113**, 1316–24.

Mortimer, J. A. & Webster, D. D. (1979). Evidence for a quantitative association between EMG stretch responses and parkinsonian rigidity. *Brain Research*, **162**, 169–73.

Naito, Y., Komatsu, Y., Kanazawa, I. & Nakanishi, T. (1988). F response abnormality in Parkinson's disease. *Japanese Journal of Psychiatry and Neurology*, **42**, 811–18.

Nakashima, K., Rothwell, J. C., Day, B. L., Thompson, P. D., Shannon, K. & Marsden, C. D. (1989). Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke. *Brain*, **112**, 681–97.

Nakashima, K., Shimoyama, R., Yokoyama, Y. & Takahashi, K. (1994). Reciprocal inhibition between the forearm muscles in patients with Parkinson's disease. *Electromyography and Clinical Neurophysiology*, **34**, 67–72.

Nardone, A., Corna, S. & Schieppati, M. (2001). Group II afferent fibres in balance control: evidence from neurological disease. In *MCC 2001 From Basic Motor Control to Functional Recovery II*, ed. N. Gantchev, pp. 331–8. Sofia: Academic Publishing House.

Neilson, P. D., O'Dwyer, N. J. & Nash, J. (1990). Control of isometric muscle activity in cerebral palsy. *Developmental Medicine and Child Neurology*, **32**, 778–88.

Nickolls, P., Collins, D. F., Gorman, R. B., Burke, D. & Gandevia, S. C. (2004). Forces consistent with plateau potentials evoked in patients with chronic spinal cord injury. *Brain*, **127**, 660–70.

Nielsen, J., Petersen, N. & Crone, C. (1995). Changes in transmission across synapses of Ia afferents in spastic patients. *Brain*, **118**, 995–1004.

Noth, J., Schurmann, M., Podoll, K. & Schwartz, M. (1988). Reconsideration of the concept of enhanced static fusimotor drive in rigidity in patients with Parkinson's disease. *Neuroscience Letters*, **84**, 239–43.

O'Dwyer, N. J., Ada, L. & Neilson, P. D. (1996). Spasticity and muscle contracture following stroke. *Brain*, **119**, 1737–49.

Obeso, J. A., Quesada, P., Artieda, J. & Martinez-Lage, J. M. (1985). Reciprocal inhibition in rigidity and dystonia. In *Clinical Neurophysiology in Parkinsonism*, ed. P. J. Delwaide & A. Agnelli, pp. 9–18. Amsterdam: Elsevier.

Okuma, Y., Mizuno, Y. & Lee, R. G. (2002). Reciprocal Ia inhibition in patients with asymmetric spinal spasticity. *Clinical Neurophysiology*, **113**, 292–7.

Olsen, P. Z. & Diamantopoulos, E. (1967). Excitability of spinal motoneurones in normal subjects and patients with spasticity, parkinsonian rigidity and cerebellar hypotonia. *Journal of Neurology, Neurosurgery and Psychiatry*, **30**, 325–31.

Ongerboer de Visser, B. W., Koelman, J. H. T. M., Bour, L. J. & Hilgevoord, A. A. J. (1993). Signs of the upper motoneuron syndrome in relation to soleus Hoffmann reflex tests. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 287–95. Heidelberg: Springer Verlag.

Ørsnes, G., Crone, C., Krarup, C., Petersen, N. & Nielsen, J. (2000). The effect of baclofen on the transmission in spinal pathways in spastic multiple sclerosis patients. *Clinical Neurophysiology*, **111**, 1372–9.

Perry, J., Hoffer, M. M., Giovan, P., Antonelli, D. & Greenberg, R. (1974). Gait analysis of the triceps surae in cerebral palsy. A preoperative and postoperative clinical and electromyographic study. *Journal of Bone and Joint Surgery*, **56**, 511–20.

Perry, J., Giovan, P., Harris, L. J., Montgomery, J. & Azaria, M. (1978). The determinants of muscle action in the hemiparetic lower extremity. *Clinical Orthopedics and Relative Research*, **131**, 71–89.

Pierrot-Deseilligny, E. (1990). Electrophysiological assessment of the spinal mechanisms underlying spasticity. In *New Trends and Advanced Techniques in Clinical Neurophysiology*, ed. P. M. Rossini & F. Mauguière, pp. 364–73. Amsterdam: Elsevier.

Pol, S., Vidailhet, M., Meunier, S., Mazevet, D., Agid, Y. & Pierrot-Deseilligny, E. (1998). Overactivity of cervical premotoneurones in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **64**, 166–71.

Pollock, L. J. & Davis, L. (1931). Studies in decerebration. VI. The effect of deafferentation upon decerebrate rigidity. *American Journal of Physiology*, **98**, 47–9.

Pompeiano, O. (2001). Role of the locus coeruleus in the static and dynamic control of posture. *Archives Italiennes de Biologie*, **139**, 109–24.

Pötter, M., Illert, M., Wenzelburger, R., Deuschl, G. & Volkmann, J. (2004). The effect of subthalamic stimulation on autogenetic inhibition in Parkinson's disease. *Neurology*, **63**, 1234–9.

Powers, R. K., Marder-Meyer, J. & Rymer, W. Z. (1988). Quantitative relations between hypertonia and stretch reflex threshold in spastic hemiparesis. *Annals of Neurology*, **23**, 115–24.

Raynor, E. M. & Shefner, J. M. (1994). Recurrent inhibition is decreased in patients with amyotrophic lateral sclerosis. *Neurology*, **44**, 2148–53.

Remy-Néris, O., Denys, P., Daniel, O., Barbeau, H. & Bussel, B. (2003). Effect of intrathecal clonidine on excitation transmitted by interneurones activated by groups I–II afferents in paraplegics. *Experimental Brain Research*, **148**, 509–14.

Ridding, M. C., Inzelberg, R. & Rothwell, J. C. (1995). Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. *Annals of Neurology*, **37**, 181–8.

Roberts, R. C., Part, M. J., Farquhar, R. & Butchart, P. (1994). Presynaptic inhibition of soleus Ia afferent terminals in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**, 1488–91.

Robertson, C. T. & Koceja, D. M. (2003). Post-activation depression of the soleus H-reflex in the elderly. *Electromyography and Clinical Neurophysiology*, **43**, 103–11.

Rothwell, J. C., Obeso, J. A., Traub, M. M. & Marsden, C. D. (1983). The behaviour of the long latency stretch reflex in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **46**, 35–44.

Russo, R. E., Nagy, F. & Hounsgaard, J. (1998). Inhibitory control of plateau properties in dorsal horn neurones in the turtle spinal cord in vitro. *Journal of Physiology (London)*, **506**, 795–808.

Sabbahi, M., Etnyre, B., Al-Jawayed, I. A., Hasson, S. & Jankovic, J. (2002). Methods of H-reflex evaluation in the early stages of Parkinson's disease. *Journal of Clinical Neurophysiology*, **19**, 67–72.

Satkunam, L. E. (2003). Rehabilitation medicine: 3. Management of adult spasticity. *Canadian Medical Association Journal*, **169**, 1173–9.

Schieppati, M. & Nardone, A. (1991). Free and supported stance in Parkinson's disease. The effect of posture and 'postural set' on leg muscle responses to perturbation, and its relation to the severity of the disease. *Brain*, **114**, 1227–44.

Schiller, H. H. & Stålberg, E. (1978). Human botulism studied with single-fiber electromyography. *Archives of Neurology*, **35**, 346–9.

Scholtz, E., Diener, H. C., Noth, J., Friedemann, H., Dichgans, J. & Bacher, M. (1987). Medium and long latency EMG responses in leg muscles: Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 66–70.

Shefner, J. M., Berman, S. A., Sarkarati, M. & Young, R. R. (1992). Recurrent inhibition is increased in patients with spinal cord injury. *Neurology*, **42**, 2162–8.

Simonetta-Moreau, M., Meunier, S., Vidailhet, M., Pol, S., Galitzky, M. & Rascol, O. (2002). Transmission of group II heteronymous pathways is enhanced in rigid lower limb of de novo patients with Parkinson's disease. *Brain*, **125**, 2125–33.

Smith, G. V., Silver, K. H. C., Goldberg, A. P. & Macko, R. F. (1999). 'Task-oriented' exercise improves hamstring strength and spastic reflexes in chronic stroke patients. *Stroke*, **30**, 2112–18.

Sommerfeld, D. K., Eek, E.U.-B., Svensson, A.-K., Holmqvist, L. W. & Von Arbin, M. H. (2004). Spasticity after stroke. Its occurrence and association with motor impairments and activity limitations. *Stroke*, **35**, 134–40.

Sommerville, J. & Ashby, P. (1978). Hemiplegic spasticity: neurophysiologic studies. *Archives of Physical Medicine and Rehabilitation*, **59**, 592–6.

Stein, R. B. (1995). Presynaptic inhibition in humans. *Progress in Neurobiology*, **47**, 533–44.

Szumski, A. J., Burg, D., Struppler, A. & Velho, F. (1974). Activity of muscle spindles during muscle twitch and clonus in normal and spastic human subjects. *Electroencephalography and Clinical Neurophysiology*, **37**, 589–97.

Takamori, M. D. (1967). H reflex study in upper motoneurone disease. *Neurology*, **17**, 32–40.

Tardieu, G., Shentoub, S. & Delarue, R. (1954). A la recherche d'une technique de mesure de la spasticité. *Revue Neurologique*, **91**, 143–4.

Tatton, W. G., Bedingham, W., Verrier, M. C. & Blair, R. D. (1984). Characteristic alterations in response to imposed wrist displacements in parkinsonian rigidity and dystonia musculorum deformans. *Canadian Journal of the Neurological Sciences*, **11**, 281–7.

Thilmann, A. F. (1993). In *Spasticity: Mechanisms & Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 1–5. Heidelberg: Springer Verlag.

Thilmann, A. F., Fellows, S. J. & Garms, E. (1990). Pathological stretch reflexes on the 'good' side of hemiparetic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **53**, 208–14.

(1991). The mechanism of spastic muscle hypertonus. *Brain*, **114**, 233–44.

Thilmann, A. F., Fellows, S. J. & Ross, H. F. (1993). Pathological changes in spastic muscle reflexes evoked by passive stretch or tendon taps. In *Spasticity: Mechanisms & Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 239–50. Heidelberg: Springer Verlag.

Trembley, F. & Trembley, L. (2002). Cortico-motor excitability of the lower limb motor representation: a comparative study in Parkinson's disease and healthy controls. *Clinical Neurophysiology*, **113**, 2006–12.

Tsai, C. H., Chen, R. S. & Lu, C. S. (1997). Reciprocal inhibition in Parkinson's disease. *Acta Neurologica Scandinavica*, **95**, 13–18.

Tsai, C. T., Chen, H. W. & Chang, C. W. (2003). Assessments of chronodispersion and tacheodispersion of F waves in patients with spinal cord injury. *American Journal of Physical Medicine and Rehabilitation*, **82**, 498–503.

Tuzson, A. E., Granata, K. P. & Abel, M. F. (2003). Spastic velocity threshold constrains functional performance in cerebral palsy. *Archives of Physical Medicine and Rehabilitation*, **84**, 1363–8.

Valls-Sole, J., Pascal-Leone, A., Brasil-Neto, J. P., Cammarota, A., McShane, L. & Hallett, M. (1994). Abnormal facilitation of the response to transcranial magnetic stimulation in patients with Parkinson's disease. *Neurology*, **44**, 735–41.

Vattanasilp, W., Ada, L. & Crosbie, J. (2000). Contribution of thixotropy, spasticity, and contracture to ankle stiffness after stroke. *Journal of Neurology, Neurosurgery and Psychiatry*, **69**, 34–9.

Vaughan, C. W., Neilson, P. D. & O'Dwyer, N. J. (1988). Motor control deficits of orofacial muscles in cerebral palsy. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 534–9.

Wallin, B. G., Hongell, A. & Hagbarth, K.-E. (1973). Recordings from muscle afferents in Parkinsonian rigidity. In *New Developments in Electromyography & Clinical Neurophysiology*, vol. 3, ed. J. E. Desmedt, pp. 263–72. Basel: Karger.

Walshe, F. M. R. (1924). Observations on the nature of the muscular rigidity of paralysis agitans, and its relationship to tremor. *Brain*, **47**, 159–77.

Watts, R. L., Wiegner, A. W. & Young, R. R. (1986). Elastic properties of muscles measured at the elbow in man. II. Patients with parkinsonian rigidity. *Journal of Neurology, Neurosurgery and Psychiatry*, **49**, 1177–81.

Yanagisawa, N. (1980). Reciprocal reflex connections in motor disorders in man. In *Spinal and Supraspinal Mechanisms of Voluntary Motor Control and Locomotion*, ed. J. E. Desmedt, pp. 129–41. Basel: Karger.

Yanagisawa, N. & Tanaka, R. (1978). Reciprocal Ia inhibition in spastic paralysis in man. In *Contemporary Clinical Neurophysiology*, ed. W. A. Cobb & H. Van Duijn, pp. 521–6. Amsterdam: Elsevier.

Yanagisawa, N., Tanaka, R. & Ito, Z. (1976). Reciprocal Ia inhibition in spastic hemiplegia of man. *Brain*, **99**, 555–74.

Yanagisawa, N., Shindo, M., Morita, H. & Yanagawa, S. (1993). Methodological problems in the Hoffmann reflex study of spasticity. In *Spasticity: Mechanisms and Management*, ed. A. F. Thilmann, D. J. Burke & W. Z. Rymer, pp. 273–86. Heidelberg: Springer Verlag.

Yap, C. B. (1967). Spinal and long-loop reflexes on spinal motoneurone excitability in spasticity and rigidity. *Brain*, **90**, 887–96.

Yelnik, A., Albert, T., Bonan, I. & Laffont, I. (1999). A clinical guide to assess the role of lower limb extensor overactivity in hemiplegic gait disorders. *Stroke*, **30**, 580–5.

Index

No references are given here to the mention of a topic in the résumés at the end of each chapter.