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Two North American bull elks contesting for cows in Yellowstone National Park. The shorter days of autumn trigger hormone production, battling, and reproductive behavior.

Study Plan

40.1 Hormones and Their Secretion

The endocrine system includes four major types of cell signaling

Hormones and local regulators can be grouped into four classes based on their chemical structure

Many hormones are regulated by feedback pathways

Body processes are regulated by coordinated hormone secretion

40.2 Mechanisms of Hormone Action

Hydrophilic hormones bind to surface receptors, activating protein kinases inside cells

Hydrophobic hormones bind to receptors inside cells, activating or inhibiting genetic regulatory proteins

Target cells may respond to more than one hormone, and different target cells may respond differently to the same hormone

40.3 The Hypothalamus and Pituitary

Under regulatory control by the hypothalamus, the anterior pituitary secretes eight hormones

The posterior pituitary secretes two hormones into the circulatory system

40.4 Other Major Endocrine Glands of Vertebrates

The thyroid hormones stimulate metabolism, development, and maturation

The parathyroid glands regulate Ca^{2+} level in the blood

The adrenal medulla secretes two "fight or flight" hormones

The adrenal cortex secretes two groups of steroid hormones that are essential for survival

The gonadal sex hormones regulate the development of reproductive systems, sexual characteristics, and mating behavior

The pancreatic islet of Langerhans hormones regulate glucose metabolism

The pineal gland regulates some biological rhythms

40.5 Endocrine Systems in Invertebrates

Hormones regulate development in insects and crustaceans

40 The Endocrine System

Why It Matters

Every September, as the days grow shorter and autumn approaches, bull elks *(Cervus canadensis)* begin to strut their stuff. Although they have grazed peacefully together at high mountain elevations from the Yukon to Arizona, they now become testy with each other. They also rasp at tree branches and plow the ground with their antlers. Soon, they descend to lower elevations, where the cow elks have been feeding in large nursery groups with their calves and yearlings.

The bulls move in among the cows and chase away the male yearlings. As part of the mating ritual, the bulls bugle, square off, strut, and circle; then they clash their antlers together, attempting to drive each other from the cows. The winning males claim harems of about 10 females each, a major prize.

After the mating season ends, tranquility returns. The cows again graze in herds; the males form now-friendly bachelor groups that also feed quietly in the meadows. Eating is their major occupation, storing nutrients in preparation for the snowy winter. The young will be born eight to nine months later, when summer returns.

The next year, the shortening days of late summer and fall again trigger the transition to mating behavior. Detected by the eyes and

registered in the brain, reduced daylength initiates changes in the secretion of long-distance signaling molecules called **hormones** (*hormaein* = to excite). Hormones are released from one group of cells and are transported through the circulatory system to other cells, their target cells, whose activities they change. Among the changes will be a rise in the concentration of hormones responsible for mating behavior.

We too are driven by our hormones. They control our day-to-day sexual behavior—often as outlandish as that of a bugling bull elk—as well as a host of other functions, from the concentration of salt in our blood, to body growth, to the secretion of digestive juices. Along with the central nervous system, hormones coordinate the activities of multicellular life.

The best-known hormones are secreted by cells of the **endocrine system** (*endo* = within; *krinein* = to separate), although hormones actually are produced by almost all organ systems in the body. The endocrine system, like the nervous system, regulates and coordinates distant organs. The two systems are structurally, chemically, and functionally related, but they control different types of activities. The nervous system, through its high-speed electrical signals, enables an organism to interact rapidly with the external environment, while the endocrine system mainly controls activities that involve slower, longer-acting responses. Typical responses to hormones may persist for hours, weeks, months, or even years.

The mechanisms and functions of the endocrine system are the subjects of this chapter. As in other chapters of this unit, we pay particular attention to the endocrine system of humans and other mammals.

40.1 Hormones and Their Secretion

Cells signal other cells using neurotransmitters, hormones, and local regulators. Recall from Chapters 37 through 39 that a neurotransmitter is a chemical released by an axon terminal at a synapse which affects the activity of a postsynaptic cell. Our focus in this chapter is hormones and local regulators, molecules that act locally rather than over long distances.

The Endocrine System Includes Four Major Types of Cell Signaling

Four types of cell signaling occur in the endocrine system: classical endocrine signaling, neuroendocrine signaling, paracrine regulation, and autocrine regulation. In *classical endocrine signaling,* hormones are secreted into the blood or extracellular fluid by the cells of ductless secretory organs called **endocrine glands** **(Figure 40.1a).** (In contrast, *exocrine glands,* such as the sweat and salivary glands, release their secretions into ducts that lead outside the body or into the cavities of the digestive tract, as described in Section 36.2.) The hormones are circulated throughout the body in the blood and, as a result, most body cells are constantly exposed to a wide variety of hormones. (The cells of the central nervous system are sequestered from the general circulatory system by the blood–brain barrier, described in Section 38.3.) Only *target cells* of a hormone, those with *receptor proteins* recognizing and binding that hormone, respond to it. Through these responses, hormones control such vital functions as digestion, osmotic balance, metabolism, cell division, reproduction, and development. The action of hormones may either speed or inhibit these cellular processes. For example, growth hormone stimulates cell division, whereas glucocorticoids inhibit glucose uptake by most cells in the body.

Hormones are cleared from the body at a steady rate by enzymatic breakdown in their target cells or in either the liver or kidneys. Breakdown products are excreted by the digestive and excretory systems; depending on the hormone, the breakdown takes minutes to days.

In *neuroendocrine signaling,* specialized neurons called **neurosecretory neurons** release a hormone called a *neurohormone* into the circulatory system when appropriately stimulated **(Figure 40.1b).** The neurohormone is distributed by the circulatory system and elicits a response in target cells that have receptors for the hormone. Note that both neurohormones and neurotransmitters are secreted by neurons. Neurohormones are distinguished from neurotransmitters in that neurohormones affect distant target cells, whereas neurotransmitters affect adjacent cells. However, both neurohormones and neurotransmitters function in the same way—they cause cellular responses by interacting with specific receptors on target cells. For instance, gonadotropin-releasing hormone, a neurohormone secreted by the hypothalamus, controls the release of luteinizing hormone from the pituitary.

In *paracrine regulation,* a cell releases a signaling molecule that diffuses through the extracellular fluid and acts on nearby cells—regulation is *local* rather than at a distance, as is the case with hormones and neurohormones **(Figure 40.1c).** In some cases the local regulator acts on the same cells that produced it; this is called *autocrine regulation* **(Figure 40.1d).** For example, many of the growth factors that regulate cell division and differentiation act in both a paracrine and autocrine fashion.

Hormones and Local Regulators Can Be Grouped into Four Classes Based on Their Chemical Structure

More than 60 hormones and local regulators have been identified in humans. Many human hormones are either identical or very similar in structure and function to those in other animals, but other vertebrates as well as invertebrates have hormones not found in humans.

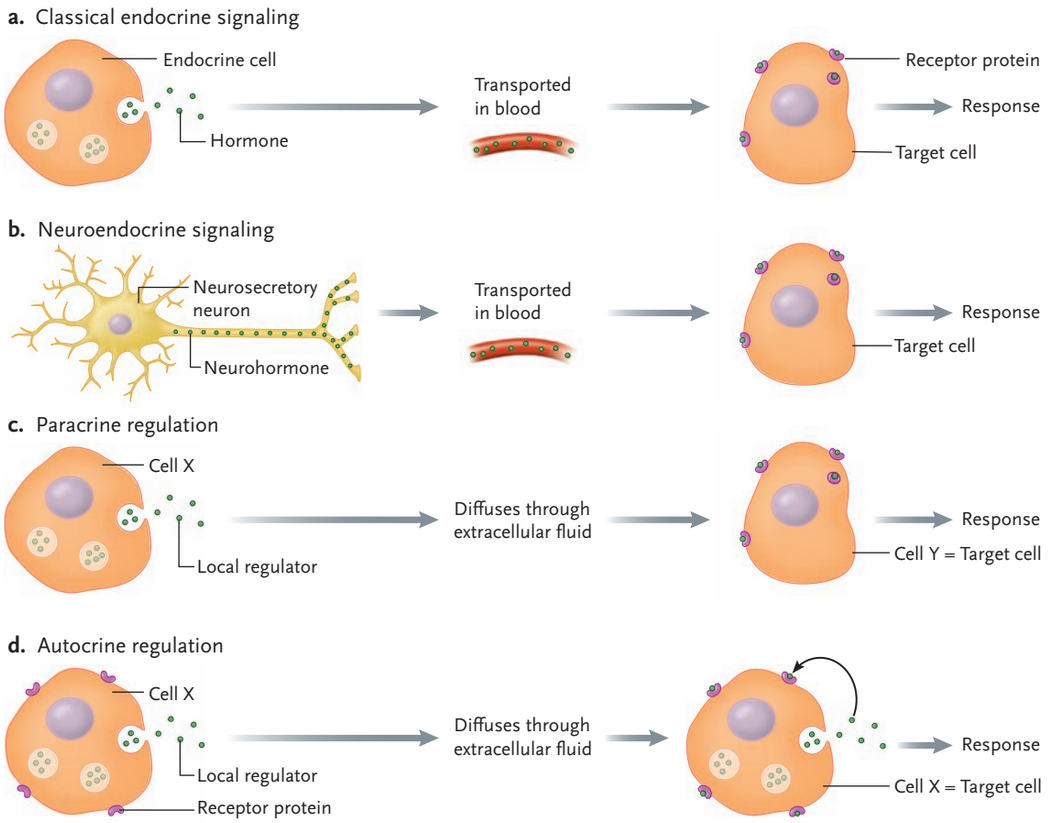


Figure 40.1
The four major types of cell signaling in the endocrine system.

Most of these chemicals can be grouped into four molecular classes: amine, peptide, steroid, and fatty acid–derived molecules.

Amine hormones are involved in classical endocrine signaling and neuroendocrine signaling. Most amine hormones are based on tyrosine. With one major exception, they are hydrophilic molecules, which diffuse readily into the blood and extracellular fluids. On reaching a target cell, they bind to receptors at the cell surface. The amines include epinephrine and norepinephrine, already familiar as neurotransmitters released by some neurons (see Section 37.3). The exception is thyroxine, a hydrophobic amine hormone secreted by the thyroid gland. This hormone, based on a pair of tyrosines, passes freely through the plasma membrane and binds to a receptor inside the target cell, as do steroid hormones (see following discussion and Section 7.5).

The *peptide hormones* consist of amino acid chains, ranging in length from as few as three amino acids to more than 200. Some have carbohydrate groups attached. They are involved in classical endocrine signaling and neuroendocrine signaling. Mostly hydrophilic hormones, peptide hormones are released into the blood or extracellular fluid by exocytosis when cytoplasmic vesicles containing the hormones fuse with the plasma membrane. One large group of peptide hormones, the **growth factors**, regulates the division and differentiation of many cell types in the body. Many growth factors act in both a paracrine and autocrine manner as well as in classical endocrine signaling. Because they can switch cell division on or off, growth factors are an important focus of cancer research.

Steroid hormones are involved in classical endocrine signaling. All are hydrophobic molecules derived from cholesterol and are insoluble in water. They combine with hydrophilic carrier proteins to form water-soluble complexes that can diffuse through extracellular fluids and enter the bloodstream. On contacting a cell, the hormone is released from its carrier protein, passes through the plasma membrane of the target cell, and binds to internal receptors in the nucleus or cytoplasm. Steroid hormones include aldosterone, cortisol, and the sex hormones. Steroid hormones may vary little in structure, but produce very different effects. For example, testosterone and estradiol, two major sex hormones responsible for the development of mammalian male and female characteristics, respectively, differ only in the presence or absence of a methyl group.

Fatty acid–derived molecules are involved in paracrine and autocrine regulation. **Prostaglandins**, for example, are important as local regulators. First discovered in the 1930s in seminal fluid, prostaglandins were so named because they were thought to be secreted by the prostate gland, although actually they are secreted by the seminal vesicles. Scientists later discovered that virtually every cell can secrete prostaglandins,

and they are present at essentially all times. In semen, they enhance the transport of sperm through the female reproductive tract by increasing the contractions of smooth muscle cells, particularly in the uterus. During childbirth, prostaglandins secreted by the placenta work with a peptide hormone called oxytocin to stimulate labor contractions. Other prostaglandins induce contraction or relaxation of smooth muscle cells in many parts of the body, including blood vessels and air passages in the lungs. When released as a product of membrane breakdown in injured cells, prostaglandins may also intensify pain and inflammation.

Many Hormones Are Regulated by Feedback Pathways

The secretion of many hormones is regulated by feedback pathways, some of which operate partially or completely independent of neuronal controls. Most of these pathways are controlled by negative feedback—that is, a product of the pathway inhibits an earlier step in the pathway (see Section 36.4). For example, in some mammals, secretion by the thyroid gland is regulated by a negative feedback loop **(Figure 40.2).** Neurosecretory neurons in the hypothalamus secrete thyroid-releasing hormone (TRH) into a vein connecting the hypothalamus to the pituitary gland. In response, the pituitary releases thyroid-stimulating hormone (TSH) into the blood, which stimulates the thyroid gland to release thyroid hormones. As the thyroid hormone concentration in the blood increases, it begins to inhibit TSH secretion by the pituitary; this action is the negative feedback step. As a result, secretion of the thyroid hormones is reduced.

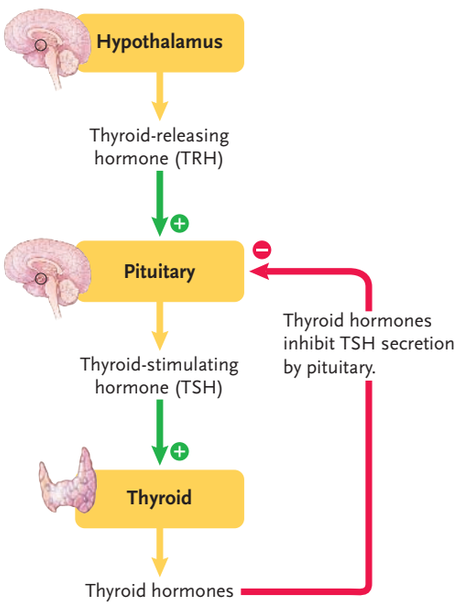


Figure 40.2
A negative feedback loop regulating secretion of the thyroid hormones. As the concentration of thyroid hormones in the blood increases, the hormones inhibit an earlier step in the pathway (indicated by the negative sign).

Body Processes Are Regulated by Coordinated Hormone Secretion

Although we will talk mostly about individual hormones in the remainder of the chapter, body processes are affected by more than one hormone. For example, the blood concentrations of glucose, fatty acids, and ions such as Ca^{2+}, K^+, and Na^+ are regulated by the coordinated activities of several hormones secreted by different glands. Similarly, body processes such as oxidative metabolism, digestion, growth, sexual development, and reactions to stress are all controlled by multiple hormones.

In many of these systems, negative feedback loops adjust the levels of secretion of hormones that act in antagonistic (opposing) ways, creating a balance in their effects that maintains body homeostasis. For example, consider the regulation of fuel molecules such as glucose, fatty acids, and amino acids in the blood. We usually eat three meals a day and fast to some extent between meals. During these periods of eating and fasting, four hormone systems act in coordinated fashion to keep the fuel levels in balance: (1) insulin and glucagon, secreted by the pancreas; (2) growth hormone, secreted by the anterior pituitary; (3) epinephrine and norepinephrine, released by the sympathetic nervous system and the adrenal medulla; and (4) glucocorticoid hormones, released by the adrenal cortex.

The entire system of hormones regulating fuel metabolism resembles the failsafe mechanisms designed by human engineers, in which redundancy, overlapping controls, feedback loops, and multiple safety valves ensure that vital functions are maintained at constant levels in the face of changing and even extreme circumstances.

Study Break

1. Distinguish between a hormone and a neurohormone.
2. Distinguish among the four major types of cell signaling.

40.2 Mechanisms of Hormone Action

Hormones control cell functions by binding to receptor molecules in their target cells. Small quantities of hormones can typically produce profound effects in cells and body functions due to **amplification.** In amplification, an activated receptor activates many proteins, which then activate an even larger number of proteins for the next step in the cellular reaction pathway, and

so on, increasing in magnitude for each subsequent step in the pathway.

Hydrophilic Hormones Bind to Surface Receptors, Activating Protein Kinases Inside Cells

Hormones that bind to receptor molecules in the plasma membrane—primarily hydrophilic amine and peptide hormones—produce their responses through signal transduction pathways (see Section 7.2). In brief, when a surface receptor binds a hormone, the receptor is activated and transmits a signal through the plasma membrane. There are two kinds of surface receptors; the cytoplasmic reactions they control when they become activated are described in detail in Sections 7.3 and 7.4. Within the cell, the signal is transduced, changed into a form that causes the cellular response **(Figure 40.3a).** Typically, the reactions of signal transduction pathways involve protein kinases, enzymes that add phosphate groups to proteins. Adding a phosphate group to a protein may activate it or inhibit it, depending on the protein and the reaction. The particular response produced by a hormone depends on the kinds of protein kinases activated, the type of cell that can respond, and the types of target proteins they phosphorylate. Importantly, a small amount of hormone can elicit a large response because of amplification (see Figure 7.6).

The peptide hormone glucagon illustrates the mechanisms triggered by surface receptors. When glucagon binds to surface receptors on liver cells, it triggers the breakdown of glycogen stored in those cells into glucose. The glucose then is released into the circulatory system.

Hydrophobic Hormones Bind to Receptors Inside Cells, Activating or Inhibiting Genetic Regulatory Proteins

After passing through the plasma membrane, the hydrophobic steroid and thyroid hormones bind to internal receptors in the nucleus or cytoplasm **(Figure 40.3b,**

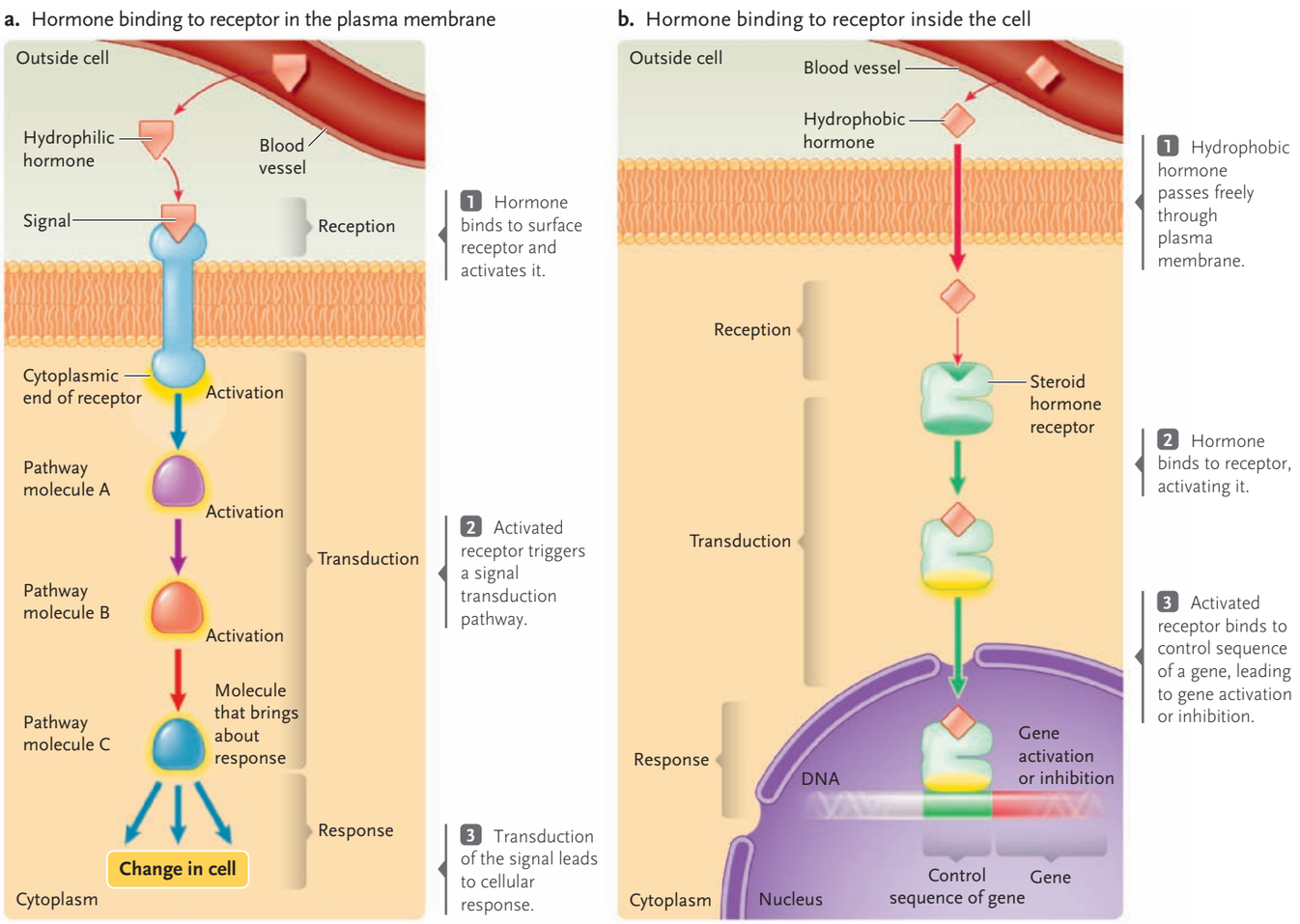


Figure 40.3
The reaction pathways activated by hormones that bind to receptor proteins in the plasma membrane **(a)** or inside cells **(b).** In both mechanisms, the signal—the binding of the hormone to its receptor—is transduced to produce the cellular response.

and described in detail in Section 7.5). Binding of the hormone activates the receptor, which then binds to a control sequence of specific genes. Depending on the gene, binding the control sequence either activates or inhibits its transcription, leading to changes in protein synthesis that accomplish the cellular response. The characteristics of the response depend on the specific genes controlled by the activated receptors, and on the presence of other proteins that modify the activity of the receptor.

One of the actions of the steroid hormone aldosterone illustrates the mechanisms triggered by internal receptors **(Figure 40.4).** If blood pressure falls below optimal levels, aldosterone is secreted by the adrenal glands. The hormone affects only kidney cells that contain the aldosterone receptor in their cytoplasm. When activated by aldosterone, the receptor binds to the control sequence of a gene, leading to the synthesis of proteins that increase reabsorption of Na^+ by the kidney cells. The resulting increase in Na^+ concentration in body fluids increases water retention and, with it, blood volume and pressure.

Target Cells May Respond to More Than One Hormone, and Different Target Cells May Respond Differently to the Same Hormone

A single target cell may have receptors for several hormones and respond differently to each hormone. For example, vertebrate liver cells have receptors for the pancreatic hormones insulin and glucagon. Insulin increases glucose uptake and conversion to glycogen, which decreases blood glucose levels, while glucagon stimulates the breakdown of glycogen into glucose, which increases blood glucose levels.

Conversely, particular hormones interact with different types of receptors in or on a range of target cells. Different responses are then triggered in each target cell type because the receptors trigger different transduction pathways. For example, the amine hormone epinephrine secreted by the adrenal medulla prepares the body for handling stress (including dangerous situations) and physical activity. (Epinephrine is discussed in more detail in Section 40.4.) In mammals, epinephrine can bind to three different plasma membrane-

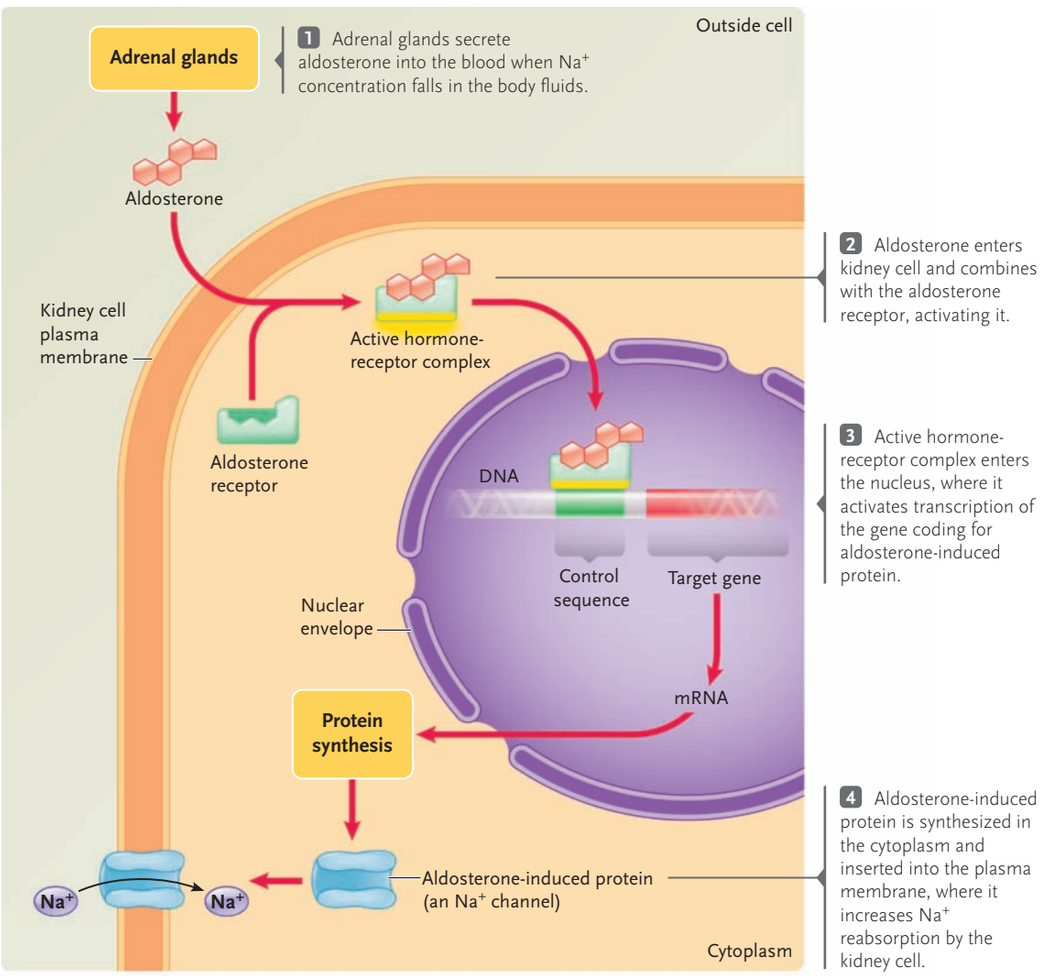


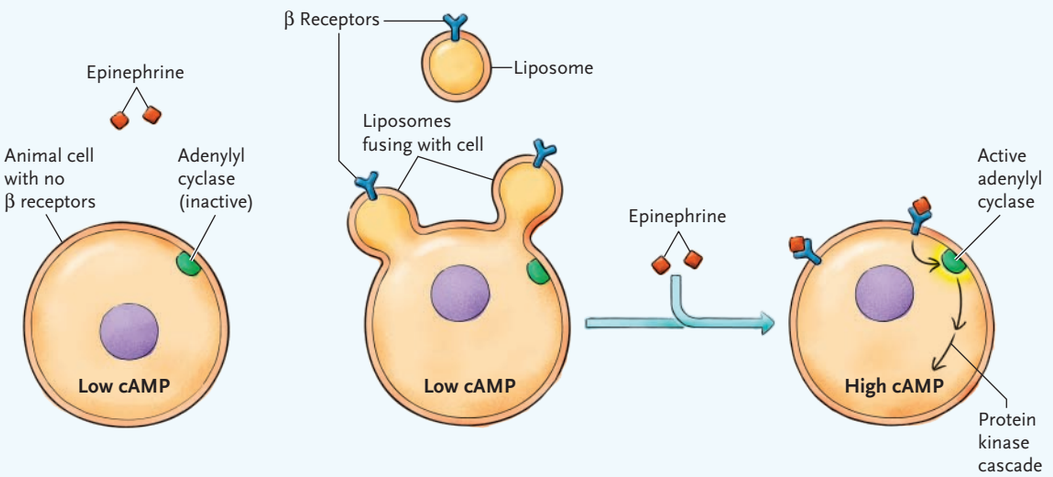
Figure 40.4
The action of aldosterone in increasing Na^+ reabsorption in the kidneys when concentration of the ion falls in the blood.

Figure 40.5 Experimental Research

Demonstration That Binding of Epinephrine to β Receptors Triggers a Signal Transduction Pathway within Cells

QUESTION: Is binding of epinephrine to β receptors necessary for triggering a signal transduction pathway within cells?

EXPERIMENT: It was known that epinephrine triggers a signal transduction pathway within cells. First, activation of adenylyl cyclase causes the level of the second messenger cAMP to increase, and then cAMP activates protein kinases in a signaling cascade that generates a cellular response (see Section 7.4 for specific details of such pathways). Richard Cerione and his colleagues at Duke University Medical Center performed experiments to show whether the signal transduction pathway is stimulated by binding of epinephrine to β receptors.



1. Epinephrine was added to animal cells lacking β receptors.

RESULT: No change occurred to the low level of cAMP in those cells. This result demonstrated that epinephrine alone was not able to trigger an increase in cAMP.

2. Liposomes—artificial spherical phospholipid membranes—containing purified β receptors were fused with the animal cells, and then epinephrine was added.

RESULT: When the liposomes fused with the animal cells, β receptors became part of the fused cell's plasma membrane. Then, adding epinephrine triggered synthesis of cAMP, resulting in high levels of cAMP in the cells. This result demonstrated that β receptors must be present in the membrane for epinephrine to trigger an increase in cAMP in the cell. The simplest interpretation was that epinephrine bound to the β receptors, activating adenylyl cyclase within the cell.

CONCLUSION: The cellular response depended upon binding of the hydrophilic hormone to a specific plasma membrane-embedded receptor.

embedded receptors: α, β_1, and β_2 receptors. (The experimental demonstration that the binding of epinephrine to a specific receptor triggers a cellular response is described in **Figure 40.5.**) When epinephrine binds to α receptors on smooth muscle cells, such as those of the blood vessels, it triggers a response pathway that causes the cells to constrict, cutting off circulation to peripheral organs. When epinephrine binds to β_1 receptors on heart muscle cells, the contraction rate of the cells increases, which in turn enhances blood supply. When epinephrine binds to β_2 receptors on liver cells, it stimulates the breakdown of glycogen to glucose, which is released from the cell. The overall effect of these, and a number of other, responses to epinephrine secretion is to supply energy to the major muscles responsible for locomotion—the body is now prepared for handling stress or for physical activity.

Different receptors binding hydrophobic hormones also may generate diverse responses. *Insights from the Molecular Revolution* describes an investigation that tested the cellular responses produced by different receptors binding the same steroid hormone.

In summary, the mechanisms by which hormones work have four major features. First, only the cells that contain surface or internal receptors for a particular hormone respond to that hormone. Second, once

Two Receptors for Estrogens

Estrogens have many effects on female sexual development, behavior, and the menstrual cycle. One negative effect is to stimulate the growth of tumors in breast and uterine cancer. This cancer-enhancing effect can be reduced by administering *antiestrogens,* estrogen-like chemicals that bind competitively to estrogen receptors and block the sites that would normally be bound by the hormone. The antiestrogen *tamoxifen,* for example, inhibits the growth of breast tumors by blocking the activity of estrogen in breast tissue, but patients receiving it are at increased risk of developing uterine cancer.

How can tamoxifen have opposite effects in two different tissues? A group of investigators led by Thomas Scanlan and Peter Kushner at the University of California, San Francisco, joined by others at the Karolinska Institute and the Karo Bio Company in Sweden, had discovered that humans have two highly similar estrogen receptors, ERα and ERβ. Could differences between them account for the opposing effects of tamoxifen in breast and uterine tissues?

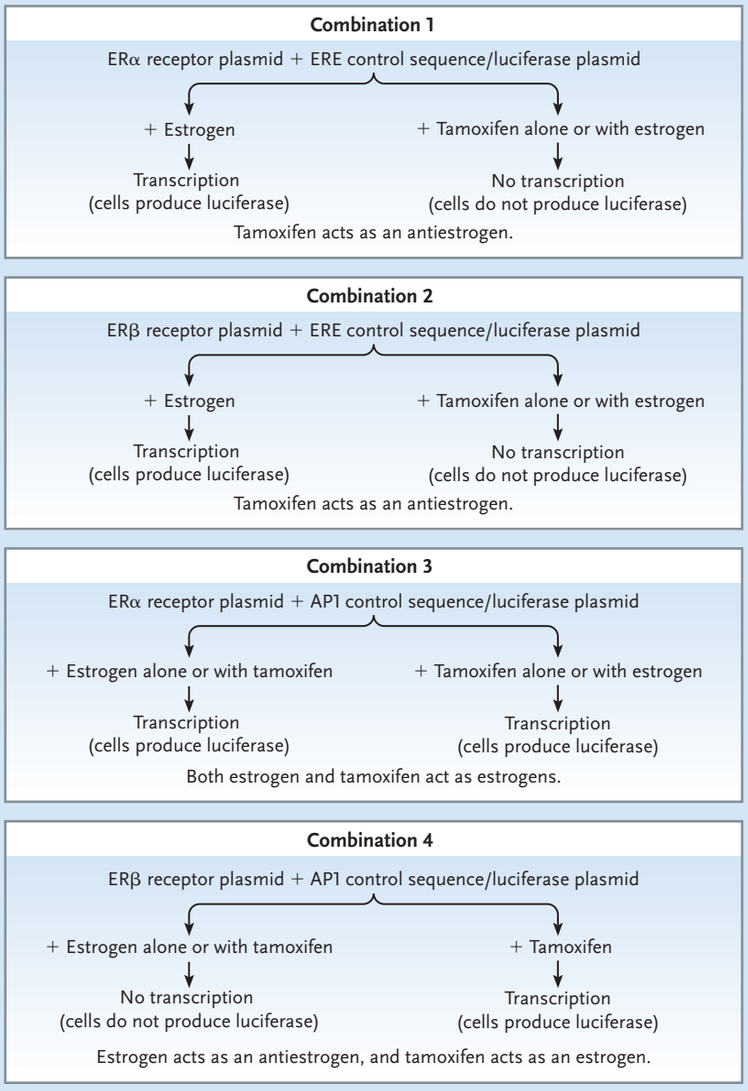
To find out, the researchers constructed two pairs of recombinant DNA plasmids. One pair consisted of either the ERα receptor gene or the ERβ receptor gene, adjacent to a promoter for continuous transcription of the receptor gene in human tissue culture cells. The other pair consisted of the firefly luciferase gene, which catalyzes a light-producing reaction, adjacent to one of two gene control sequences, AP1 or ERE, which act in estrogen-regulated systems.

One receptor plasmid and one luciferase plasmid were introduced together into human cell lines that do not normally make estrogen receptors in four possible combinations (see **figure**), with two cell lines making the ERα receptor and two making the ERβ receptor. Estrogen receptors are produced in all four of the resulting cell lines because the gene for the receptor is transcribed from the introduced plasmid.

With this experimental design, the researchers could test whether the ERα or ERβ receptor is activated by binding estrogen, and also whether the activated receptor would bind to the luciferase plasmid. If these two conditions were met, luciferase would be synthesized, and its activity could be measured using a special apparatus. (In this experiment, the luciferase gene acts as a *reporter* for the biological reactions that are occurring—luciferase has nothing to do with estrogen or estrogen activity.)

When the researchers added estrogen to cell lines containing luciferase plasmid with ERE (combinations 1 and 2 in the figure), all the cells produced luciferase. This indicated that both ERα and ERβ could bind the hormone, were activated, and could combine with ERE. When they added tamoxifen alone or along with the estrogen, the cells did not produce luciferase, indicating that tamoxifen acts as an antiestrogen and could combine with either receptor type to block the action of estrogen.

The results were different when the experiment was conducted using cell lines containing luciferase plasmid with AP1 (combinations 3 and 4 in the figure). If the estrogen and tamoxifen were added either separately or together to cells containing gene combination 3, the cells produced luciferase. This result demonstrated that ERα was activated and could combine with the AP1 control sequence, whether it was bound to estrogen or tamoxifen. Thus, in these cells the tamoxifen acted the same as an estrogen.



When estrogen was added, alone or with tamoxifen, to cells containing combination 4, no luciferase was produced. However, tamoxifen, if added alone, caused the cells to produce luciferase. These results indicate that ERβ combined with estrogen does not bind and activate AP1. ERβ combined with tamoxifen, however, can bind to AP1 and induce transcription of the luciferase gene. Evidently, estrogen actually acted as an antiestrogen in cells with combination 4—when added along with tamoxifen, the cells did not produce luciferase, indicating that the hormone blocked the action of tamoxifen.

The experiments indicate that the previously baffling and opposing effects of tamoxifen on breast and uterine tissues occur because different estrogen receptors are present, acting on genes controlled by either the ERE or AP1 control sequences. The results emphasize the fact that hormones can have distinct effects in different cell types depending on the types of receptors present. The research also opens the possibility of new cancer treatments that take advantage of the receptor differences.

bound by their receptors, hormones may produce a response that involves stimulation or inhibition of cellular processes through the specific types of internal molecules triggered by the hormone action. Third, because of the amplification that occurs in both the surface and internal receptor mechanisms, hormones are effective in very small concentrations. Fourth, the response to a hormone differs among target organs.

In the next two sections we discuss the major endocrine cells and glands of vertebrates. The locations of these cells and glands in the human body and their functions are summarized in **Figure 40.6** and **Table 40.1.** Pep-

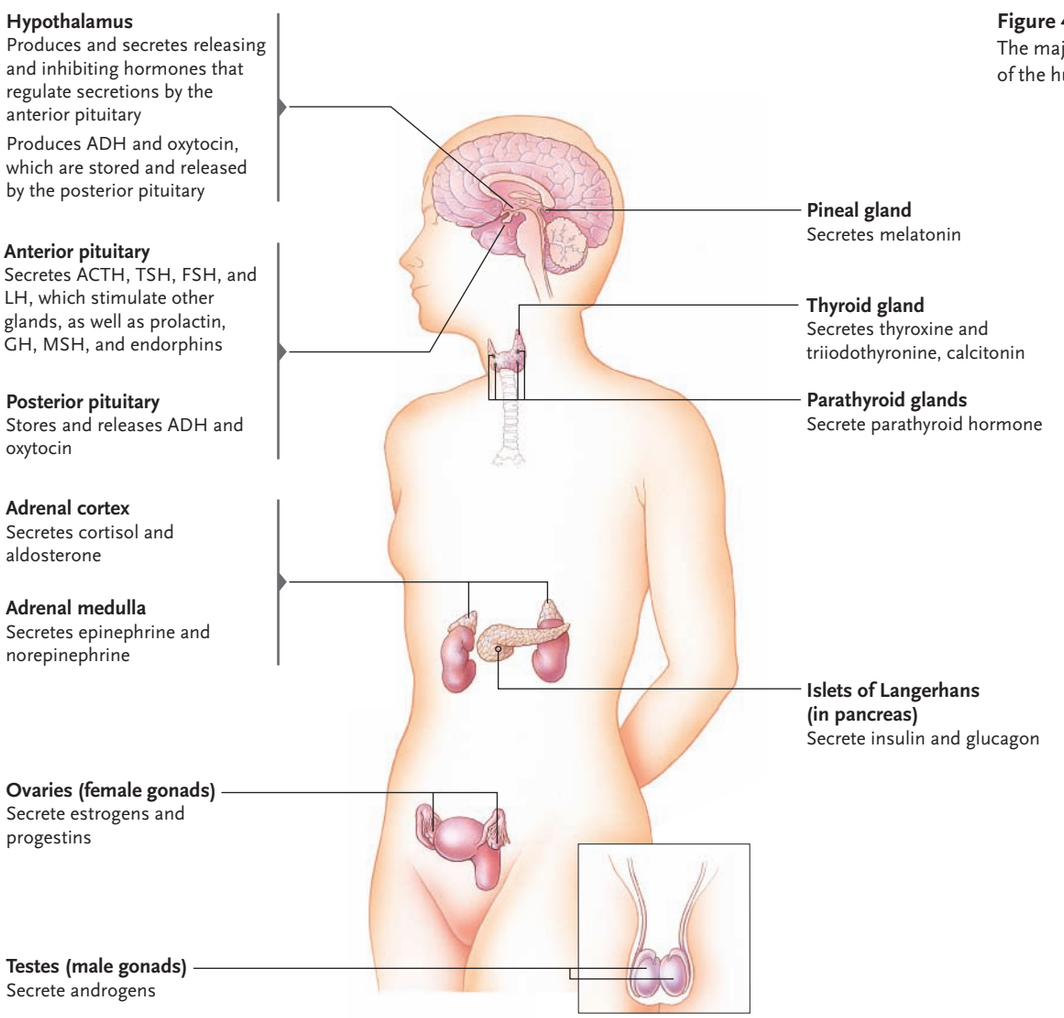


Figure 40.6
The major endocrine cells and glands of the human body.

Table 40.1 The Major Human Endocrine Glands and Hormones

Secretory Tissue or Gland	Hormones	Molecular Class	Target Tissue	Principal Actions
Hypothalamus	Releasing and inhibiting hormones	Peptide	Anterior pituitary	Regulate secretion of anterior pituitary hormones
Anterior pituitary	Thyroid-stimulating hormone (TSH)	Peptide	Thyroid gland	Stimulates secretion of thyroid hormones and growth of thyroid gland
	Adrenocorticotropic hormone (ACTH)	Peptide	Adrenal cortex	Stimulates secretion of glucocorticoids by adrenal cortex
	Follicle-stimulating hormone (FSH)	Peptide	Ovaries in females, testes in males	Stimulates egg growth and development and secretion of sex hormones in females; stimulates sperm production in males
	Luteinizing hormone (LH)	Peptide	Ovaries in females, testes in males	Regulates ovulation in females and secretion of sex hormones in males
	Prolactin (PRL)	Peptide	Mammary glands	Stimulates breast development and milk secretion
	Growth hormone (GH)	Peptide	Bone, soft tissue	Stimulates growth of bones and soft tissues; helps control metabolism of glucose and other fuel molecules
	Melanocyte-stimulating hormone (MSH)	Peptide	Melanocytes in skin of some vertebrates	Promotes darkening of the skin
	Endorphins	Peptide	Pain pathways of PNS	Inhibit perception of pain
Posterior pituitary	Antidiuretic hormone (ADH)	Peptide	Kidneys	Raises blood volume and pressure by increasing water reabsorption in kidneys
	Oxytocin	Peptide	Uterus, mammary glands	Promotes uterine contractions; stimulates milk ejection from breasts
Thyroid gland	Calcitonin	Peptide	Bone	Lowers calcium concentration in blood
	Thyroxine and triiodothyronine	Amine	Most cells	Increase metabolic rate; essential for normal body growth
Parathyroid glands	Parathyroid hormone (PTH)	Peptide	Bone, kidneys, intestine	Raises calcium concentration in blood; stimulates vitamin D activation
Adrenal medulla	Epinephrine and norepinephrine	Amine	Sympathetic receptor sites throughout body	Reinforce sympathetic nervous system; contribute to responses to stress
Adrenal cortex	Aldosterone (mineralocorticoid)	Steroid	Kidney tubules	Helps control body's salt-water balance by increasing Na^+ reabsorption and K^+ excretion in kidneys
	Cortisol (glucocorticoid)	Steroid	Most body cells, particularly muscle, liver, and adipose cells	Increases blood glucose by promoting breakdown of proteins and fats
Testes	Androgens, such as testosterone*	Steroid	Various tissues	Control male reproductive system development and maintenance; most androgens are made by the testes
	Oxytocin	Peptide	Uterus	Promotes uterine contractions when seminal fluid ejaculated into vagina during sexual intercourse
Ovaries	Estrogens, such as estradiol**	Steroid	Breast, uterus, other tissues	Stimulate maturation of sex organs at puberty, and development of secondary sexual characteristics
	Progestins, such as progesterone**	Steroid	Uterus	Prepare and maintain uterus for implantation of fertilized egg and the growth and development of embryo

*Small amounts secreted by ovaries and adrenal cortex.
**Small amounts secreted by testes.

Table 40.1 The Major Human Endocrine Glands and Hormones (Continued)

Secretory Tissue or Gland	Hormones	Molecular Class	Target Tissue	Principal Actions
Pancreas (islets of Langerhans)	Glucagon (alpha cells)	Peptide	Liver cells	Raises glucose concentration in blood; promotes release of glucose from glycogen stores and production from noncarbohydrates
	Insulin (beta cells)	Peptide	Most cells	Lowers glucose concentration in blood; promotes storage of glucose, fatty acids, and amino acids
Pineal gland	Melatonin	Amine	Brain, anterior pituitary, reproductive organs, immune system, possibly others	Helps synchronize body's biological clock with day length; may inhibit gonadotropins and initiation of puberty
Many cell types	Growth factors	Peptide	Most cells	Regulate cell division and differentiation
	Prostaglandins	Fatty acid	Various tissues	Have many diverse roles

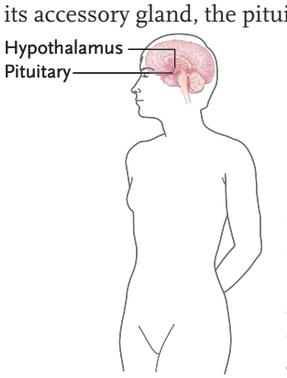
tide hormones secreted by other body regions, including the stomach and small intestine, the thymus gland, the kidneys, and the heart will be described in the chapters in which these tissues and organs are discussed.

Study Break

1. Compare and contrast the mechanisms by which glucagon and aldosterone cause their specific responses.
2. Explain how one type of target cell could respond to different hormones, and how the same hormone could produce different effects in different cells.

40.3 The Hypothalamus and Pituitary

The hormones of vertebrates work in coordination with the nervous system. The action of several hormones is closely coordinated by the hypothalamus and its accessory gland, the pituitary.



The hypothalamus is a region of the brain located in the floor of the cerebrum (see Section 38.3). The **pituitary gland**, consisting mostly of two fused lobes, is suspended just below it by a slender stalk of tissue that contains both neurons and blood vessels **(Figure 40.7).** The **posterior pituitary** contains axons and nerve endings of neurosecretory neurons that originate in the hypothalamus. The **anterior pituitary** contains nonneuronal endocrine cells that form a distinct gland. The two lobes are separate in structure and embryonic origins.

Under Regulatory Control by the Hypothalamus, the Anterior Pituitary Secretes Eight Hormones

The secretion of hormones from the anterior pituitary is controlled by peptide neurohormones called **releasing hormones (RHs)** and **inhibiting hormones (IHs)**, which are released by the hypothalamus. These neurohormones are carried in the blood from the hypothalamus to the anterior pituitary in a *portal vein,* a special vein that connects the capillaries of the two glands. The portal vein provides a critical link between the brain and the endocrine system, ensuring that most of the blood reaching the anterior pituitary first passes through the hypothalamus.

RHs and IHs are **tropic hormones** (*tropic* = stimulating, not to be confused with *trophic,* which means "nourishing"), hormones that regulate hormone secretion by another endocrine gland. RHs and IHs regulate the anterior pituitary's secretion of another group of hormones; those hormones in turn control many other endocrine glands of the body, and also control some body processes directly.

Secretion of hypothalamic RHs is controlled by neurons containing receptors that monitor the blood to detect changes in body chemistry and temperature. For example, TRH, discussed earlier, is secreted in response to a drop in body temperature. Input to the hypothalamus also comes through numerous connections from control centers elsewhere in the brain, including the brain stem and limbic system. Negative feedback pathways regulate secretion of the releasing hormones, such as the pathway regulating TRH secretion.

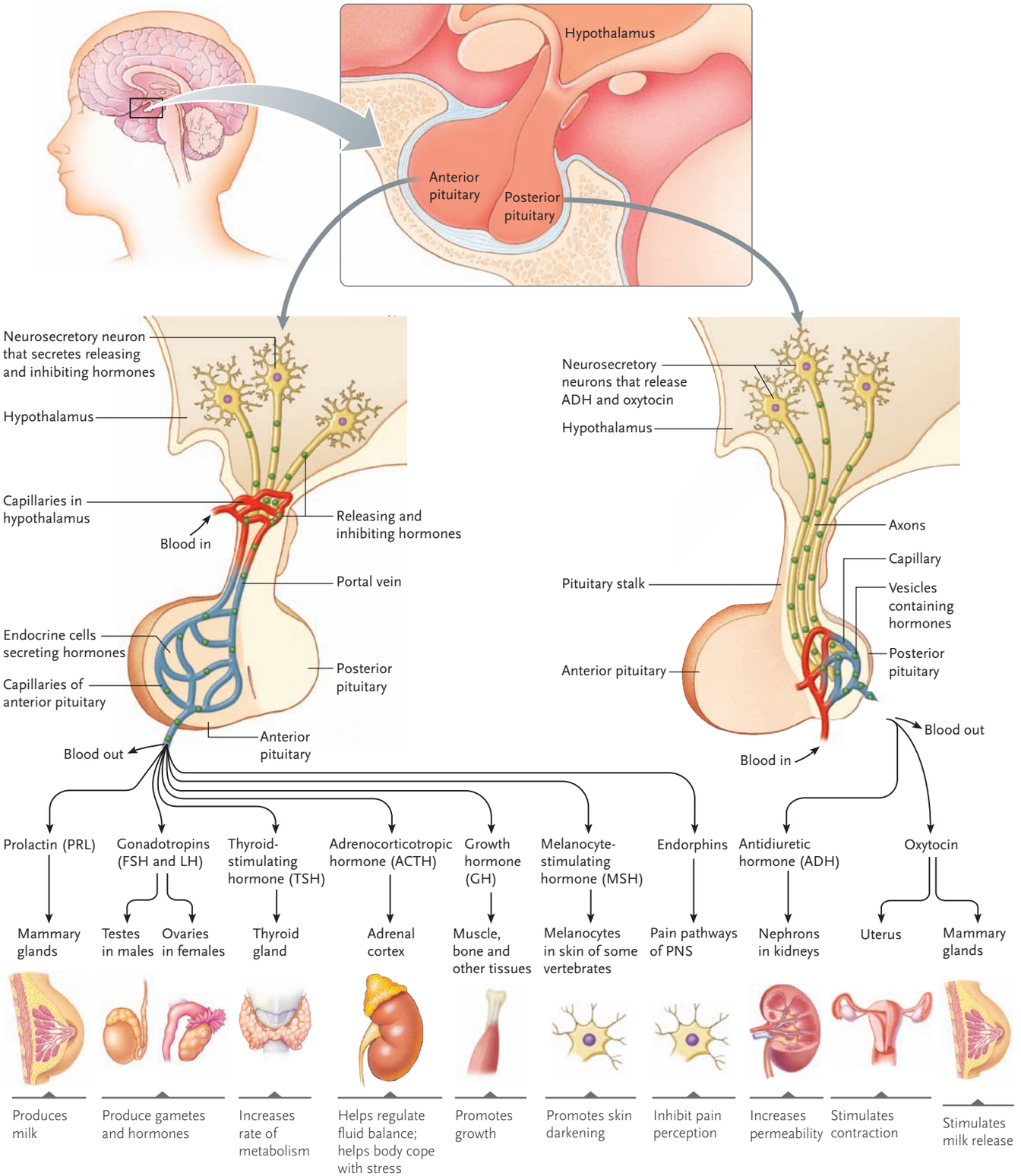


Figure 40.7
The hypothalamus and pituitary. Hormones secreted by the anterior and posterior pituitary are controlled by neurohormones released in the hypothalamus.

Under the control of the hypothalamic RHs, the anterior pituitary secretes six major hormones into the bloodstream: prolactin, growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, follicle-stimulating hormone, and luteinizing hormone, and two other hormones, melanocyte-stimulating hormone (MSH) and endorphins. **Prolactin (PRL),** a *nontropic hormone* (a hormone that does not regulate hormone secretion by another endocrine gland), influences reproductive activities and parental care in vertebrates. In mammals, PRL stimulates development of the secretory cells of mammary glands during late pregnancy, and stimulates milk synthesis after a female mammal gives birth. Stimulation of the mammary glands and the nipples, as occurs during suckling, leads to PRL release.

Growth hormone (GH) stimulates cell division, protein synthesis, and bone growth in children and adolescents, thereby causing body growth. GH also stimulates protein synthesis and cell division in adults. For these actions, GH acts as a tropic hormone by binding to target tissues, mostly liver cells, causing them to release insulin-like growth factor **(IGF),** a peptide that directly stimulates growth processes. GH also acts as a nontropic hormone to control a number of major metabolic processes in mammals of all ages, including the conversion of glycogen to glucose and fats to fatty acids as a means of regulating their levels in the blood. In addition, GH stimulates body cells to take up fatty acids and amino acids and limits the rate at which muscle cells take up glucose. These actions help maintain the availability of glucose and fatty acids to tissues and organs between feedings; this is particularly important for the brain. In humans, deficiencies in GH secretion during childhood produce *pituitary dwarfs,* who remain small in stature **(Figure 40.8).** Overproduction of GH during childhood or adolescence, often due to a tumor of the anterior pituitary, produces *pituitary giants,* who may grow above seven feet in height.

The other four major hormones secreted by the anterior pituitary are tropic hormones that control endocrine glands elsewhere in the body. **Thyroid-stimulating hormone (TSH)** stimulates the thyroid gland to grow in size and secrete thyroid hormones. **Adrenocorticotropic hormone (ACTH)** triggers hormone secretion by cells in the adrenal cortex. **Follicle-stimulating hormone (FSH)** controls egg development and the secretion of sex hormones in female mammals, and sperm production in males. **Luteinizing hormone (LH)** regulates part of the menstrual cycle in human females and the secretion of sex hormones in males. FSH and LH are grouped together as **gonadotropins** because they regulate the activity of the gonads (ovaries and testes). The roles of the gonadotropins and sex hormones in the reproductive cycle are described in Chapter 47.

Melanocyte-stimulating hormone (MSH) and **endorphins** are nontropic hormones produced by the anterior pituitary. MSH is named because of its effect in some vertebrates on melanocytes, skin cells that contain the black pigment melanin. For example, an increase in secretion of MSH produces a marked darkening of the skin of fishes, amphibians, and reptiles. The darkening is produced by a redistribution of melanin from the centers of the melanocytes throughout the cells. In humans, an increase in MSH secretion also causes skin darkening, although the effect is by no means as obvious as in the other vertebrates mentioned. For example, MSH secretion increases in pregnant women. That, with the effects of increased estrogens, results in increased skin pigmentation; the effects fade after birth of the child.

Endorphins, nontropic peptide hormones produced by the hypothalamus and pituitary, are also released by the anterior pituitary. In the peripheral nervous system (PNS), endorphins act as neurotransmitters in pathways that control pain, thereby inhibiting the perception of pain. Hence, endorphins are often called "natural painkillers."

Figure 40.8
The results of overproduction and underproduction of growth hormone by the anterior pituitary. The man on the left is of normal height. The man in the center is a pituitary giant, whose pituitary produced excess GH during childhood and adolescence. The man on the right is a pituitary dwarf, whose pituitary produced too little GH.

The Posterior Pituitary Secretes Two Hormones into the Circulatory System

The neurosecretory neurons in the posterior pituitary secrete two nontropic peptide hormones, antidiuretic hormone and oxytocin, directly into the circulatory system (see Figure 40.7).

Antidiuretic hormone (ADH) stimulates kidney cells to absorb more water from urine, thereby increas-

ing the volume of the blood. The hormone is released when sensory receptor cells of the hypothalamus detect an increase in the blood's Na^+ concentration during periods of body dehydration or after a salty meal. Ethyl alcohol and caffeine inhibit ADH secretion, explaining in part why alcoholic drinks and coffee increase the volume of urine excreted. Nicotine and emotional stress, in contrast, stimulate ADH secretion and water retention. After severe stress is relieved, the return to normal ADH secretion often makes a trip to the bathroom among our most pressing needs. The hypothalamus also releases a flood of ADH when an injury results in heavy blood loss or some other event triggers a severe drop in blood pressure. ADH helps maintain blood pressure by reducing water loss and also by causing small blood vessels in some tissues to constrict.

Hormones with structure and action similar to ADH are also secreted in fishes, amphibians, reptiles, and birds. In amphibians, these ADH-like hormones increase the amount of water entering the body through the skin and from the urinary bladder.

We have noted that **oxytocin** stimulates the ejection of milk from the mammary glands of a nursing mother. Stimulation of the nipples in suckling sends neuronal signals to the hypothalamus, and leads to release of oxytocin from the posterior pituitary. The released oxytocin stimulates more oxytocin secretion by a positive feedback mechanism. Oxytocin causes the smooth muscle cells surrounding the mammary glands to contract, forcibly expelling the milk through the nipples. The entire cycle, from the onset of suckling to milk ejection, takes less than a minute in mammals. Oxytocin also plays a key role in childbirth, as we discussed in Section 36.4.

In males, oxytocin is secreted into the seminal fluid by the testes. Like prostaglandins, when the seminal fluid is ejaculated into the vagina during sexual intercourse, oxytocin stimulates contractions of the uterus that aid movement of sperm through the female reproductive tract.

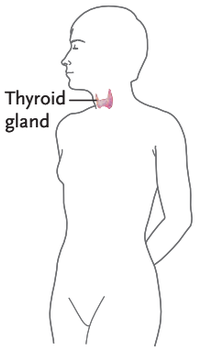
Study Break

1. Summarize the functional interactions between the hypothalamus and the anterior pituitary gland.
2. Distinguish between how tropic hormones and nontropic hormones produce responses.

40.4 Other Major Endocrine Glands of Vertebrates

Besides the hypothalamus and pituitary, the body has seven major endocrine glands or tissues, many of them regulated by the hypothalamus-pituitary connection. These glands are the thyroid gland, parathyroid glands, adrenal medulla, adrenal cortex, gonads, pancreas, and pineal gland (shown in Figure 40.6 and summarized in Table 40.1).

The Thyroid Hormones Stimulate Metabolism, Development, and Maturation



The **thyroid gland**, which is located in the front of the throat in humans, has a shape similar to that of a bowtie. It secretes the same hormones in all vertebrates. The primary thyroid hormone, **thyroxine**, is known as $\mathbf{T_4}$ because it contains four iodine atoms. The thyroid also secretes smaller amounts of a closely related hormone, **triiodothyronine** or $\mathbf{T_3}$, which contains three iodine atoms. A supply of iodine in the diet is necessary for production of these hormones. Normally, their concentrations are kept at finely balanced levels in the blood by negative feedback loops such as that described in Figure 40.2.

Both T_4 and T_3 enter cells; however, once inside, most of the T_4 is converted to T_3, the form that combines with internal receptors. Binding of T_3 to receptors alters gene expression, which brings about the hormone's effects.

The thyroid hormones are vital to growth, development, maturation, and metabolism in all vertebrates. They interact with GH for their effects on growth and development. Thyroid hormones also increase the sensitivity of many body cells to the effects of epinephrine and norepinephrine, hormones released by the adrenal medulla as part of the "fight or flight response" (discussed further later).

In amphibians such as frogs, thyroid hormones trigger **metamorphosis**, or change in body form from tadpole to adult **(Figure 40.9).** Thyroid hormones also contribute to seasonal changes in the plumage of birds and coat color in mammals.

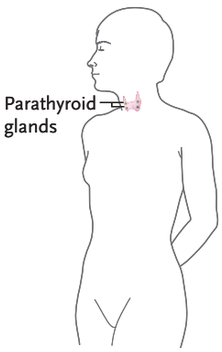
In human adults, low thyroid output, *hypothyroidism,* causes affected individuals to be sluggish mentally and physically; they have a slow heart rate and weak pulse, and often feel confused and depressed. Hypothyroidism in infants and children leads to cretinism, that is, stunted growth and diminished intelligence. Overproduction of thyroid hormones in human adults, *hyperthyroidism,* produces nervousness and emotional instability, irritability, insomnia, weight loss, and a rapid, often irregular heartbeat. The most common form of hyperthyroidism is *Graves' disease,* characterized by inflamed, protruding eyes in addition to the other symptoms mentioned.

Insufficient iodine in the diet can cause *goiter,* enlargement of the thyroid. Without iodine, the thyroid cannot make T_3 and T_4 in response to stimulation by

TSH. Because the thyroid hormone concentration remains low in the blood, TSH continues to be secreted, and the thyroid grows in size. Dietary iodine deficiency has been eliminated in developed regions of the world by the addition of iodine to table salt.

In mammals, the thyroid also has specialized cells that secrete **calcitonin**, a nontropic peptide hormone. The hormone lowers the level of Ca^{2+} in the blood by inhibiting the ongoing dissolution of calcium from bone. Calcitonin secretion is stimulated when Ca^{2+} levels in blood rise above the normal range and inhibited when Ca^{2+} levels fall below the normal range.

The Parathyroid Glands Regulate Ca^{2+} Level in the Blood



The **parathyroid glands** occur only in tetrapod vertebrates—amphibians, reptiles, birds, and mammals. Each is a spherical structure about the size of a pea. Mammals have four parathyroids located on the posterior surface of the thyroid gland, two on each side. The single hormone they produce, a nontropic hormone called **parathyroid hormone (PTH)**, is secreted in response to a fall in blood Ca^{2+} levels. PTH stimulates bone cells to dissolve the mineral matter of bone tissues, releasing both calcium and phosphate ions into the blood. The released Ca^{2+} is available for enzyme activation, conduction of nerve signals across synapses, muscle contraction, blood clotting, and other uses. How blood Ca^{2+} levels control PTH and calcitonin secretion is shown in **Figure 40.10.**

PTH also stimulates enzymes in the kidneys that convert **vitamin D**, a steroidlike molecule, into its fully active form in the body. The activated vitamin D increases the absorption of Ca^{2+} and phosphates from ingested food by promoting the synthesis of a calcium-binding protein in the intestine; it also increases the release of Ca^{2+} from bone in response to PTH.

PTH underproduction causes Ca^{2+} concentration to fall steadily in the blood, disturbing nerve and muscle function—the muscles twitch and contract uncontrollably, and convulsions and cramps occur. Without treatment, the condition is usually fatal, because the severe muscular contractions interfere with breathing. Overproduction of PTH results in the loss of so much calcium from the bones that they become thin and fragile. At the same time, the elevated Ca^{2+} concentration in the blood causes calcium deposits to form in soft tissues, especially in the lungs, arteries, and kidneys (where the deposits form kidney stones).

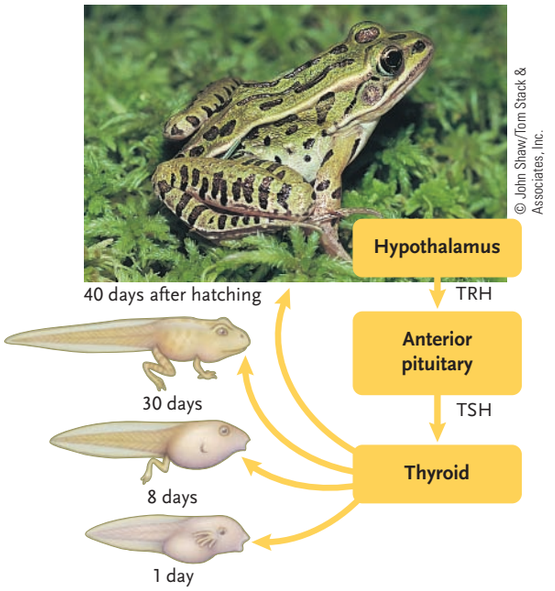
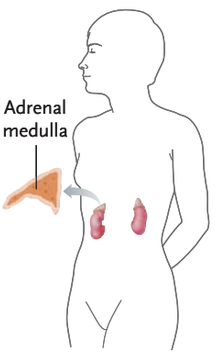


Figure 40.9
Metamorphosis of a tadpole into an adult frog, under the control of thyroid hormones. As a part of the metamorphosis, changes in gene activity lead to a change from an aquatic to a terrestrial habitat. TRH, thyroid-releasing hormone; TSH, thyroid-stimulating hormone.

The Adrenal Medulla Releases Two "Fight or Flight" Hormones



The adrenal glands (*ad* = next to, *renes* = kidneys) of mammals consist of two distinct regions. The central region, the **adrenal medulla**, contains neurosecretory neurons; the tissue surrounding it, the **adrenal cortex**, contains endocrine cells. The two regions secrete hormones with entirely different functions. Nonmammalian vertebrates have glands equivalent to the adrenal medulla and adrenal cortex of mammals, but they are separate. Most of the hormones produced by these glands have essentially the same functions in all vertebrates. The only major exception is aldosterone, which is secreted by the adrenal cortex or its equivalent only in tetrapod vertebrates.

In most species, the adrenal medulla secretes two nontropic amine hormones, **epinephrine** and **norepinephrine**, which are **catecholamines**, chemical compounds derived from the amino acid tyrosine that circulate in the bloodstream. They bind to receptors in the plasma membranes of their target cells. (Epinephrine is also secreted by some cells of the CNS, and norepinephrine is also secreted by some cells of the CNS and neurons of the sympathetic nervous system. In these cases, epinephrine and norepinephrine

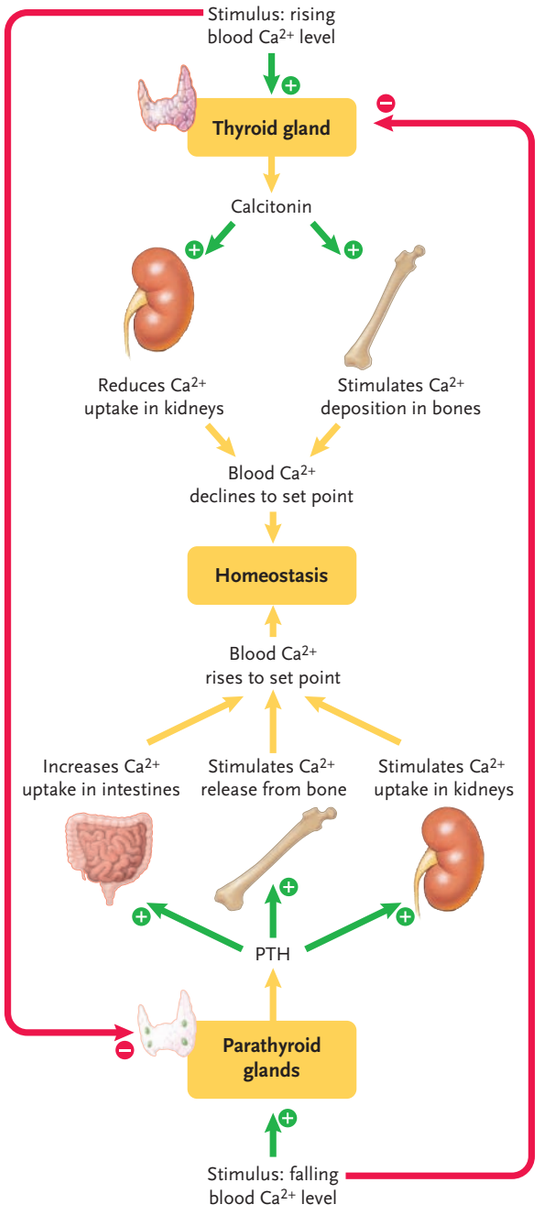


Figure 40.10
Negative feedback control of PTH and calcitonin secretion by blood Ca^{2+} levels.

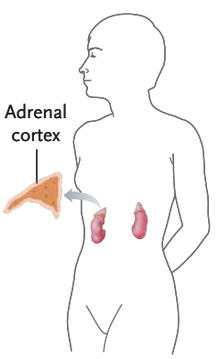
function as neurotransmitters between interneurons involved in a diversity of brain and body functions; see Section 37.3.)

Epinephrine and norepinephrine, which reinforce the action of the sympathetic nervous system, are secreted when the body encounters stresses such as emotional excitement, danger (fight-or-flight situations), anger, fear, infections, injury, even midterm and final exams. Epinephrine in particular prepares the body for handling stress or physical activity. The heart rate increases. Glycogen and fats break down, releasing glucose and fatty acids into the blood as fuel molecules. In the heart, skeletal muscles, and lungs, the blood vessels dilate to increase blood flow. Elsewhere in the body, the blood vessels constrict, raising blood pressure, reducing blood flow to the intestine and kidneys, and inhibiting smooth muscle contractions, which reduces water loss and slows down the digestive system. Airways in the lungs also dilate, helping to increase the flow of air.

The effects of norepinephrine on heart rate, blood pressure, and blood flow to the heart muscle are similar to those of epinephrine. However, in contrast to epinephrine, norepinephrine causes blood vessels in skeletal muscles to constrict. This antagonistic effect is largely canceled out because epinephrine is secreted in much greater quantities.

No known human diseases are caused by underproduction of the hormones of the adrenal medulla, as long as the sympathetic nervous system is intact. Overproduction of epinephrine and norepinephrine, which can occur if there is a tumor in the adrenal medulla, leads to symptoms duplicating a stress response.

The Adrenal Cortex Secretes Two Groups of Steroid Hormones That Are Essential for Survival



The adrenal cortex of mammals secretes two major types of steroid hormones: **glucocorticoids** help maintain the blood concentration of glucose and other fuel molecules, and **mineralocorticoids** regulate the levels of Na^+ and K^+ ions in the blood and extracellular fluid.

The Glucocorticoids. The glucocorticoids help maintain glucose levels in the blood by three major mechanisms: (1) stimulating the synthesis of glucose from noncarbohydrate sources such as fats and proteins, (2) reducing glucose uptake by body cells except those in the central nervous system, and (3) promoting the breakdown of fats and proteins, which releases fatty acids and amino acids into the blood as alternative fuels when glucose supplies are low. The absence of down-regulation of glucose uptake to the CNS keeps the brain well supplied with glucose between meals and during periods of extended fasting. **Cortisol** is the major glucocorticoid secreted by the adrenal cortex.

Secretion of glucocorticoids is ultimately under control of the hypothalamus **(Figure 40.11).** Low glucose concentrations in the blood, or elevated levels of epinephrine secreted by the adrenal medulla in response to stress, are detected in the hypothalamus, leading to secretion of the tropic hormone ACTH by the anterior pituitary. ACTH promotes the secretion of glucocorticoids by the adrenal cortex.

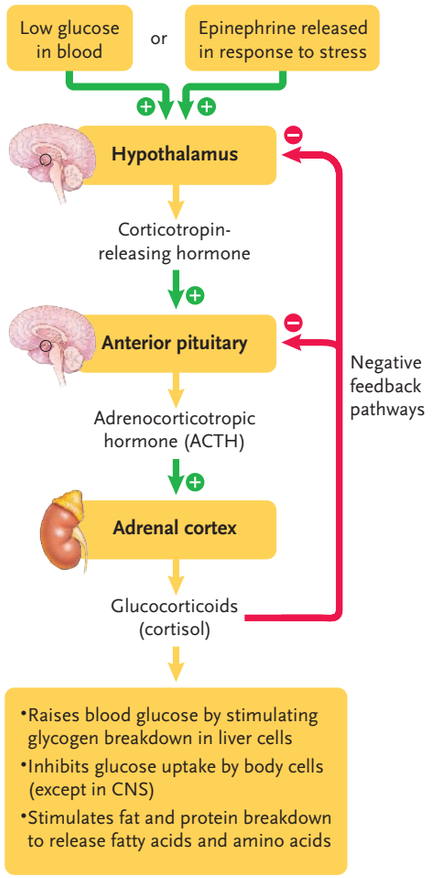


Figure 40.11
Pathways linking secretion of glucocorticoids to low blood sugar and epinephrine secretion in response to stress.

Overproduction of glucocorticoids makes blood glucose rise and increases fat deposition in adipose tissue and protein breakdown in muscles and bones. The loss of proteins from muscles causes weakness and fatigue; loss of proteins from bone, particularly collagens, makes the bones fragile and susceptible to breakage. Underproduction of glucocorticoids causes blood glucose concentration to fall below normal levels in the blood and diminishes tolerance to stress.

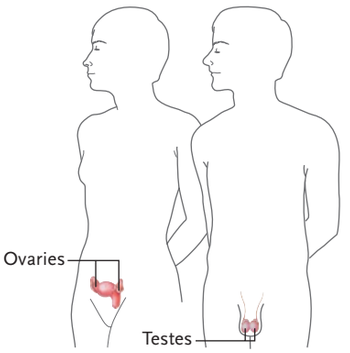
Glucocorticoids have anti-inflammatory properties and, consequently, they are used clinically to treat conditions such as arthritis or dermatitis. They also suppress the immune system and are used in the treatment of autoimmune diseases such as rheumatoid arthritis.

The Mineralocorticoids. In tetrapods, the mineralocorticoids, primarily **aldosterone**, increase the amount of Na^+ reabsorbed from the fluids processed by the kidneys and absorbed from foods in the intestine. They also reduce the amount of Na^+ secreted by salivary and sweat glands and increase the rate of K^+ excretion by the kidneys. The net effect is to keep Na^+ and K^+ balanced at the levels required for normal cellular functions, including those of the nervous system. Relatedly, secretion of aldosterone is tightly linked to blood volume and indirectly to blood pressure (see Section 40.2 and Chapter 46).

Moderate overproduction of aldosterone causes excessive water retention in the body, so that tissues swell and blood pressure rises. Conversely, moderate underproduction can lead to excessive water loss and dehydration. Severe underproduction is rapidly fatal unless mineralocorticoids are supplied by injection or other means.

The adrenal cortex also secretes small amounts of androgens, steroid sex hormones responsible for maintenance of male characteristics, which are synthesized primarily by the gonads. These hormones have significant effects only if they are overproduced, as can occur with some tumors in the adrenal cortex. The result is altered development of primary or secondary sex characteristics.

The Gonadal Sex Hormones Regulate the Development of Reproductive Systems, Sexual Characteristics, and Mating Behavior



The **gonads**, the testes and ovaries, are the primary source of sex hormones in vertebrates. The steroid hormones they produce, the **androgens**, **estrogens**, and **progestins**, have similar functions in regulating the development of male and female reproductive systems, sexual characteristics, and mating behavior. Both males and females produce all three types of hormones, but in different proportions. Androgen production is predominant in males, while estrogen and progestin production is predominant in females. An outline of the actions of these hormones is presented here, and a more complete picture is given in Chapter 47.

The **testes** of male vertebrates secrete androgens, steroid hormones that stimulate and control the development and maintenance of male reproductive systems. The principal androgen is **testosterone**, the male sex hormone. In young adult males, a jump in testosterone levels stimulates puberty and the development of secondary sexual characteristics, including the growth of facial and body hair, muscle development,

Focus on Research

Basic Research: Neuroendocrine and Behavioral Effects of Anabolic–Androgenic Steroids in Humans

Anabolic–androgenic steroids (AAS) are synthetic derivatives of the natural steroid hormone testosterone. They were designed to have potent anabolic (tissue building) activity and low androgenic (masculinizing) activity in therapeutic doses. Overall, there are about 60 AAS that vary in chemical structure and, therefore, in their physiological effects.

AAS are used for treating conditions such as delayed puberty and subnormal growth in children, as well as for therapy in chronic conditions such as cancer, AIDS, severe burns, liver and kidney failure, and anemias. AAS are not used exclusively for medical purposes, however. Because of their anabolic effects, which include an increase in muscle mass, strength, and endurance, as well as acceleration of recovery from injuries, AAS are used by athletes such as bodybuilders, weight lifters, baseball players, and football players. This use is actually abuse, because the doses typically administered are far higher than therapeutic doses. AAS abuse is significant: in the early 1990s, about one million Americans had used or were using AAS to increase strength, muscle mass, or athletic ability. While originally limited to elite athletes, use has trickled down to average athletes, including adolescents. It is estimated that perhaps 4% of high school students have used AAS. The greatest increase in AAS abuse over the past decade has been by adolescent girls.

Are AAS harmful at high doses? When researchers gave rodents doses of AAS comparable to those associated with human AAS abuse, they observed significant increases in aggression, anxiety, and sexual behaviors. These changes occur as a result of alterations in the neurotransmitters and other signaling molecules associated with those behaviors. All of these changes have been hypothesized to occur in human AAS abusers.

To study the effect of high doses of AAS on the human endocrine system, R. C. Daly and colleagues at the National Institute of Mental Health, in Bethesda, Maryland, administered the AAS methyltestosterone (MT) to normal (medication-free) human volunteers over a period of time in an inpatient clinic. The subjects were examined for the effects of MT on pituitary–gonadal, pituitary–thyroid, and pituitary–adrenal hormones, and the researchers attempted to correlate endocrine changes with psychological symptoms caused by the MT.

The researchers found, for instance, that high doses of MT caused a significant decrease in the levels of gonadotropins and gonadal steroid hormones in the blood. At the same time, thyroxine and TSH levels increased. No significant increases were seen in pituitary–adrenal hormones.

The decrease in testosterone levels correlated significantly with cognitive problems, such as increased distractibility and forgetfulness. The increase in thyroxine correlated significantly with a rise in aggressive behavior, notably anger, irritability, and violent feelings. There were no changes in activities associated with pituitary–adrenal hormones—energy, disturbed sleep, and sexual arousal—as was expected by the lack of change in those hormones.

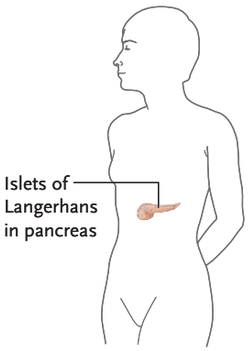
In sum, behavioral changes associated with high doses of an AAS suggest that AAS-induced hormonal changes may well contribute to the adverse behavioral and mood changes that occur during AAS abuse. Clearly, there is every reason to believe that taking high doses of AAS for athletic gain alters the normal hormonal balance in humans, as it does in rodents.

changes in vocal cord morphology, and development of normal sex drive. The synthesis and secretion of testosterone by cells in the testes is controlled by the release of luteinizing hormone (LH) from the anterior pituitary, which in turn is controlled by **gonadotropin releasing hormone (GnRH)**, a tropic hormone secreted by the hypothalamus.

Androgens are natural types of **anabolic steroids**, hormones that stimulate muscle development. Natural and synthetic anabolic steroids have been in the news over the years because of their use by bodybuilders and other athletes from sports in which muscular strength is important. *Focus on Research* discusses the potential adverse effects of anabolic–androgenic steroids, synthetic derivatives of testosterone, in humans.

The **ovaries** of females produce estrogens, steroid hormones that stimulate and control the development and maintenance of female reproductive systems. The principal estrogen is **estradiol**, which stimulates maturation of sex organs at puberty and the development of secondary sexual characteristics. Ovaries also produce progestins, principally **progesterone**, the steroid hormone that prepares and maintains the uterus for implantation of a fertilized egg and the subsequent growth and development of an embryo. The synthesis and secretion of progesterone by cells in the ovaries is controlled by the release of follicle-stimulating hormone (FSH) from the anterior pituitary, which in turn is controlled by the same GnRH as in males.

The Pancreatic Islet of Langerhans Hormones Regulate Glucose Metabolism



Most of the **pancreas,** a relatively large gland located just behind the stomach, forms an exocrine gland that secretes digestive enzymes into the small intestine (see Chapter 45). However, about 2% of the cells in the pancreas are endocrine cells that form the **islets of Langerhans.** Found in all vertebrates, the islets secrete the peptide hormones insulin and glucagon into the bloodstream.

Insulin and glucagon regulate the metabolism of fuel substances in the body. **Insulin,** secreted by *beta cells* in the islets, acts mainly on cells of nonworking skeletal muscles, liver cells, and adipose tissue (fat). (Brain cells do not require insulin for glucose uptake.) Insulin lowers blood glucose, fatty acid, and amino acid levels and promotes their storage. That is, the actions of insulin include stimulation of glucose transport into cells, glycogen synthesis from glucose, uptake of fatty acids by adipose tissue cells, fat synthesis from fatty acids, and protein synthesis from amino acids. Insulin also inhibits glycogen degradation to glucose, fat degradation to fatty acids, and protein degradation to amino acids.

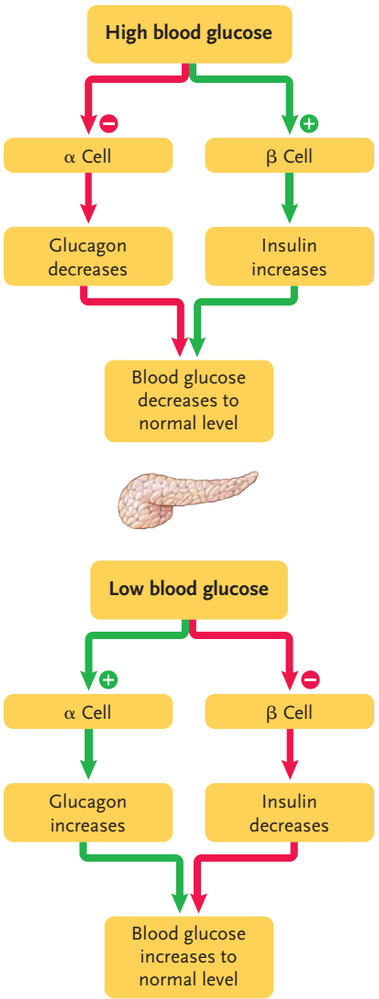


Figure 40.12
The action of insulin and glucagon in maintaining the concentration of blood glucose at an optimal level.

Glucagon, secreted by *alpha cells* in the islets, has effects opposite to those of insulin: it stimulates glycogen, fat, and protein degradation. Glucagon also uses amino acids and other noncarbohydrates as the input for glucose synthesis; this aspect of glucagon function operates during fasting. Negative feedback mechanisms that are keyed to the concentration of glucose in the blood control secretion of both insulin and glucagon to maintain glucose homeostasis **(Figure 40.12).**

Diabetes mellitus, a disease that afflicts more than 14 million people in the United States, results from problems with insulin production or action. The three classic diabetes symptoms are frequent urination, increased thirst (and consequently increased fluid intake), and increased appetite. Frequent urination occurs because without insulin, body cells are not stimulated to take up glucose, leading to abnormally high glucose concentration in the blood; excretion of the excess glucose in the urine requires water to carry it, which causes increased fluid loss and frequent trips to the bathroom. The need to replace the excreted water causes increased thirst. Increased appetite comes about because cells have low glucose levels and, therefore, proteins and fats are broken down as energy sources. Food intake is necessary to offset the negative energy balance or else weight loss will occur. Two of these classic symptoms gave the disease its name: *diabetes* is derived from a Greek word meaning "siphon," referring to the frequent urination, and *mellitus,* a Latin word meaning "sweetened with honey," refers to the sweet taste of a diabetic's urine. (Before modern blood or urine tests were developed, physicians tasted a patient's urine to detect the disease.)

The disease occurs in two major forms called *type 1* and *type 2.* Type 1 diabetes (insulin-dependent diabetes), which occurs in about 10% of diabetics, results from insufficient insulin secretion by the pancreas. This type of diabetes is usually caused by an autoimmune reaction in which an antibody destroys pancreatic beta cells. To survive, type 1 diabetics must receive regular insulin injections (typically, a genetically engineered human insulin called Humulin); careful dieting and exercise also have beneficial effects, because active skeletal muscles do not require insulin to take up and utilize glucose.

In type 2 diabetes (non-insulin-dependent diabetes), insulin is usually secreted at or above normal levels, but target cells have altered receptors that make

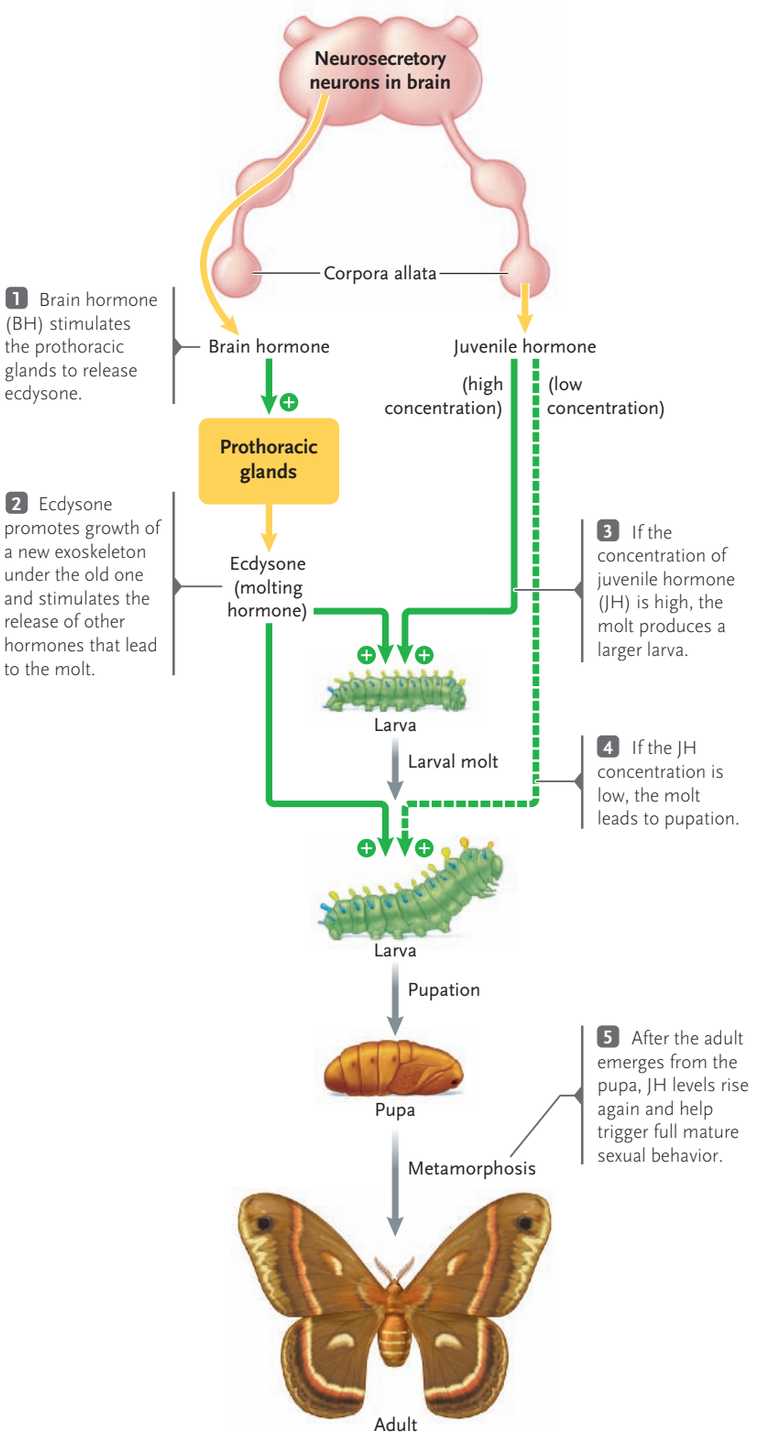
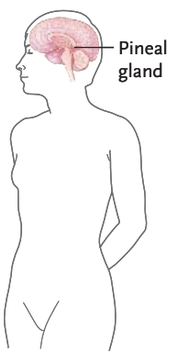


Figure 40.13
The roles of brain hormone, ecdysone, and juvenile hormone in the development of a silkworm moth.

them less responsive to the hormone than cells in normal individuals. About 90% of patients in the developed world who develop type 2 diabetes are obese. A genetic predisposition can also be a factor. Most affected people can lead a normal life by controlling their diet and weight, exercising, and taking drugs that enhance insulin action or secretion.

Diabetes has long-term effects on the body. Its cells, unable to utilize glucose as an energy source, start breaking down proteins and fats to generate energy. The protein breakdown weakens blood vessels throughout the body, particularly in the arms and legs and in critical regions such as the kidneys and retina of the eye. The circulation becomes so poor that tissues degenerate in the arms, legs, and feet. Bleeding in the retina causes blindness at advanced stages of the disease. The breakdown of circulation in the kidneys can lead to kidney failure. In addition, in type 1 diabetes, acidic products of fat breakdown (ketones) are produced in abnormally high quantities and accumulate in the blood. The lowering of blood pH that results can disrupt heart and brain function, leading to coma and death if the disease is untreated.

The Pineal Gland Regulates Some Biological Rhythms



The **pineal gland** is found at different locations in the brains of vertebrates—for example, in mammals, it is at roughly the center of the brain, while in birds and reptiles, it is on the surface of the brain just under the skull. The pineal gland regulates some biological rhythms.

The earliest vertebrates had a third, light-sensitive eye at the top of the head, and some species, such as lizards and tuataras (New Zealand reptiles), still have an eyelike structure in this location. In most vertebrates, the third eye became modified into a pineal gland, which in many groups retains some degree of photosensitivity. In mammals it is too deeply buried in the brain to be affected directly by light; nonetheless, specialized photoreceptors in the eyes make connections to the pineal gland.

In mammals, the pineal gland secretes a peptide hormone, **melatonin,** which helps to maintain daily biorhythms. Secretion of melatonin is regulated by an inhibitory pathway. Light hitting the eyes generates signals that inhibit melatonin secretion; consequently, the hormone is secreted most actively during periods of darkness. Melatonin targets a part of the hypothalamus called the *suprachiasmatic nucleus,* which is the primary biological clock coordinating body activity to a daily cycle. The nightly release of melatonin may help synchronize the biological clock with daily cycles of light and darkness. The physical and mental discomfort associated with jet lag may reflect the time required for melatonin secretion to reset a traveler's daily biological clock to match the period of daylight in a new time zone.

Melatonin also plays a role in other vertebrates. In some fishes, amphibians, and reptiles, melatonin and other hormones produce changes in skin color through their effects on *melanophores,* the pigment-containing

cells of the skin. Skin color may vary with the season, the animal's breeding status, or the color of the background.

Study Break

1. What effect does parathyroid hormone have on the body?
2. What hormones are secreted by the adrenal medulla, and what are their functions?
3. What are the two types of hormones secreted by the adrenal cortex, and what are their functions?
4. To what molecular class of hormones do estradiol and progesterone belong, and what are their functions?

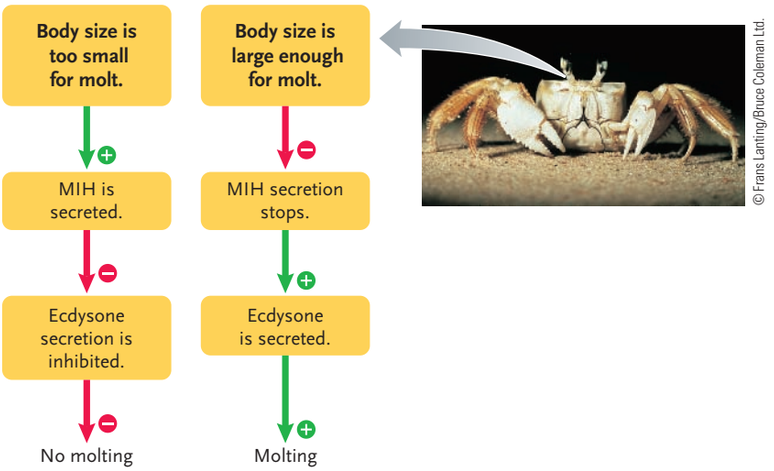


Figure 40.14
Control of molting by molt-inhibiting hormone (MIH), which is secreted by a gland in the eye stalks of crustaceans such as this crab.

40.5 Endocrine Systems in Invertebrates

Invertebrates have fewer hormones, regulating a narrower range of body processes and responses, than vertebrates do. However, in even the simplest animals, such as the cnidarian *Hydra,* hormones produced by neurosecretory neurons control reproduction, growth, and development of some body features. In annelids, arthropods, and mollusks, endocrine cells and glands produce hormones that regulate reproduction, water balance, heart rate, and sugar levels.

Some hormones occur in related forms in invertebrates and vertebrates. For example, both fruit flies and humans have insulin-like hormones and receptors, even though molecular studies suggest that their last common ancestor existed more than 800 million years ago. Both invertebrates and vertebrates secrete peptide and steroid hormones, but most of the hormones have different structures in the two groups, and therefore most have no effect when injected into members of the other group. However, the reaction pathways stimulated by the hormones are the same in both groups, suggesting that these regulatory mechanisms appeared very early in animal evolution.

Hormones Regulate Development in Insects and Crustaceans

Hormones have been studied in detail in only a few invertebrate groups, with the most extensive studies focusing on regulation of metamorphosis in insects. Butterflies, moths, and flies undergo the most dramatic changes as they mature into adults. They hatch from the egg as a caterpillar-like *larva*. During the larval stage, growth is accompanied by one or more *molts,* in which an old exoskeleton is shed and a new one forms. The insects then enter an inactive stage, the *pupa,* in which the body forms a thick, resistant coating, and finally is transformed into an adult.

Three major hormones regulate molting and metamorphosis in insects: **brain hormone** (BH), a peptide hormone secreted by neurosecretory neurons in the brain; **ecdysone** (*ekdysis* = emerging from), a steroid hormone secreted by the *prothoracic glands;* and **juvenile hormone** (JH), a peptide hormone secreted by the *corpora allata,* a pair of glands just behind the brain **(Figure 40.13).** The outcome of the molt depends on the level of JH. If it is high, the molt produces a larger larva; if it is low, the molt leads to pupation and the emergence of the adult.

Hormones that control molting have also been detected in crustaceans, including lobsters, crabs, and crayfish. Before growth reaches the stage at which the exoskeleton is shed, **molt-inhibiting hormone (MIH),** a peptide neurohormone secreted by a gland in the eye stalks, inhibits ecdysone secretion **(Figure 40.14).** As body size increases to the point requiring a molt, MIH secretion is inhibited, ecdysone secretion increases, and the molt is initiated.

In the next chapter we discuss the structure and functions of muscles, and their interactions with the skeletal system to cause movement. Muscle function depends primarily on the action of the nervous system, but the endocrine system plays a role in the control of smooth muscle contraction.

Study Break

How do hormones compare structurally and functionally in invertebrates and vertebrates?

Unanswered Questions

What are the cellular mechanisms for insulin resistance in patients with type 2 diabetes?

Insulin resistance is the condition in which the normal physiological levels of insulin are inadequate to produce a normal insulin response in the body. It plays an important role in the development of type 2 diabetes. Gerald Shulman and his research group at Yale Medical School have a long-term goal of elucidating the cellular mechanisms of insulin resistance. Once the mechanisms are known, therapeutic agents can then be developed to reverse insulin resistance in patients with this type of diabetes. In their research, Shulman's group studies patients with type 2 diabetes as well as transgenic mouse models of insulin resistance.

Recall from the chapter that one of the effects of insulin is the conversion of glucose to glycogen. In one set of experiments, Shulman's group studied the rate of glucose incorporation into muscle glycogen. They discovered that muscle glycogen synthesis plays a major role in causing insulin resistance in patients with type 2 diabetes. More detailed studies showed that defects in insulin-stimulated glucose transport and glucose phosphorylation activity in muscles correlate with the early stages in the onset of type 2 diabetes.

Could the defect in glucose transport and phosphorylation activity be reversed? Shulman's group answered this question in a study of lean offspring of type 2 diabetes parents. The offspring examined were insulin-resistant and synthesized insulin-stimulated muscle glycogen at a level only 50% that of normal individuals but, in contrast with their parents, they showed normal blood glucose levels. The potential for these individuals to develop type 2 diabetes later in life is high; that is, they are considered to be prediabetic. After six weeks of following a four-times-a-week aerobic exercise regime on a StairMaster, their insulin-stimulated muscle glycogen synthesis rates returned to normal due to correction of the glucose transport and glucose phosphorylation defects. Thus, the results suggest that regular aerobic exercise potentially could be useful in reversing insulin resistance in prediabetic individuals such as these offspring and, hence, that it might prevent the development of type 2 diabetes. More research is needed to see if that is the case.

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Review

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40.1 Hormones and Their Secretion

- Hormones are substances secreted by cells that control the activities of cells elsewhere in the body. The cells that respond to a hormone are its target cells. The best-known hormones are secreted by the endocrine system.
- The endocrine system includes four major types of cell signaling: classical endocrine signaling, in which endocrine glands secrete hormones; neuroendocrine signaling, in which neurosecretory neurons release neurohormones into the circulatory system; paracrine regulation, in which cells release local regulators that diffuse through the extracellular fluid to regulate nearby cells; and autocrine regulation, in which cells release local regulators that regulate the same cells that produced it (Figure 40.1).
- Most hormones and local regulators fall into one of four molecular classes: amines, peptides, steroids, and fatty acids.
- Many hormones are controlled by negative feedback mechanisms (Figure 40.2).

Animation: Major human endocrine glands

40.2 Mechanisms of Hormone Action

- Hormones typically are effective in very low concentrations in the body fluids because of amplification.
- Hydrophilic hormones bind to receptor proteins embedded in the plasma membrane, activating them. The activated receptors transmit a signal through the plasma membrane, triggering signal transduction pathways that cause a cellular response. Hydrophobic hormones bind to receptors in the cytoplasm or nucleus, activating them. The activated receptors control the expression of specific genes, the products of which cause the cellular response (Figure 40.3).
- As a result of the types of receptors they have, target cells may respond to more than one hormone, or they may respond differently to the same hormone.
- The major endocrine cells and glands of vertebrates are the hypothalamus, pituitary gland, thyroid gland, parathyroid glands, adrenal medulla, adrenal cortex, testes, ovaries, islets of Langerhans of the pancreas, and pineal gland. Hormones are also secreted by endocrine cells in the stomach and intestine, thymus gland, kidneys, and heart. Most body cells are capable of releasing prostaglandins (Figure 40.6).

Animation: Hormones and target cell receptors

40.3 The Hypothalamus and Pituitary

- The hypothalamus and pituitary together regulate many other endocrine cells and glands in the body (Figure 40.7).
- The hypothalamus produces tropic hormones (releasing hormones and inhibiting hormones) that control the secretion of eight hormones by the anterior pituitary: prolactin (PRL), growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), melanocyte-stimulating hormone (MSH), and endorphins.
- The posterior pituitary secretes antidiuretic hormone (ADH), which regulates body water balance, and oxytocin, which stimulates the contraction of smooth muscle in the uterus as a part of childbirth and triggers milk release from the mammary glands during suckling of the young.

Animation: Posterior pituitary function

Animation: Anterior pituitary function

40.4 Other Major Endocrine Glands of Vertebrates

- The thyroid gland secretes the thyroid hormones and, in mammals, calcitonin. The thyroid hormones stimulate the oxidation of carbohydrates and lipids, and coordinate with growth hormone to stimulate body growth and development. Calcitonin lowers the Ca^{2+} level in the blood by inhibiting the release of Ca^{2+} from bone. In amphibians, such as the frog, thyroid hormones trigger metamorphosis (Figure 40.9).
- The parathyroid glands secrete parathyroid hormone, which stimulates bone cells to release Ca^{2+} into the blood. PTH also stimulates the activation of vitamin D, which promotes Ca^{2+} absorption into the blood from the small intestine (Figure 40.10).
- The adrenal medulla secretes epinephrine and norepinephrine, which reinforce the sympathetic nervous system in responding to stress. The adrenal cortex secretes glucocorticoids, which help maintain glucose at normal levels in the blood, and mineralocorticoids, which regulate Na^{+} balance and extracellular fluid volume. The adrenal cortex also secretes small amounts of androgens (Figure 40.11).
- The gonadal sex hormones—androgens, estrogen, and progestins—play a major role in regulating the development of reproductive systems, sexual characteristics, and mating behavior.
- The islet of Langerhans cells of the pancreas secrete insulin and glucagon, which together regulate the concentration of fuel substances in the blood. Insulin lowers the concentration of glucose in the blood and inhibits the conversion of noncarbohydrate molecules into glucose. Glucagon raises blood glucose by stimulating glycogen, fat, and protein degradation (Figure 40.12).
- The pineal gland secretes melatonin, which interacts with the hypothalamus to set the body's daily rhythms.

Animation: Parathyroid hormone action

Animation: Hormones and glucose metabolism

40.5 Endocrine Systems in Invertebrates

- Hormones control development and function of the gonads, manage salt and water balance in the body fluids, and control molting in insects and crustaceans.
- Three major hormones—brain hormone (BH), ecdysone, and juvenile hormone (JH)—control molting and metamorphosis in insects. Hormones that control molting are also present in crustaceans (Figures 40.13 and 40.14).

Questions

Self-Test Questions

1. Amine hormones are usually:
   a. hydrophilic when secreted by the thyroid gland.
   b. based on tyrosine.
   c. paracrine but not autocrine.
   d. not transported by the blood.
   e. repelled by the plasma membrane.
2. Prostaglandins would be best described as inducers of:
   a. male and female characteristics.
   b. cell division.
   c. nerve transmission.
   d. smooth muscle contractions.
   e. cell differentiation.
3. When the concentration of thyroid hormone in the blood increases, it:
   a. inhibits TRH secretion by the hypothalamus.
   b. stimulates a secretion by the hypothalamus.
   c. stimulates the pituitary to secrete TRH.
   d. stimulates the pituitary to secrete TSH.
   e. activates a positive feedback loop.
4. Which of the following statements about endocrine targeting and reception is correct?
   a. The idea that one hormone affects one type of tissue is illustrated when epinephrine binds to smooth muscle cells in blood vessels as well as to beta cells in heart muscle.
   b. The idea that one hormone affects one type of tissue is shown when epinephrine cannot activate both the receptors on liver cells and the beta receptors of heart muscle.
   c. The idea that a target cell can respond to more than one hormone is seen when a vertebrate liver cell can respond to insulin and glucagon.
   d. The idea that a minute concentration of hormone can cause widespread effects demonstrates the specificity of cells for certain hormones.
   e. The idea that the response to a hormone is the same among different target cells is shown when different liver cells are activated by insulin.
5. The posterior pituitary secretes:
   a. tropic hormones, which control the hypothalamus.
   b. IGF, which simulates cell division and protein synthesis.
   c. ADH, which increases water absorption by the kidneys.
   d. oxytocin, which controls egg and sperm development.
   e. prolactin, which stimulates milk synthesis.
6. Blood levels of calcium are regulated directly by:
   a. insulin synthesized by the alpha cells of the pancreas.
   b. PTH made by the pituitary.
   c. vitamin D activated in the liver.
   d. prolactin synthesized by the anterior pituitary.
   e. calcitonin secreted by specialized thyroid cells.
7. If the human body is stressed, glucocorticoids:
   a. promote the breakdown of proteins in the muscles and bones.
   b. increase the amount of sodium reabsorbed from urine in the kidneys.
   c. decrease potassium secretion from the kidneys.
   d. decrease glucose uptake by cells in the nervous system.
   e. inhibit the synthesis of glucose from noncarbohydrate sources.
8. When blood glucose rises:
   a. the alpha cells increase glucagon secretion.
   b. the beta cells increase insulin secretion.
   c. in uncontrolled Type I diabetes, urination decreases.
   d. glucagon uses amino acids as an energy source.
   e. target cells decrease their insulin receptors.
9. In mammals:
   a. the suprachiasmatic nucleus of the pineal gland controls both male and female reproductive systems.
   b. estradiol is produced by the hypothalamus to control ovulation.
   c. melatonin controls anabolic steroid production.
   d. GnRH stimulates LH to control testosterone production.
   e. progesterone increases the secretion of LH from the posterior pituitary.

10. Insect development is regulated by:
    a. ecdysone, a peptide secreted by the brain.
    b. juvenile hormone, a peptide secreted by the corpora allata near the brain.
    c. molt-inhibiting hormone, a steroid secreted by the prothoracic glands.
    d. brain hormone, a steroid secreted by the hypothalamus.
    e. melatonin, a peptide secreted by the brain in the larval stage.

Questions for Discussion

1. A physician sees a patient whose symptoms include sluggishness, depression, and intolerance to cold. What disorder do these symptoms suggest?
2. Cushing's syndrome occurs when an individual overproduces cortisol; this rare disorder is also known as hypercortisolism. In children and teenagers, symptoms include extreme weight gain, retarded growth, excess hair growth, acne, high blood pressure, tiredness and weakness, and either very early or late puberty. Adults with the disease may also exhibit extreme weight gain, excess hair growth, and high blood pressure, and in addition may show muscle and bone weakness, moodiness or depression, sleep disorders, and reproductive disorders. Propose some hypotheses for the overproduction of cortisol in individuals with Cushing's syndrome.
3. A 20-year-old woman with a malignant brain tumor has her pineal gland removed. What kinds of side effects might this loss have?
4. In integrated pest management, a farmer uses a variety of tools to combat unwanted insects. These include applications of either hormones or hormone-inhibiting compounds to prevent insects from reproducing successfully. How might each of these hormone-based approaches disrupt reproduction?

Experimental Analysis

The Environmental Protection Agency (EPA) defines endocrine disruptors as chemical substances that can "interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis (normal cell metabolism), reproduction, development, and/or behavior." The chemicals, sometimes called environmental estrogens, come from both natural and man-made sources. A simple hypothesis is that endocrine disruptors act by mimicking hormones in the body. Many endocrine disruptors affect sex hormone function and, therefore, reproduction.

Examples of endocrine disruptors are the synthetic chemicals DDT (a pesticide) and dioxins, and natural chemicals such as phytoestrogens (estrogen-like molecules in plants), which are found in high levels in soybeans, carrots, oats, onions, beer, and coffee.

Design an experiment to investigate whether a new synthetic chemical (pick your own interesting scenario) is an endocrine disruptor. (Hint: You probably want to work with a model organism.)

Evolution Link

Which endocrine system evolved earlier, endocrine glands or neurosecretory neurons? Support your conclusion with information obtained from online research.

How Would You Vote?

Crop yields that sustain the human population currently depend on agricultural pesticides, some of which may disrupt hormone function in frogs and other untargeted species. Should chemicals that may cause problems remain in use while researchers investigate them? Go to www.thomsonedu.com/login to investigate both sides of the issue and then vote.