

47 Metabolism of Muscle at Rest and During Exercise

*There are three types of muscle cells: **smooth**, **skeletal**, and **cardiac**. In all types of muscle, contraction occurs via an actin/myosin sliding filament system, which is regulated by oscillations in **intracellular calcium levels**.*

*Muscle cells use stored glycogen and circulating glucose, fatty acids, and amino acids as energy sources. Muscle glycolysis is regulated differently from the liver, with the key difference being the regulation of **phosphofructokinase-2 (PFK-2)**. Muscle PFK-2 is not inhibited by phosphorylation; cardiac PFK-2 is actually activated by an insulin-stimulated protein kinase. Thus, under conditions in which liver PFK-2 is inactive, and glycolysis is running slowly, muscle glycolysis is either unaffected, or even stimulated, depending on the isoform of PFK-2 being expressed.*

*Although muscle cells do not synthesize fatty acids, they do contain an isozyme of **acetyl CoA carboxylase (ACC-2)** to regulate the **rate of fatty acid oxidation**. ACC-2 produces malonyl CoA, which inhibits carnitine palmitoyl transferase I, thereby blocking fatty acid entry into the mitochondria. Muscle also contains **malonyl CoA decarboxylase**, which catalyzes the conversion of malonyl CoA to acetyl CoA and carbon dioxide. Thus, both the synthesis and degradation of malonyl CoA is carefully regulated in muscle cells to balance glucose and fatty acid oxidation. Both allosteric and covalent means of regulation are employed. Citrate activates ACC-2, and phosphorylation of ACC-2 by the adenosine monophosphate (AMP)-activated protein kinase inhibits ACC-2 activity. Phosphorylation of malonyl CoA decarboxylase by the AMP-activated protein kinase activates the enzyme, further enhancing fatty acid oxidation when energy levels are low.*

*Muscles use **creatine phosphate** to store high-energy bonds. Creatine is derived from arginine and glycine in the kidney, and the guanidinoacetate formed is methylated (using S-adenosyl methionine) in the liver to form creatine. The enzyme **creatine phosphokinase (CPK)** then catalyzes the reversible transfer of a high-energy phosphate from adenosine triphosphate (ATP) to creatine, forming creatine-phosphate and adenosine diphosphate (ADP). Creatine phosphate is unstable and spontaneously cyclizes to form **creatinine**, which is excreted in the urine. The spontaneous production of creatinine occurs at a constant rate and is proportional to body muscle mass. Thus, the amount of creatinine excreted each day (the creatinine clearance rate) is constant and can be used as an indicator of the normalcy of the excretory function of the kidneys.*

*Skeletal muscle cells can be subdivided into **type I** and **type II fibers**. Type I fibers are **slow-twitch** fibers that use primarily **oxidative metabolism** for energy, whereas the type II fibers (**fast-twitch**) use **glycolysis** as their primary energy-generating pathway.*

***Glucose transport** into muscle cells can be stimulated during exercise because of the activity of the **AMP-activated protein kinase**. Fatty acid uptake into exercising muscle is dependent on the levels of circulating fatty acids, which are increased by **epinephrine** release.*



THE WAITING ROOM



Rena Felya, a 9-year-old girl, complained of a severe pain in her throat and difficulty in swallowing. She had chills, sweats, headache, and a fever of 102.4° F. When her symptoms persisted for several days, her mother took her to the pediatrician, who found diffuse erythema (redness) in her posterior pharynx (throat) with yellow exudates (patches) on her tonsils. Large, tender lymph nodes were present under her jaw on both sides of her neck. A throat culture was taken, and therapy with penicillin was begun.

Although the sore throat and fever improved, 8 days after the onset of the original infection, Rena's eyes and legs became swollen and her urine suddenly turned the color of "Coca-Cola." Her blood pressure was elevated. Protein and red blood cells were found in her urine. Her serum creatinine level was elevated at 1.8 mg/dL (reference range = 0.3–0.7 for a child). Because the throat culture grew out group A β -hemolytic streptococci, the doctor ordered a Streptozyme test. This test was positive for antibodies to streptolysin O and several other streptococcal antigens. As a result, a diagnosis of acute poststreptococcal glomerulonephritis was made. Supportive therapy, including bed rest and treatment for hypertension, was initiated.

I. MUSCLE CELL TYPES

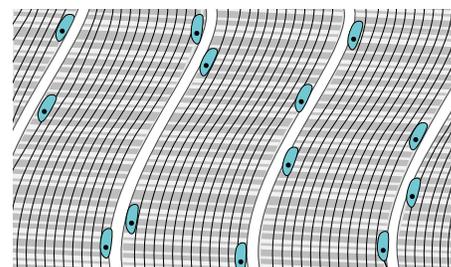
Muscle consists of three different types: skeletal, smooth, and cardiac (Fig. 47.1). The metabolism of each is similar, but the functions of the muscle are quite different.

A. Skeletal Muscle

Skeletal muscles are those muscles that are attached to bone and facilitate the movement of the skeleton. Skeletal muscles are found in pairs, which are responsible for opposing, coordinated directions of motion on the skeleton. The muscles appear striated under the microscope, and are controlled voluntarily (you think about moving a specific muscle group, and then it happens).

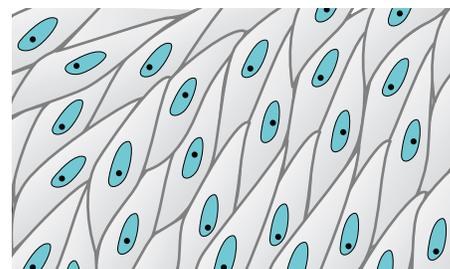
Skeletal muscle cells are long, cylindrical fibers that run the length of the muscle. The fibers are multinucleated because of cell fusion during embryogenesis. The cell membrane surrounding the fibers is called the sarcolemma, and the sarcoplasm is the intracellular milieu, which contains the proteins, organelles, and contractile apparatus of the cell. The sarcoplasmic reticulum is analogous to the endoplasmic reticulum in other cell types and is an internal membrane system that runs throughout the length of the muscle fiber. Another membrane structure, the transverse tubules (T-tubules), are thousands of invaginations of the sarcolemma that tunnel from the surface toward the center of the muscle fiber to make contact with the terminal cisterns of the sarcoplasmic reticulum. Because the T tubules are open to the outside of the muscle fiber and filled with extracellular fluid, the muscle action potential that propagates along the surface of the muscle fiber's sarcolemma travels into the T tubules and to the sarcoplasmic reticulum.

The striations in skeletal muscle are attributable to the presence and organization of myofibrils in the cells. Myofibrils are thread-like structures consisting of thin and thick filaments. The contractile proteins actin and myosin are contained within the filaments; myosin within the thick filaments, actin within the thin filaments. The sliding of these filaments relative to each other, using myosin-catalyzed ATP hydrolysis as an energy source, allows for the contraction and relaxation of the muscle (see Fig. 19.4).



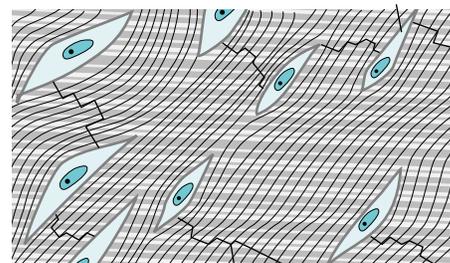
A. Skeletal muscle

Nuclei



B. Smooth muscle

Nuclei



C. Cardiac muscle

Intercalated disks

Fig. 47.1. Structures of the three different muscle types. Smooth Cardiac. Adapted from Basic Histology, Text and Atlas, Junqueira and Carneiro, 10th Ed. Lange, McGraw-Hill, 2002.



Duchenne's muscular dystrophy is caused by the absence of the protein dystrophin, which is a structural protein located in the sarcolemma. Dystrophin is required to maintain the integrity of the sarcolemma, and when absent leads to a loss of muscle function, caused by breakdown of the sarcolemma. The gene is X-linked, and mutations that lead to Duchenne's muscular dystrophy generally result from large deletions of the gene, such that dystrophin is absent from the membrane. Becker's muscular dystrophy, a milder form of disease, is caused by point mutations in the dystrophin gene. In Becker's muscular dystrophy, dystrophin is present in the sarcolemma, but in a mutated form.

Muscle fibers can be classified as either fast-twitch or slow-twitch. The slow-twitch fibers, or type I fibers (also called slow-oxidative), contain large amounts of mitochondria and myoglobin (giving them a red color), utilize respiration and oxidative phosphorylation for energy, and are relatively resistant to fatigue. Compared with fast-twitch fibers, their glycogen content is low. The slow-twitch fibers develop force slowly but maintain contractions longer than fast-twitch muscle.

The fast-twitch fibers, or type II, can be subdivided as type IIa or IIb. Type IIb fibers (also called fast-glycolytic) have few mitochondria and low levels of myoglobin (hence, they appear white). They are rich in glycogen and use glycogenolysis and glycolysis as their primary energy source. These muscles are prone to fatigue, because a continued reliance on glycolysis to produce ATP leads to an increase in lactic acid levels, resulting in a drop in the intracellular pH. As the pH drops, the ability of the muscle to produce ATP also diminishes. However, fast-twitch muscle can develop greater forces than slow-twitch muscle, such that contractions occur more rapidly. Type IIa fibers (also called fast-oxidative glycolytic) have properties of both type I and IIb fibers and thus display functional characteristics of both fiber types. The properties of types I, IIa, and IIb fibers are summarized in Table 47.1.

Muscles are a mixture of the different fiber types, but depending on the function a muscle could have a preponderance of one fiber type over another. Type I fibers are found in postural muscles such as the psoas in the back musculature or the soleus in the leg. The percentage of type I to type II will vary with the muscle. The triceps, which functions phasically, has 32.6% type I, whereas the soleus, which functions tonically, has 87.7% type I. Type II fibers are more prevalent in the large muscles of the limbs that are responsible for sudden, powerful movements. Extraocular muscles would also have more of these fibers than type I.

B. Smooth Muscle Cells

Smooth muscle cells are found in the digestive system, blood vessels, bladder, airways, and uterus. The cells have a spindle shape with a central nucleus (see Fig. 47.1B). The designation of smooth refers to the fact that these cells, which contain a single nucleus, display no striations under the microscope. The contraction of smooth muscle is controlled involuntarily (the cells contract and relax without any conscious attempt to have them do so; examples of smooth muscle activity include moving food

Table 47.1. Properties of Muscle Fiber Types

| Type I Fibers | Type II Fibers | |
|--|--|---|
| | Type IIa | Type IIb |
| <ul style="list-style-type: none"> • Slow-twitch (slow speed of contraction) • Slow-oxidative (low glycogen content) • High myoglobin content (appear red) • Small fiber diameter • Increased concentration of capillaries surrounding muscle (greater oxygen delivery) • High capacity for aerobic metabolism • High resistance to fatigue • Used for prolonged, aerobic exercise | <ul style="list-style-type: none"> • Intermediate-twitch (fast speed of contraction) • Fast-oxidative glycolytic fibers (intermediate glycogen levels) • Intermediate fiber diameter • High myoglobin content (appear red) • Increased oxidative capacity on training • Intermediate resistance to fatigue | <ul style="list-style-type: none"> • Fast-twitch (fast speed of contraction) • Fast-glycolytic (high glycogen content) • Low myoglobin content (appear white) • Low mitochondrial content • Limited aerobic metabolism • Large fiber diameter • More sensitive to fatigue as compared with other fiber types • Least efficient use of energy, primarily glycolytic • Used for sprinting and resistance tasks |

along the digestive tract, altering the diameter of the blood vessels, and expelling urine from the bladder). In contrast to skeletal muscle, these cells have the ability to maintain tension for extended periods, and do so efficiently, with a low use of energy.

C. Cardiac Muscle Cells

The cardiac cells are similar to skeletal muscle in that they are striated (contain fibers), but like smooth muscle cells they are regulated involuntarily (we do not have to think about making our heart beat). The cells are quadrangular in shape (see Fig. 47.1C) and form a network with multiple other cells through tight membrane junctions and gap junctions. The multicellular contacts allow the cells to act as a common unit and to contract and relax synchronously. Cardiac muscle cells are designed for endurance and consistency. They depend on aerobic metabolism for their energy needs because they contain many mitochondria and very little glycogen. These cells thus generate only a small amount of their energy from glycolysis using glucose derived from glycogen.

II. NEURONAL SIGNALS TO MUSCLE

For an extensive review of how muscle contracts or a detailed view of the signaling to allow muscle contraction, consult a medical physiology book. Only a brief overview is presented here.

The nerve–muscle cell junction is called the neuromuscular junction (Fig. 47.2). When appropriately stimulated, the nerve cell releases acetylcholine at the junction, which binds to acetylcholine receptors on the muscle membrane. This binding stimulates the opening of sodium channels on the sarcolemma. The massive influx of sodium ions results in the generation of an action potential in the sarcolemma at the edges of the motor end plate of the neuromuscular junction. The action potential sweeps across the surface of the muscle fiber and down the transverse tubules to the sarcoplasmic reticulum, where it initiates the release of calcium from its lumen, via the ryanodine receptor (Fig. 47.3). The calcium ion binds to troponin, resulting in a conformational change in the troponin–tropomyosin complexes such that they move away from the myosin-binding sites on the actin. When the binding site becomes available, the myosin head attaches to the myosin-binding site on the actin. The binding is followed by a conformational change (pivoting) in the myosin head, which shortens the sarcomere. After the pivoting, ATP binds the myosin head, which detaches from the actin and is available to bind another myosin-binding site on the



A reduced flow of oxygen-rich blood to the heart muscle may lead to a myocardial infarction (heart attack). The amount of ATP that can be generated by glycolysis alone is not sufficient to meet the energy requirements of the contracting heart.



The ryanodine receptors are calcium release channels found in the endoplasmic reticulum and sarcoplasmic reticulum of muscle cells. One type of receptor can be activated by a depolarization signal (depolarization-induced calcium release). Another receptor type is activated by calcium ions (calcium-induced calcium release). The proteins received their name because they bind ryanodine, a toxin obtained from the stem and roots of the plant *Ryania speciosa*. Ryanodine inhibits sarcoplasmic reticulum calcium release, and acts as a paralytic agent. It was first used commercially in insecticides.

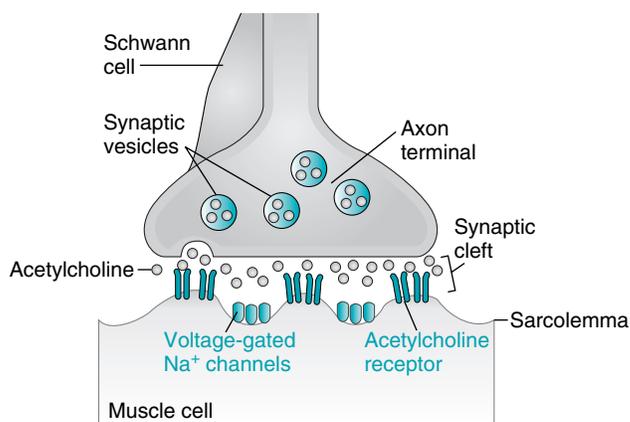


Fig. 47.2. The neuromuscular junction. When appropriately stimulated, the synaptic vesicles, containing acetylcholine, fuse with the axonal membrane and release acetylcholine into the synaptic cleft. The acetylcholine binds to its receptors on the muscle cells, which will initiate signaling for muscle contraction.

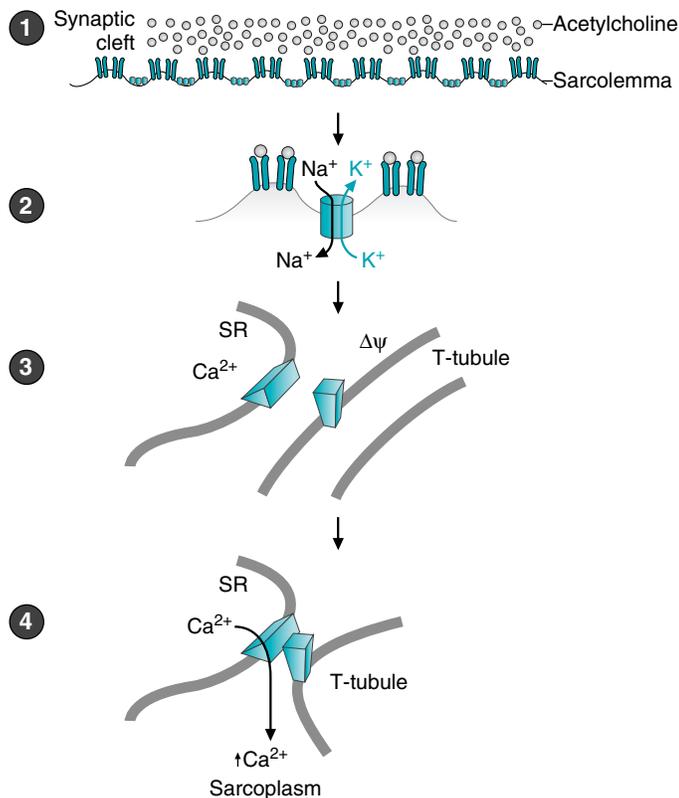


Fig. 47.3. Events leading to sarcoplasmic reticulum calcium release in skeletal muscle. 1. Acetylcholine, released at the synaptic cleft, binds to acetylcholine receptors on the sarcolemma, leading to a change of conformation of the receptors such that they now act as an ion pore. This allows sodium to enter the cell and potassium to leave. 2. The membrane polarization that results from these ion movements is transmitted throughout the muscle fiber by the T-tubule system. 3. A receptor in the T-tubules (the dihydropyridine receptor, DHPR) is activated by membrane polarization (a voltage-gated activation) such that activated DHPR physically binds to and activates the ryanodine receptor in the sarcoplasmic reticulum (depolarization-induced calcium release). 4. The activation of the ryanodine receptor, which is a calcium channel, leads to calcium release from the SR into the sarcoplasm. In cardiac muscle, activation of DHPR leads to calcium release from the T-tubules, and this small calcium release is responsible for the activation of the cardiac ryanodine receptor (calcium-induced calcium release) to release large amounts of calcium into the sarcoplasm.



Acetylcholine levels in the neuro-muscular junction are rapidly reduced by the enzyme acetylcholinesterase. A number of nerve gas poisons act to inhibit acetylcholinesterase (such as sarin and VX), such that muscles are continuously stimulated to contract. This leads to blurred vision, bronchoconstriction, seizures, respiratory arrest, and death. The poisons are covalent modifiers of acetylcholinesterase; therefore, recovery from exposure to such poisons requires the synthesis of new enzyme. A new generation of acetylcholinesterase inhibitors, which act reversibly (i.e., they do not form covalent bonds with the enzyme), are now being used to treat dementia, in particular dementia as brought about by Alzheimer's disease.

actin. As long as calcium ion and ATP remain available, the myosin heads will repeat this cycle of attachment, pivoting, and detachment (Fig. 47.4). This movement requires ATP, and when ATP levels are low (such as occurs during ischemia), the ability of the muscle to relax or contract is compromised. As the calcium release channel closes, the calcium is pumped back into the sarcoplasmic reticulum against its concentration gradient by use of the energy-requiring protein SERCA (sarcoplasmic reticulum Ca²⁺ ATPase), and contraction stops. This basic process occurs in all muscle cell types, with some slight variations between cell types.

III. GLYCOLYSIS AND FATTY ACID METABOLISM IN MUSCLE CELLS

The pathways of glycolysis and fatty acid oxidation in muscle are the same as has been previously described (see Chapters 22 and 23). The difference between muscles and other tissues is how these pathways are regulated.

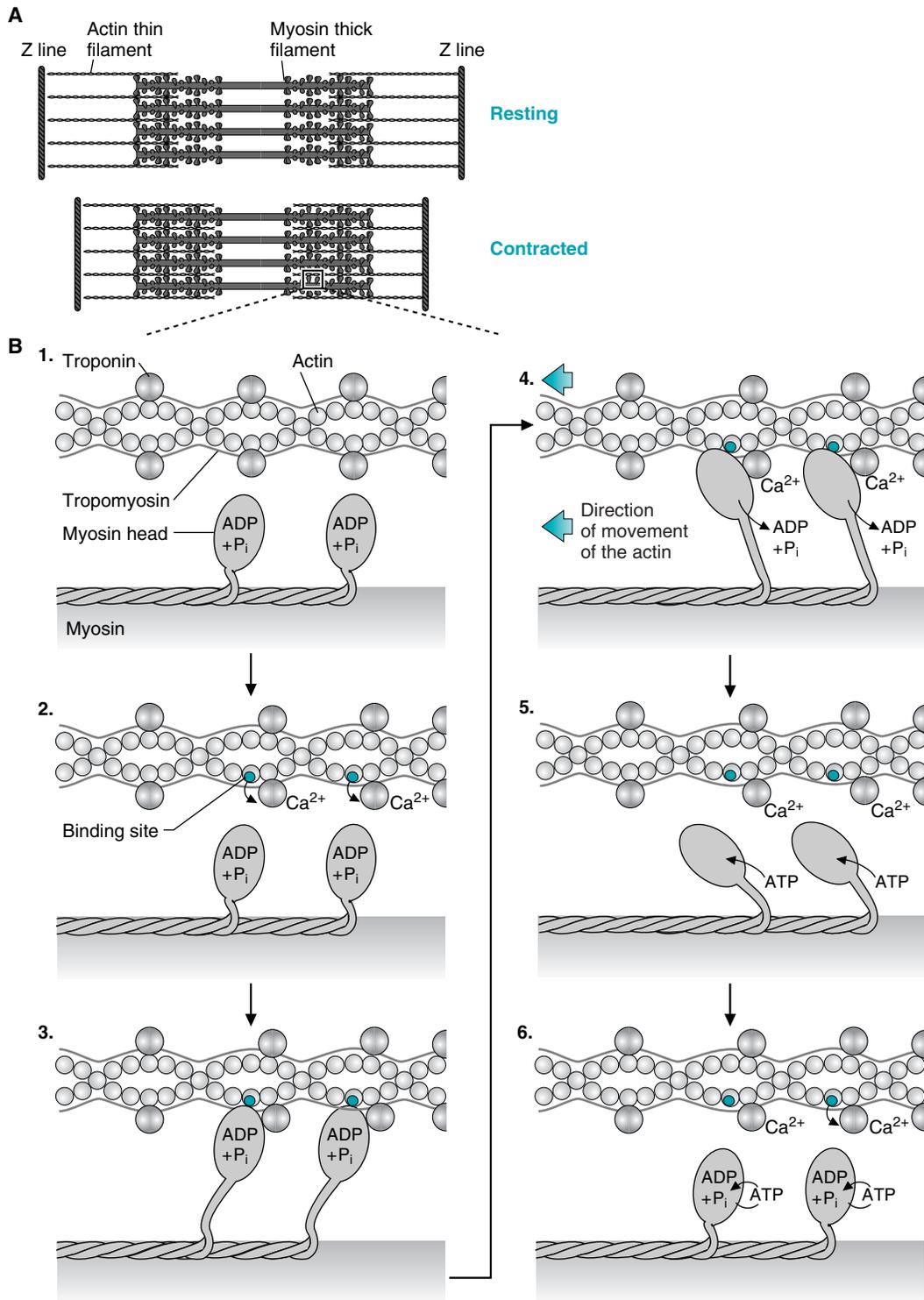


Fig. 47.4. An overview of muscle contraction. **A.** Muscle contraction. During muscle contraction, the myosin head binds to the actin thin filament. A pivoting of the myosin head toward the center of the sarcomere pulls the Z-lines closer together, with subsequent shortening of the sarcomere. **B.** A closer look at myosin-actin interactions. 1. A resting sarcomere. The troponin-tropomyosin complex is blocking the myosin-binding sites on the actin. The myosin head is already energized to power a contraction. 2. Exposure of the active site. After calcium binding to troponin, a conformational change in the troponin molecule pulls the troponin away from the binding site. 3. Cross-bridge attachment. Once the binding sites on the actin are exposed, the myosin head binds to it. 4. Myosin head pivoting. After cross-bridge attachment, the energy stored in the myosin head is released, and the myosin head pivots toward the center of the sarcomere (power stroke). Now the ADP and phosphate bound to the myosin head are released. 5. Detachment of the cross-bridge. Now a molecule of ATP binds to the myosin head with simultaneous detachment of the myosin head from the binding site on the actin molecule. 6. Reactivation of the myosin head. The ATPase activity of the myosin head hydrolyzes the ATP into ADP and phosphate. The energy released from the hydrolysis of this high-energy bond is used to re-energize the myosin head, and the entire cycle can be repeated as long as calcium is present and there are sufficient ATP reserves.



ACC-1 is the isozyme of acetyl-coA carboxylase, which is used to synthesize malonyl-CoA for fatty acid synthesis. Muscle cells do not synthesize fatty acids; however, they do carefully regulate the oxidation of fatty acids through the synthesis and destruction of malonyl-CoA. ACC-1 is a cytosolic protein, whereas ACC-2 is mitochondrial, closely linked to CPT-I in the outer mitochondrial membrane. Mice that have been bred to lack ACC-2 have a 50% reduction of fat stores as compared with “normal” mice. This was shown to be attributable to a 30% increase in skeletal muscle fatty acid oxidation because of the dysregulation of CPT-I, because malonyl CoA could not be produced to regulate the rate at which fatty acid oxidation occurred.



Under conditions in which ketone bodies are produced, fatty acid levels in the plasma are also elevated. Because the heart preferentially burns fatty acids as a fuel rather than the ketone bodies produced by the liver, the ketone bodies are spared for use by the nervous system.

Phosphofructokinase 2 (PFK-2) is negatively regulated by phosphorylation in the liver (the enzyme that catalyzes the phosphorylation is the cyclic adenosine monophosphate [cAMP]–dependent protein kinase). However, in skeletal muscle, PFK-2 is not regulated by phosphorylation. This is because the skeletal muscle isozyme of PFK-2 lacks the regulatory serine residue, which is phosphorylated in the liver. However, the cardiac isozyme of PFK-2 is phosphorylated and activated by a kinase cascade initiated by insulin. This allows the heart to activate glycolysis and to use blood glucose when blood glucose levels are elevated.

Fatty acid uptake by muscle requires the participation of fatty acid–binding proteins and the usual enzymes of fatty acid oxidation. Fatty acyl-CoA uptake into the mitochondria is controlled by malonyl-CoA, which is produced by an isozyme of acetyl-coA carboxylase (ACC-2; the ACC-1 isozyme is found in liver and adipose tissue and is used for fatty acid biosynthesis). ACC-2 is inhibited by phosphorylation by the AMP-activated protein kinase (AMP-PK) such that when energy levels are low the levels of malonyl CoA will drop, allowing fatty acid oxidation by the mitochondria. In addition, muscle cells also contain the enzyme malonyl CoA decarboxylase, which is activated by phosphorylation by the AMP-PK. Malonyl CoA decarboxylase converts malonyl CoA to acetyl CoA, thereby relieving the inhibition of carnitine palmitoyl transferase I (CPT-I) and stimulating fatty acid oxidation (Fig. 47.5). Muscle cells do not synthesize fatty acids; the presence of acetyl CoA carboxylase in muscle is exclusively for regulatory purposes.

IV. FUEL UTILIZATION IN CARDIAC MUSCLE

A. Normal Conditions

The heart primarily uses fatty acids (60–80%), lactate, and glucose (20–40%) as its energy sources. Ninety-eight percent of cardiac ATP is generated by oxidative means; 2% is derived from glycolysis. The lactate used by the heart is taken up by a monocarboxylate transporter in the cell membrane that is also used for the transport of ketone bodies. However, ketone bodies are not a preferred fuel for the heart, because the heart prefers to use fatty acids.

Lactate is generated by red blood cells and working skeletal muscle. When the lactate is used by the heart, it is oxidized to carbon dioxide and water, following the

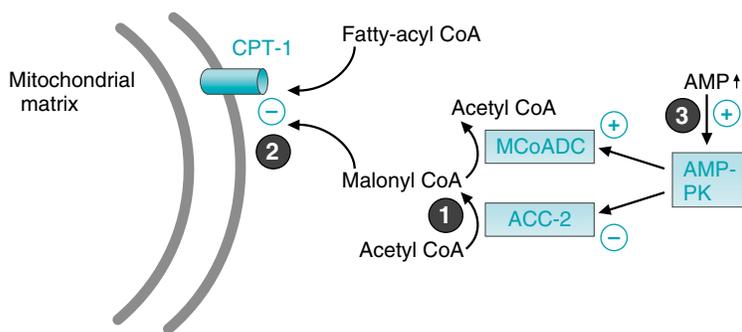


Fig. 47.5. Regulation of fatty acyl CoA entry into muscle mitochondria. 1. Acetyl CoA carboxylase-2 (ACC-2) converts acetyl CoA to malonyl CoA, which inhibits carnitine palmitoyl transferase I (CPT-I), thereby blocking fatty acyl CoA entry into the mitochondria. 2. However, as energy levels drop, AMP levels rise because of the activity of the adenylate kinase reaction. 3. The increase in AMP levels activates the AMP-activated protein kinase (AMP-PK), which phosphorylates and inactivates ACC-2, and also phosphorylates and activates malonyl CoA decarboxylase (MCoADC). The decarboxylase converts malonyl CoA to acetyl CoA, thereby relieving the inhibition of CPT-1, and allowing fatty acyl CoA entry into the mitochondria. This allows the muscle to generate ATP via the oxidation of fatty acids.

pathway lactate to pyruvate, pyruvate to acetyl-coA, acetyl CoA oxidation in the TCA cycle, and ATP synthesis through oxidative phosphorylation. An alternative fate for lactate is its utilization in the reactions of the Cori cycle in the liver.

Glucose transport into the cardiocyte occurs via both GLUT1 and GLUT4 transporters, although approximately 90% of the transporters are GLUT4. Insulin stimulates an increase in the number of GLUT4 transporters in the cardiac cell membrane, as does myocardial ischemia. This ischemia-induced increase in GLUT4 transporter number is additive to the effect of insulin on the translocation of GLUT4 transporters to the plasma membrane.

Fatty acid uptake into cardiac muscle is similar to that for other muscle cell types and requires fatty acid-binding proteins and carnitine palmitoyl transferase I for transfer into the mitochondria. Fatty acid oxidation in cardiac muscle cells is regulated by altering the activities of ACC-2 and malonyl CoA decarboxylase.

B. Ischemic Conditions

When blood flow to the heart is interrupted, the heart switches to anaerobic metabolism. The rate of glycolysis increases, but the accumulation of protons (via lactate formation) is detrimental to the heart. Ischemia also increases the levels of free fatty acids in the blood and, surprisingly, when oxygen is reintroduced to the heart, the high rate of fatty acid oxidation in the heart is detrimental to the recovery of the damaged heart cells. Fatty acid oxidation occurs so rapidly that NADH accumulates in the mitochondria, leading to a reduced rate of NADH shuttle activity, an increased cytoplasmic NADH level, and lactate formation, which generates more protons. In addition, fatty acid oxidation increases the levels of mitochondrial acetyl CoA, which inhibits pyruvate dehydrogenase, leading to cytoplasmic pyruvate accumulation and lactate production. As lactate production increases and the intracellular pH of the heart drops, it is more difficult to maintain ion gradients across the sarcolemma. ATP hydrolysis is required to repair these gradients, which are essential for heart function. However, the use of ATP for gradient repair reduces the amount of ATP available for the heart to use in contraction, which, in turn, compromises the ability of the heart to recover from the ischemic event.



A new class of drugs, known as partial fatty acid oxidation (pFOX) inhibitors, are being developed to reduce the extensive fatty acid oxidation in heart after an ischemic episode (the prototype drug is ranolazine). The reduction in fatty acid oxidation induced by the drug will allow glucose oxidation to occur and reduce lactate buildup in the damaged heart muscle. Other possible targets of such drugs, which have yet to be developed, include ACC-2, malonyl CoA decarboxylase, and carnitine palmitoyl transferase I.

V. FUEL UTILIZATION IN SKELETAL MUSCLE

Skeletal muscles use many fuels to generate ATP. The most abundant immediate source of ATP is creatine phosphate. ATP also can be generated from glycogen stores either anaerobically (generating lactate) or aerobically, in which case pyruvate is converted to acetyl CoA for oxidation via the TCA cycle. All human skeletal muscles have some mitochondria and thus are capable of fatty acid and ketone body oxidation. Skeletal muscles are also capable of completely oxidizing the carbon skeletons of alanine, aspartate, glutamate, valine, leucine, and isoleucine, but not other amino acids. Each of these fuel oxidation pathways plays a somewhat unique role in skeletal muscle metabolism.

A. ATP and Creatine Phosphate

ATP is not a good choice as a molecule to store in quantity for energy reserves. Many reactions are allosterically activated or inhibited by ATP levels, especially those that generate energy. Muscle cells solve this problem by storing high-energy phosphate bonds in the form of creatine phosphate. When energy is required, creatine phosphate will donate a phosphate to ADP, to regenerate ATP for muscle contraction (Fig. 47.6).

Creatine synthesis begins in the kidney and is completed in the liver. In the kidney, glycine combines with arginine to form guanidinoacetate. In this reaction, the guanidinium group of arginine (the group that also forms urea), is transferred to

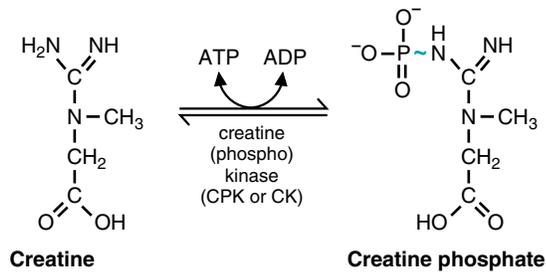


Fig. 47.6. The creatine phosphokinase reaction. The high-energy bond is the unusual nitrogen–phosphate bond, as indicated by the blue squiggle.

glycine, and the remainder of the arginine molecule is released as ornithine. Guanidinoacetate then travels to the liver, where it is methylated by S-adenosyl methionine to form creatine (Fig 47.7).

The creatine formed is released from the liver and travels through the bloodstream to other tissues, particularly skeletal muscle, heart, and brain, where it reacts with ATP to form the high-energy compound creatine phosphate (see Fig. 47.6). This reaction, catalyzed by creatine phosphokinase (CK, also abbreviated as CPK), is reversible. Therefore, cells can use creatine phosphate to regenerate ATP.

Creatine phosphate serves as a small reservoir of high-energy phosphate that can readily regenerate ATP from ADP. As a result, it plays a particularly important role in muscle during exercise. It also carries high-energy phosphate from

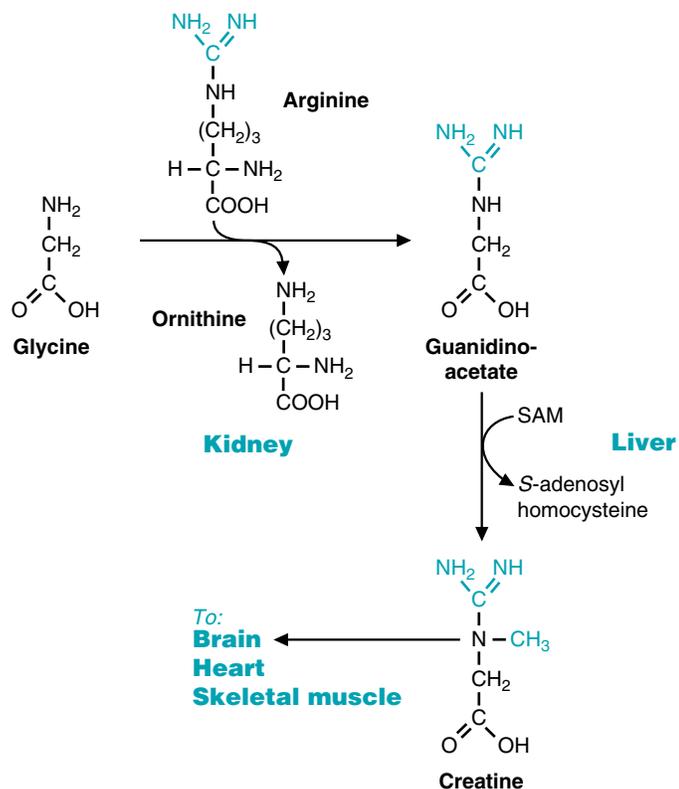


Fig. 47.7. The synthesis of creatine from arginine, glycine, and S-adenosyl methionine. Synthesis originates in the kidney and is completed in the liver.

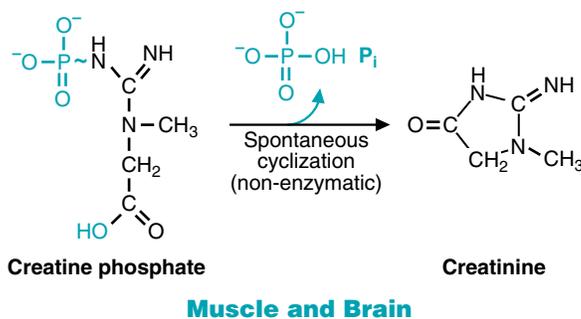


Fig. 47.8. The spontaneous production of creatinine from creatine phosphate.

mitochondria, where ATP is synthesized, to myosin filaments, where ATP is used for muscle contraction.

Creatine phosphate is an unstable compound. It spontaneously cyclizes, forming creatinine (Fig. 47.8). Creatinine cannot be further metabolized and is excreted in the urine. The amount of creatinine excreted each day is constant and depends on body muscle mass. Therefore, it can be used as a gauge for determining the amounts of other compounds excreted in the urine as well as an indicator of renal excretory function. The daily volume of urine is determined by such factors as the volume of blood reaching the renal glomeruli and the amount of renal tubular fluid reabsorbed from the tubular urine back into the interstitial space of the kidneys over time. At any given moment, the concentration of a compound in a single urine specimen does not give a good indication of the total amount that is being excreted on a daily basis. However, if the concentration of the compound is divided by the concentration of creatinine, the result provides a better indication of the true excretion rate.

B. Fuel Utilization at Rest

Muscle fuel utilization at rest is dependent on the serum levels of glucose, amino acids, and fatty acids. If blood glucose and amino acids are elevated, glucose will be converted to glycogen, and branched-chain amino acid metabolism will be high. Fatty acids will be used for acetyl CoA production and will satisfy the energy needs of the muscle under these conditions.

There is a balance between glucose oxidation and fatty acid oxidation, which is regulated by citrate. When the muscle cell has adequate energy, citrate leaves the mitochondria and activates ACC-2, which produces malonyl CoA. The malonyl CoA inhibits carnitine palmitoyl transferase-1, thereby reducing fatty acid oxidation by the muscle. Malonyl CoA decarboxylase is also inactive, because the AMP-PK is not active in the fed state. Thus, the muscle regulates its oxidation of glucose and fatty acids in part through monitoring of cytoplasmic citrate levels.

C. Fuel Use during Starvation

As blood glucose levels drop, insulin levels drop. This reduces the levels of GLUT4 transporters in the muscle membrane, and glucose use by muscle drops significantly. This conserves glucose for use by the nervous system and red blood cells. In cardiac muscle, PFK-2 is phosphorylated and activated by insulin. The lack of insulin results in a reduced use of glucose by these cells as well. Pyruvate dehydrogenase is inhibited by the high levels of acetyl CoA and NADH being produced by fatty acid oxidation.

Fatty acids become the muscle's preferred fuel under starvation conditions. The AMP-PK is active because of lower than normal ATP levels, ACC-2 is inhibited, and malonyl CoA decarboxylase is activated, thereby retaining full activity of CPT-1.



Each kidney normally contains approximately one million glomerular units. Each unit is supplied by arterial blood via the renal arteries and acts as a "filter." Metabolites such as creatinine leave the blood by passing through pores or channels in the glomerular capillaries and enter the fluid within the proximal kidney tubule for eventual excretion in the urine. When functionally intact, these glomerular tissues are impermeable to all but the smallest of proteins. When acutely inflamed, however, this barrier function is lost, and albumin and other proteins may appear in the urine.

The marked inflammatory changes in the glomerular capillaries that accompany post-streptococcal glomerulonephritis significantly reduce the flow of blood to the filtering surfaces of these vessels. As a result, creatinine, urea, and other circulating metabolites that are filtered into the urine at a normal rate (the glomerular filtration rate or GFR) in the absence of kidney disease now fail to reach the filters, and, therefore, they accumulate in the plasma.

These changes explain **Rena Felya's** laboratory profile during her acute inflammatory glomerular disease.



Muscle and brain cells contain large amounts of creatine phosphokinase (CK), and damage to these cells causes the enzyme to leak into the blood. Serum CK is measured to diagnose and evaluate patients who have had strokes and heart attacks. The presence of 5% or more of the CK in the blood as the muscle isoform is indicative of a heart attack (see Chapters 8 and 9).



Recall that in prolonged starvation muscle proteolysis is induced to provide substrates for gluconeogenesis by the liver. This does not, however, alter the use of fatty acids by the muscle for its own energy needs under these conditions.

The lack of glucose reduces the glycolytic rate, and glycogen synthesis does not occur because of the inactivation of glycogen synthase by epinephrine-stimulated phosphorylation.

D. Fuel Utilization during Exercise

The rate of ATP utilization in skeletal muscle during exercise can be as much as 100 times greater than that in resting skeletal muscles; thus, the pathways of fuel oxidation must be rapidly activated during exercise to respond to the much greater demand for ATP. ATP and creatine phosphate would be rapidly used up if they were not continuously regenerated. The synthesis of ATP occurs from glycolysis (either aerobic or anaerobic) and oxidative phosphorylation (which requires a constant supply of oxygen).

Anaerobic glycolysis is especially important as a source of ATP in three conditions. The first is during the initial period of exercise before exercise-stimulated increase in blood flow and substrate and oxygen delivery begin, allowing aerobic processes to occur. The second condition in which anaerobic glycolysis is important is exercise by muscle containing predominately fast-twitch glycolytic muscle fibers, because these fibers have low oxidative capacity and generate most of their ATP through glycolysis. The third condition is during strenuous activity, when the ATP demand exceeds the oxidative capacity of the tissue, and the increased ATP demand is met by anaerobic glycolysis.

1. ANAEROBIC GLYCOLYSIS AT THE ONSET OF EXERCISE

During rest, most of the ATP required in all types of muscle fibers is obtained from aerobic metabolism. However, as soon as exercise begins, the demand for ATP increases. The amount of ATP present in skeletal muscle could sustain exercise for only 1.2 seconds if not regenerated, and the amount of phosphocreatine could sustain exercise for only 9 seconds if it were not regenerated. It takes longer than 1 minute for the blood supply to exercising muscle to increase significantly due to vasodilation, and therefore oxidative metabolism of blood-borne glucose and fatty acids cannot increase rapidly at the onset of exercise. Thus, for the first few minutes of exercise, the conversion of glycogen to lactate provides a considerable portion of the ATP requirement.

2. ANAEROBIC GLYCOLYSIS IN THE TYPE IIB FAST-TWITCH GLYCOLYTIC FIBER

Although the human has no muscles that consist entirely of this fiber type, many animals do. Examples are white abdominal muscles of fish and the pectoral muscle of game birds (turkey white meat). These muscles contract rapidly and vigorously (the fast twitch refers to the time to peak tension), but only for short periods. Thus, they are used for activities such as flight in birds and sprinting and weight-lifting in humans.

In such muscles, the glycolytic capacity is high because the enzymes of glycolysis are present in large amounts (thus, the overall V_{\max} [maximum velocity] is large). The levels of hexokinase, however, are low, so very little circulating glucose is used. The low levels of hexokinase in fast-twitch glycolytic fibers prevent the muscle from drawing on blood glucose to meet this high demand for ATP, thus avoiding hypoglycemia. Glucose 6-phosphate, formed from glycogenolysis, further inhibits hexokinase. The tissues rely on endogenous fuel stores (glycogen and creatine phosphate) to generate ATP, following the pathway of glycogen breakdown to glucose 1-phosphate, the conversion of glucose 1-phosphate to glucose 6-phosphate, and the metabolism of glucose 6-phosphate to lactate. Thus, anaerobic glycolysis is the main source of ATP during exercise of these muscle fibers.

3. ANAEROBIC GLYCOLYSIS FROM GLYCOGEN

Glycogenolysis and glycolysis during exercise are activated together because both PFK-1 (the rate-limiting enzyme of glycolysis) and glycogen phosphorylase b (the inhibited form of glycogen phosphorylase) are allosterically activated by AMP.

AMP is an ideal activator because its concentration is normally kept low by the adenylate kinase (also called myokinase in muscle) equilibrium [$2 \text{ ADP} \leftrightarrow \text{AMP} + \text{ATP}$]. Thus, whenever ATP levels decrease slightly, the AMP concentration increases manyfold (Fig. 47.9)

Starting from a molecule of glucose 1-phosphate derived from glycogenolysis, three ATP molecules are produced in anaerobic glycolysis, as compared with 32 to 34 moles of ATP in aerobic glycolysis. To compensate for the low ATP yield of anaerobic glycolysis, fast-twitch glycolytic fibers have a much higher content of glycolytic enzymes, and the rate of glucose 6-phosphate utilization is more than 12 times as fast as slow-twitch fibers.

Muscle fatigue during exercise generally results from a lowering of the pH of the tissue to approximately 6.4. Both aerobic and anaerobic metabolism lowers the pH. Both the lowering of pH and lactate production can cause pain.

Metabolic fatigue also can occur once muscle glycogen is depleted. Muscle glycogen stores are used up in less than 2 minutes of anaerobic exercise. If you do pushups, you can prove this to yourself. The muscle used in pushups, a high-strength exercise, is principally fast-twitch glycolytic fibers. Time yourself from the start of your pushups. No matter how well you have trained, you probably cannot do pushups for as long as 2 minutes. Furthermore, you will feel the pain as the muscle pH drops as lactate production continues.

The regulation of muscle glycogen metabolism is complex. Recall that glycogen degradation in muscle is not sensitive to glucagon (muscles lack glucagon receptors), so there is little change in muscle glycogen stores during overnight fasting or long-term fasting, if the individual remains at rest. Glycogen synthase is inhibited during exercise but can be activated in resting muscle by the release of insulin after a high-carbohydrate meal. Unlike the liver form of glycogen phosphorylase, the muscle isozyme contains an allosteric site for AMP binding. When AMP binds to muscle glycogen phosphorylase b, the enzyme is activated even though it is not phosphorylated. Thus, as muscle begins to work and the myosin-ATPase hydrolyzes existing ATP stores to ADP, AMP will begin to accumulate (due to the myokinase reaction), and glycogen degradation will be enhanced. The activation of muscle glycogen phosphorylase b is further enhanced by the release of Ca^{2+} from the sarcoplasmic reticulum, which occurs when muscles are stimulated to contract. The increase in sarcoplasmic Ca^{2+} also leads to the allosteric activation of glycogen phosphorylase kinase (through binding to the calmodulin subunit of the enzyme), which phosphorylates muscle glycogen phosphorylase b, fully activating it. And, finally, during intense exercise, epinephrine release stimulates the activation of adenylate cyclase in muscle cells, thereby activating the

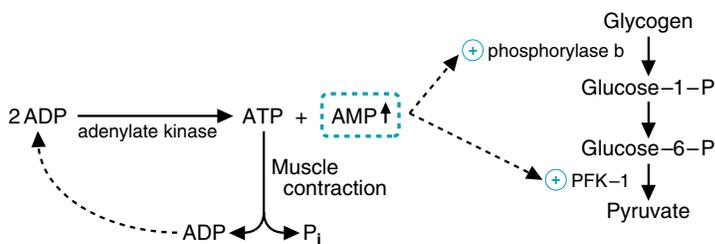


Fig. 47.9. Activation of muscle glycogenolysis and glycolysis by AMP. As muscle contracts, ATP is converted to ADP and P_i . In the adenylate kinase reaction, two ADP react to form ATP and AMP. The ATP is used for contraction. As AMP accumulates, it activates glycogenolysis and glycolysis.

cAMP-dependent protein kinase (see Fig. 28.10). Protein kinase A phosphorylates and fully activates glycogen phosphorylase kinase such that continued activation of muscle glycogen phosphorylase can occur. The hormonal signal is slower than the initial activation events triggered by AMP and calcium (Fig. 47.10).

4. ANAEROBIC GLYCOLYSIS DURING HIGH-INTENSITY EXERCISE

Once exercise begins, the electron transport chain, the TCA cycle, and fatty acid oxidation are activated by the increase of ADP and the decrease of ATP. Pyruvate dehydrogenase remains in the active, nonphosphorylated state as long as NADH can be reoxidized in the electron transport chain and acetyl CoA can enter the TCA cycle. However, even though mitochondrial metabolism is working at its maximum capacity, additional ATP may be needed for very strenuous, high-intensity exercise. When this occurs, ATP is not being produced rapidly enough to meet the muscle's needs, and AMP begins to accumulate. Increased AMP levels activate PFK-1 and glycogenolysis, thereby providing additional ATP from anaerobic glycolysis (the additional pyruvate

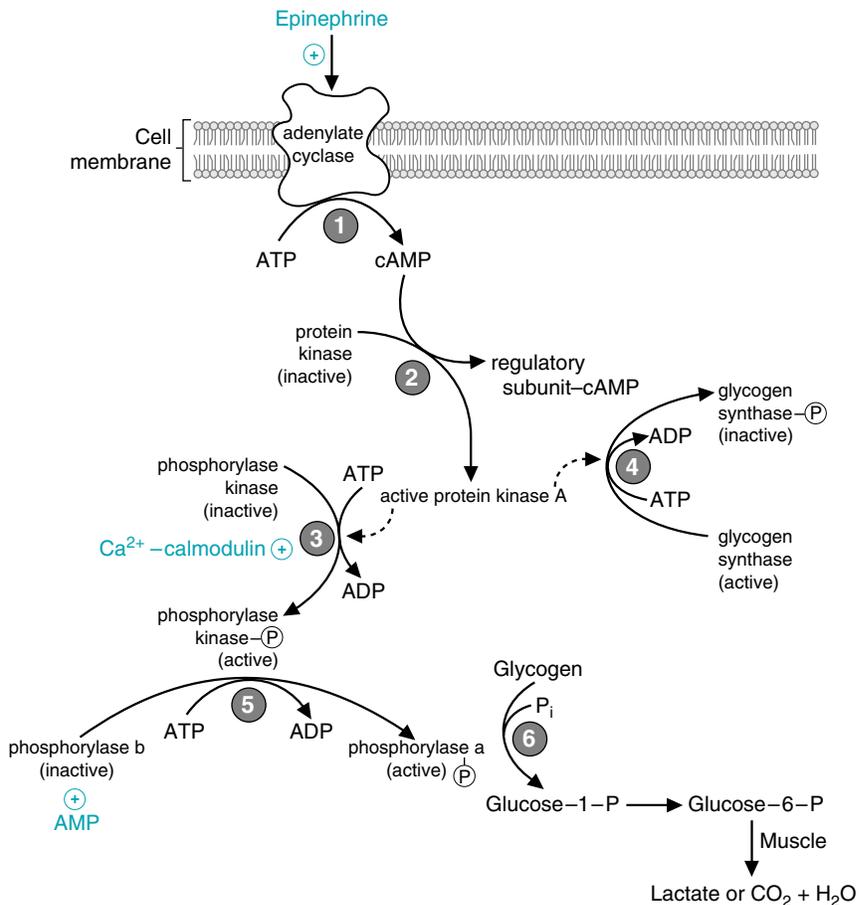


Fig. 47.10. Stimulation of glycogenolysis in muscle by epinephrine. 1. Epinephrine binding to its receptor leads to the activation of adenylate cyclase, which increases cAMP levels. 2. cAMP binds to the regulatory subunits of protein kinase A, thereby activating the catalytic subunits. 3. Active protein kinase A phosphorylates and activates phosphorylase kinase. Phosphorylase kinase also can be activated partially by the Ca²⁺-calmodulin complex as Ca²⁺ levels increase as muscles contract. 4. Protein kinase A phosphorylates and inactivates glycogen synthase. 5. Active phosphorylase kinase converts glycogen phosphorylase b to glycogen phosphorylase a. 6. Glycogen degradation forms glucose 1-phosphate, which is converted to glucose 6-phosphate, which enters the glycolytic pathway for energy production.

produced does not enter the mitochondria but rather is converted to lactate such that glycolysis can continue). Thus, under these conditions, most of the pyruvate formed by glycolysis enters the TCA cycle whereas the remainder is reduced to lactate to regenerate NAD^+ for continued use in glycolysis.

5. FATE OF LACTATE RELEASED DURING EXERCISE

The lactate that is released from skeletal muscles during exercise can be used by resting skeletal muscles or by the heart, a muscle with a large amount of mitochondria and very high oxidative capacity. In such muscles, the NADH/NAD^+ ratio will be lower than in exercising skeletal muscle, and the lactate dehydrogenase reaction will proceed in the direction of pyruvate formation. The pyruvate that is generated is then converted to acetyl CoA and oxidized in the TCA cycle, producing energy by oxidative phosphorylation.

The second potential fate of lactate is that it will return to the liver through the Cori cycle, where it will be converted to glucose (see Fig. 22.10).

VI. MILD AND MODERATE-INTENSITY LONG-TERM EXERCISE

A. Lactate Release Decreases with Duration of Exercise

Mild to moderate-intensity exercise can be performed for longer periods than can high-intensity exercise. This is because of the aerobic oxidation of glucose and fatty acids, which generates more energy per fuel molecule than anaerobic metabolism, and which also produces acid at a slower rate than anaerobic metabolism. Thus, during mild and moderate-intensity exercise, the release of lactate diminishes as the aerobic metabolism of glucose and fatty acids becomes predominant.

B. Blood Glucose as a Fuel

At any given time during fasting, the blood contains only approximately 5 g glucose, enough to support a person running at a moderate pace for a few minutes. Therefore, the blood glucose supply must be constantly replenished. The liver performs this function by processes similar to those used during fasting. The liver produces glucose by breaking down its own glycogen stores and by gluconeogenesis. The major source of carbon for gluconeogenesis during exercise is, of course, lactate, produced by the exercising muscle, but amino acids and glycerol are also used (Fig. 47.11). Epinephrine released during exercise stimulates liver glycogenolysis and gluconeogenesis by causing cAMP levels to increase.

During long periods of exercise, blood glucose levels are maintained by the liver through hepatic glycogenolysis and gluconeogenesis. The amount of glucose that the liver must export is greatest at higher work loads, in which case the muscle is using a greater proportion of the glucose for anaerobic metabolism. With increasing duration of exercise, an increasing proportion of blood glucose is supplied by gluconeogenesis. However, for up to 40 minutes of mild exercise, glycogenolysis is mainly responsible for the glucose output of the liver. However, after 40 to 240 minutes of exercise, the total glucose output of the liver decreases. This is caused by the increased utilization of fatty acids, which are being released from adipose tissue triacylglycerols (stimulated by epinephrine release). Glucose uptake by the muscle is stimulated by the increase in AMP levels and the activation of the AMP-activated protein kinase, which stimulates the translocation of GLUT4 transporters to the muscle membrane.

The hormonal changes that direct the increased hepatic glycogenolysis, hepatic gluconeogenesis, and adipose tissue include a decrease in insulin and an increase in glucagon, epinephrine, and norepinephrine. Plasma levels of growth hormone, cortisol, and thyroid-stimulating hormone (TSH) also increase and may make a contribution to



If **Otto Shape** runs at a pace at which his muscles require approximately 500 Calories per hour, how long could he run on the amount of glucose that is present in circulating blood? Assume the blood volume is 5 liters.

A: Remember from Chapter 1 that a food Calorie is equivalent to 1 kcal of energy. One gram of glucose can give rise to 4 kcal of energy, so at a rate of consumption of 500 Calories per hour we have the following:

$$(500 \text{ Calories/hr}) \times (1 \text{ gram glucose}/4 \text{ Calories energy}) \times (1 \text{ hour}/60 \text{ minutes}) = 2 \text{ grams of glucose/min.}$$

Thus, Otto must use 2 grams of glucose per minute to run at his current pace. In the fasting state, blood glucose levels are approximately 90 mg/dL, or 900 mg/L. Because blood volume is estimated at 5 liters, Otto has 4.5 grams glucose available. If not replenished, that amount of glucose would only support 2.5 minutes of running, at 2 grams glucose per minute.

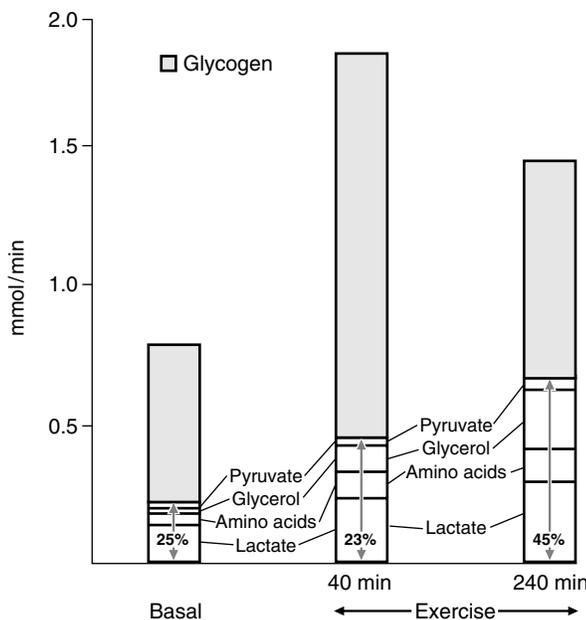


Fig. 47.11. Production of blood glucose by the liver from various precursors during rest and during prolonged exercise. The shaded area represents the contribution of liver glycogen to blood glucose, and the open area represents the contribution of gluconeogenesis. From Wahren J, et al. In: Howald H, Poortmans JR, eds. *Metabolic Adaptation to Prolonged Physical Exercise*. Cambridge, MA: Birkhauser, 1973:148.

fuel mobilization as well (see Chapter 43). The activation of hepatic glycogenolysis occurs through glucagon and epinephrine release. Hepatic gluconeogenesis is activated by the increased supply of precursors (lactate, glycerol, amino acids, and pyruvate), the induction of gluconeogenic enzymes by glucagon and cortisol (this only occurs in prolonged exercise), and the increased supply of fatty acids to provide the ATP and NADH needed for gluconeogenesis and the regulation of gluconeogenic enzymes.

C. Free Fatty Acids as a Source of ATP

The longer the duration of the exercise, the greater the reliance of the muscle on free fatty acids for the generation of ATP (Fig. 47.12). Because ATP generation from

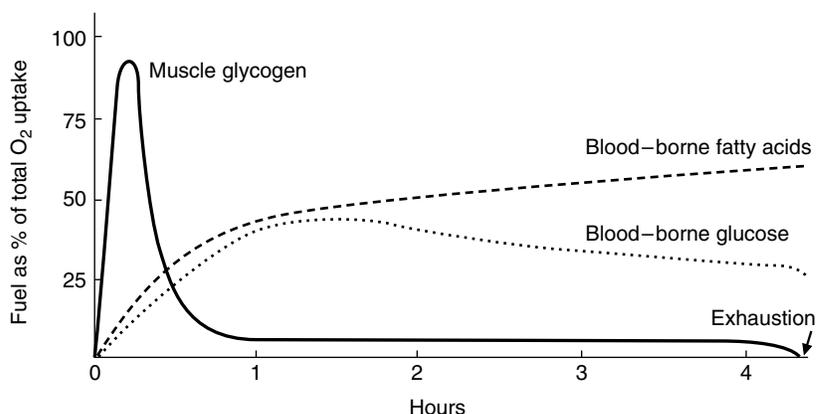


Fig. 47.12. Fuels used during exercise. The pattern of fuel utilization changes with the duration of the exercise. From Felig P, et al. *Endocrinology & Metabolism*. New York: McGraw-Hill, 1981:796.

free fatty acids depends on mitochondria and oxidative phosphorylation, long-distance running uses muscles that are principally slow-twitch oxidative fibers, such as the gastrocnemius. It is also important to realize that resting skeletal muscle uses free fatty acids as a principle fuel. At almost anytime except the postprandial state (right after eating), free fatty acids are the preferred fuel for skeletal muscle.

The preferential utilization of fatty acids over glucose as a fuel in skeletal muscle depends on the following factors:

1. The availability of free fatty acids in the blood, which depends on their release from adipose tissue triacylglycerols by hormone-sensitive lipase. During prolonged exercise, the small decrease of insulin, and increases of glucagon, epinephrine and norepinephrine, cortisol, and possibly growth hormone all activate adipocyte tissue lipolysis.
2. Inhibition of glycolysis by products of fatty acid oxidation. Pyruvate dehydrogenase activity is inhibited by acetyl CoA, NADH, and ATP, all of which are elevated as fatty acid oxidation proceeds. As AMP levels drop, and ATP levels rise, PFK-1 activity is decreased (see Chapter 22).
3. Glucose transport may be reduced during long-term exercise. Glucose transport into skeletal muscles via the GLUT 4 transporter is greatly activated by either insulin or exercise. During long-term exercise, the effect of falling insulin levels or increased fatty acid levels may counteract the stimulation of glucose transport by the exercise itself.
4. Ketone body oxidation also increases during exercise. Their utilization as a fuel is dependent on their rate of production by the liver. Ketone bodies are, however, never a major fuel for skeletal muscle (muscles prefer free fatty acids).
5. Acetyl-CoA carboxylase (isozyme ACC-2) must be inactivated for the muscle to use fatty acids. This occurs as the AMP-PK is activated and phosphorylates ACC-2, rendering it inactive.

D. Branched-Chain Amino Acids

Branched-chain amino acid oxidation has been estimated to supply a maximum of 20% of the ATP supply of resting muscle. Oxidation of branched-chain amino acids in muscle serves two functions. The first is the generation of ATP, and the second is the synthesis of glutamine, which effluxes from the muscle. The highest rates of branched-chain amino acid oxidation occur under conditions of acidosis, in which there is a higher demand for glutamine to transfer ammonia to the kidney and to buffer the urine as ammonium ion during proton excretion. Recall that glutamine synthesis occurs from the carbon skeletons of branched-chain amino acid oxidation (valine and isoleucine) after the initial five steps of the oxidative pathway.

E. The Purine Nucleotide Cycle

Exercise increases the activity of the purine nucleotide cycle, which converts aspartate to fumarate plus ammonia (see Fig. 41.13). The ammonia is used to buffer the proton production and lactate production from glycolysis, and the fumarate is recycled and can form glutamine.

F. Acetate

Acetate is an excellent fuel for skeletal muscle. It is treated by the muscle as a very-short-chain fatty acid. It is activated to acetyl CoA in the cytosol and then transferred into the mitochondria via acylcarnitine transferase, an isozyme of carnitine palmitoyl transferase. Sources of acetate include the diet (vinegar is acetic acid) and acetate produced in the liver from alcohol metabolism. Certain commercial power bars for athletes contain acetate.

VII. METABOLIC EFFECTS OF TRAINING ON MUSCLE METABOLISM

The effect of training depends, to some extent, on the type of training. In general, training increases the muscle glycogen stores and increases the number and size of mitochondria. The fibers thus increase their capacity for generation of ATP from oxidative metabolism and their ability to use fatty acids as a fuel. The winners in marathon races seem to use muscle glycogen more efficiently than others.

Training to improve strength, power, and endurance of muscle performance is called resistance training. Its goal is to increase the size of the muscle fibers (hypertrophy of the muscle). Muscle fibers can develop a maximal force of 3 to 4 kg/cm² of muscle area. Thus, if one can increase their muscle size from 80 to 120 cm², the maximal resistance that could be lifted would increase from 240 to 360 kg. Hypertrophy occurs by increased protein synthesis in the muscle and a reduction in existing protein turnover.

CLINICAL COMMENTS



Poststreptococcal glomerulonephritis (PSGN) may follow pharyngeal or cutaneous infection with one of a limited number of “nephritogenic” strains of group A β -hemolytic streptococci. The pathogenesis of PSGN involves a host immune (antibody) response to one or more of the enzymes secreted by the bacterial cells. The antigen–antibody complexes are deposited on the tissues of glomerular units, causing a local acute inflammatory response. Hypertension may occur as a consequence of sodium and water retention caused by an inability of the inflamed glomerular units to filter sodium and water into the urine. Proteinuria is usually mild if the immune response is self-limited.

Overall, one of the most useful clinical indicators of glomerular filtration rate in both health and disease is the serum creatinine concentration. The endogenous production of creatinine, which averages approximately 15 mg/kg of body weight per day, is correlated with muscle mass and, therefore, tends to be constant for a given individual if renal function is normal. Any rise in serum creatinine in patients such as **Rena Felya**, therefore, can be assumed to result from decreased excretion of this metabolite into the urine. The extent of the rise in the blood is directly related to the severity of the pathologic process involving the glomerular units within the kidneys.

BIOCHEMICAL COMMENTS



The SERCA pump is a transmembrane protein of 110 kDa present in several different isoforms throughout the body. Three genes encode SERCA proteins, designated SERCA1, SERCA2, and SERCA3. The SERCA1 gene produces two alternatively spliced transcripts, SERCA1a and SERCA1b. SERCA1b is expressed in the fetal and neonatal fast-twitch skeletal muscles, and is replaced by SERCA1a in adult fast-twitch muscle. The SERCA2 gene also undergoes alternative splicing, producing the SERCA2a and SERCA2b isoforms. The SERCA2b isoform is expressed in all cell types and is associated with inositol trisphosphate (IP₃)-regulated calcium stores. SERCA2a is the primary isoform expressed in cardiac tissue. SERCA3 produces at least five different alternatively spliced isoforms, which are specifically expressed in different tissues.

SERCA2a plays an important role in cardiac contraction and relaxation. Contraction is initiated by the release of calcium from intracellular stores, whereas relaxation

occurs as the calcium is re-sequestered in the sarcoplasmic reticulum, in part mediated by the SERCA2a protein. The SERCA2a pump is regulated, in part, by its association with the protein phospholamban (PLN). PLN is a pentameric molecule consisting of five identical subunits of molecular weight 22,000 Daltons. PLN associates with SERCA2a in the sarcoplasmic reticulum and reduces its pumping activity. Because new contractions cannot occur until cytosolic calcium has been re-sequestered into the sarcoplasmic reticulum, a reduction in SERCA2a activity increases the relaxation time. However, when called on, the heart can increase its rate of contractions by inhibiting the activity of phospholamban. This is accomplished by phosphorylation of phospholamban by protein kinase A (PKA). Epinephrine release stimulates the heart to beat faster. This occurs through epinephrine binding to its receptor, activating a G protein, which leads to adenylyl cyclase activation, elevation of cAMP levels, and activation of protein kinase A. PKA phosphorylates PLN, thereby reducing its association with SERCA2a and relieving the inhibition of pumping activity. This results in reduced relaxation times and more frequent contractions.

Mutations in PLN lead to cardiomyopathies, primarily an autosomal dominant form of dilated cardiomyopathy. This mutation leads to an arginine in place of cysteine at position 9 in PLN, which forms an inactive complex with PKA and blocks PKA phosphorylation of PLN. Individuals with this form of PLN develop cardiomyopathy in their teens. In this condition, the cardiac muscle does not pump well (because of the constant inhibition of SERCA2a), and becomes enlarged (dilated). Because of the poor pumping action of the heart, fluid can build up in the lungs. The pulmonary congestion results in a sense of breathlessness (left heart failure). Eventually, progressive left heart failure leads to fluid accumulation in other tissues and organs of the body, such as the legs and ankles (right heart failure).

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REVIEW QUESTIONS—CHAPTER 47

1. The process of stretching before exercise has which of the following biochemical benefits?
 - (A) Stimulates the release of epinephrine
 - (B) Activates glycolysis in the liver
 - (C) Increases blood flow to the muscles
 - (D) Activates glycolysis in the muscles
 - (E) Stimulates glycogenolysis in the liver
2. The major metabolic fuel for participating in a prolonged aerobic exercise event is which of the following?
 - (A) Liver glycogen
 - (B) Muscle glycogen
 - (C) Brain glycogen
 - (D) Adipose triacylglycerol
 - (E) Red blood cell–produced lactate

3. A 24-hour urine collection showed that an individual's excretion of creatinine was much lower than normal. Decreased excretion of creatinine could be caused by which of the following?
- (A) A decreased dietary intake of creatine
 - (B) A higher than normal muscle mass resulting from weight lifting
 - (C) A genetic defect in the enzyme that converts creatine phosphate to creatinine
 - (D) Kidney failure
 - (E) A vegetarian diet
4. In the biosynthetic pathways for the synthesis of heme, creatine, and guanine, which one of the following amino acids directly provides carbon atoms that appear in the final product?
- (A) Serine
 - (B) Aspartate
 - (C) Cysteine
 - (D) Glutamate
 - (E) Glycine
5. In skeletal muscle, increased hydrolysis of ATP during muscular contraction leads to which of the following?
- (A) A decrease in the rate of palmitate oxidation to acetyl CoA
 - (B) A decrease in the rate of NADH oxidation by the electron transport chain
 - (C) The activation of PFK-1
 - (D) An increase in the proton gradient across the inner mitochondrial membrane.
 - (E) The activation of glycogen synthase