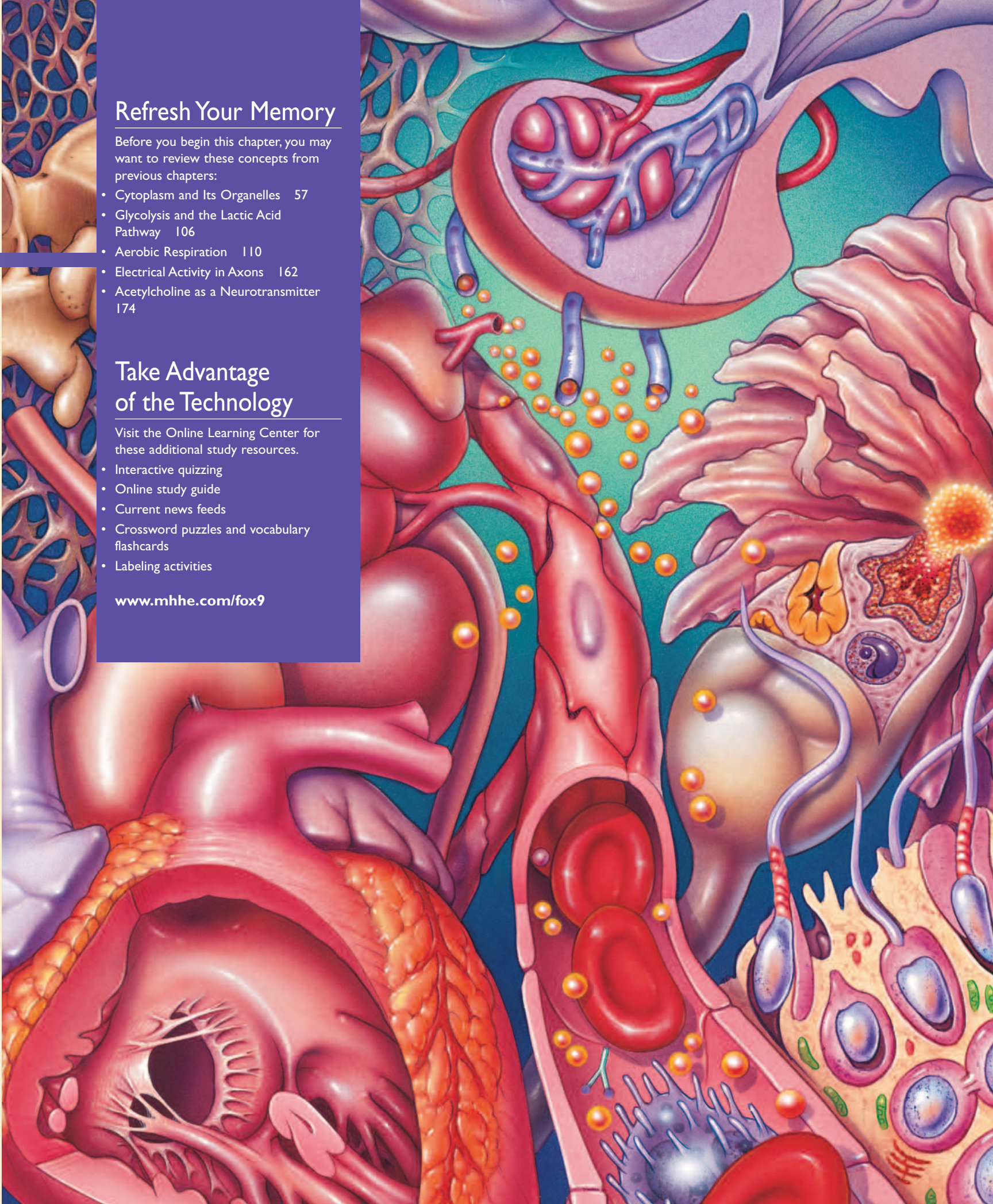
12 Muscle
Mechanisms of Contraction and Neural Control

Objectives

After studying this chapter, you should be able to . . .

1. describe the gross and microscopic structure of skeletal muscles.
2. describe the nature of a muscle twitch and explain how summation and tetanus are produced.
3. distinguish among isometric, isotonic, and eccentric contractions.
4. explain how the series-elastic component affects muscle contraction.
5. define the term *motor unit* and explain how motor units are used to control muscle contraction.
6. describe the structure of myofibrils and explain how it accounts for the striated appearance of skeletal muscle fibers.
7. explain what is meant by the sliding filament theory of contraction.
8. list the events that occur during cross-bridge cycles and describe the role of ATP in muscle contraction.
9. explain how tropomyosin and troponin control muscle contraction and relaxation, and describe the role of Ca^{2+} and the sarcoplasmic reticulum in excitation-contraction coupling.
10. describe the structure and functions of muscle spindles and explain the mechanisms involved in a stretch reflex.
11. describe the function of Golgi tendon organs and explain why a slow, gradual muscle stretch could avoid the spasm that may result from a rapid stretch.
12. explain what is meant by reciprocal innervation and describe the neural pathways involved in a crossed-extensor reflex.
13. explain the significance of gamma motoneurons in the neural control of muscle contraction and in the maintenance of muscle tone.
14. describe the neural pathways involved in the pyramidal and extrapyramidal systems.
15. explain the significance of the maximal oxygen uptake and describe the function of phosphocreatine in muscles.
16. explain how slow-twitch, fast-twitch, and intermediate fibers differ in structure and function.
17. describe skeletal muscle metabolism during exercise, and explain how muscles fatigue and how muscle fibers change as a result of physical training.
18. compare cardiac muscle and skeletal muscle in terms of structure and physiology.
19. describe the structure of smooth muscle and explain how its contraction is regulated.

Chapter at a Glance



Refresh Your Memory

Before you begin this chapter, you may want to review these concepts from previous chapters:

- Cytoplasm and Its Organelles 57
- Glycolysis and the Lactic Acid Pathway 106
- Aerobic Respiration 110
- Electrical Activity in Axons 162
- Acetylcholine as a Neurotransmitter 174

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Clinical Investigation

Maria, an energetic 40-year-old who plays softball and has been active in athletics most of her life, complains that she is experiencing fatigue and muscle pain and that her body just doesn't seem as limber as it should. Upon exercise testing, she is found to have a high maximal oxygen uptake. Her muscles, though not large, are well toned—perhaps excessively so. Laboratory tests reveal a normal blood level of creatine phosphokinase but an elevated blood Ca^{2+} concentration. She has hypertension, which is well controlled with a calcium channel-blocking drug.

What might be responsible for Maria's fatigue and muscle pain?

Table 12.1 Skeletal Muscle Actions

Category	Action
Extensor	Increases the angle at a joint
Flexor	Decreases the angle at a joint
Abductor	Moves limb away from the midline of the body
Adductor	Moves limb toward the midline of the body
Levator	Moves insertion upward
Depressor	Moves insertion downward
Rotator	Rotates a bone along its axis
Sphincter	Constricts an opening

Skeletal Muscles

Skeletal muscles are composed of individual muscle fibers that contract when stimulated by a motor neuron. Each motor neuron branches to innervate a number of muscle fibers, and all of these fibers contract when their motor neuron is activated. Activation of varying numbers of motor neurons, and thus varying numbers of muscle fibers, results in gradations in the strength of contraction of the whole muscle.

Skeletal muscles are usually attached to bone on each end by tough connective tissue tendons. When a muscle contracts, it shortens, and this places tension on its tendons and attached bones. The muscle tension causes movement of the bones at a joint, where one of the attached bones generally moves more than the other. The more movable bony attachment of the muscle, known as its *insertion,* is pulled toward its less movable attachment known as its *origin.* A variety of skeletal movements are possible, depending on the type of joint involved and the attachments of the muscles (table 12.1). When *flexor muscles* contract, for example, they decrease the angle of a joint. Contraction of *extensor muscles* increases the angle of their attached bones at the joint. The prime mover of any skeletal movement is called the **agonist muscle;** in flexion, for example, the flexor is the agonist muscle. Flexors and extensors that act on the same joint to produce opposite actions are **antagonistic muscles.**

Structure of Skeletal Muscles

The fibrous connective tissue proteins within the tendons extend around the muscle in an irregular arrangement, forming a sheath known as the *epimysium* (*epi* = above; *my* = muscle). Connective tissue from this outer sheath extends into the body of the muscle, subdividing it into columns, or *fascicles* (these are the "strings" in stringy meat). Each of these fascicles is thus surrounded by its own connective tissue sheath, which is known as the *perimysium* (*peri* = around).

Dissection of a muscle fascicle under a microscope reveals that it, in turn, is composed of many **muscle fibers,** or *myofibers.* Each is surrounded by a plasma membrane, or **sarcolemma,** enveloped by a thin connective tissue layer called an *endomysium* (fig. 12.1). Since the connective tissue of the tendons, epimysium, perimysium, and endomysium is continuous, muscle fibers do not normally pull out of the tendons when they contract.

CLINICAL

Duchenne's muscular dystrophy is the most severe of the muscular dystrophies, afflicting 1 out of 3,500 boys each year. This disease, inherited as an X-linked recessive trait, involves progressive muscular wasting; patients are usually confined to a wheelchair by age 12 and may die in their 20s. The product of the defective genes is a protein called *dystrophin,* which is just under the sarcolemma (plasma membrane of the muscle fiber). Dystrophin provides support for the muscle fiber by bridging the cytoskeleton and myofibrils in the fiber (fig. 12.1) with the extracellular matrix. When dystrophin is defective, muscle wasting occurs. Using this information, scientists have recently developed laboratory tests that can detect this disease in fetal cells obtained by amniocentesis. This research has been aided by the development of a strain of mice that exhibit an equivalent form of the disease. When the "good genes" for dystrophin are inserted into mouse embryos of this strain, the mice do not develop the disease. Insertion of the gene into large numbers of mature muscle cells, however, is more difficult, and so far has met with only limited success.

Despite their unusual elongated shape, muscle fibers have the same organelles that are present in other cells: mitochondria, endoplasmic reticulum, glycogen granules, and others. Unlike most other cells in the body, skeletal muscle fibers are multinucleate—that is, they contain multiple nuclei. This is because, as described in chapter 1, each muscle fiber is a syncytial structure. That is, each muscle fiber is formed from the union of several embryonic myoblast cells. The most distinctive feature of skeletal muscle fibers, however, is their **striated** appearance when viewed microscopically (fig. 12.2). The striations (stripes) are produced by alternating dark and light bands that appear to span the width of the fiber.

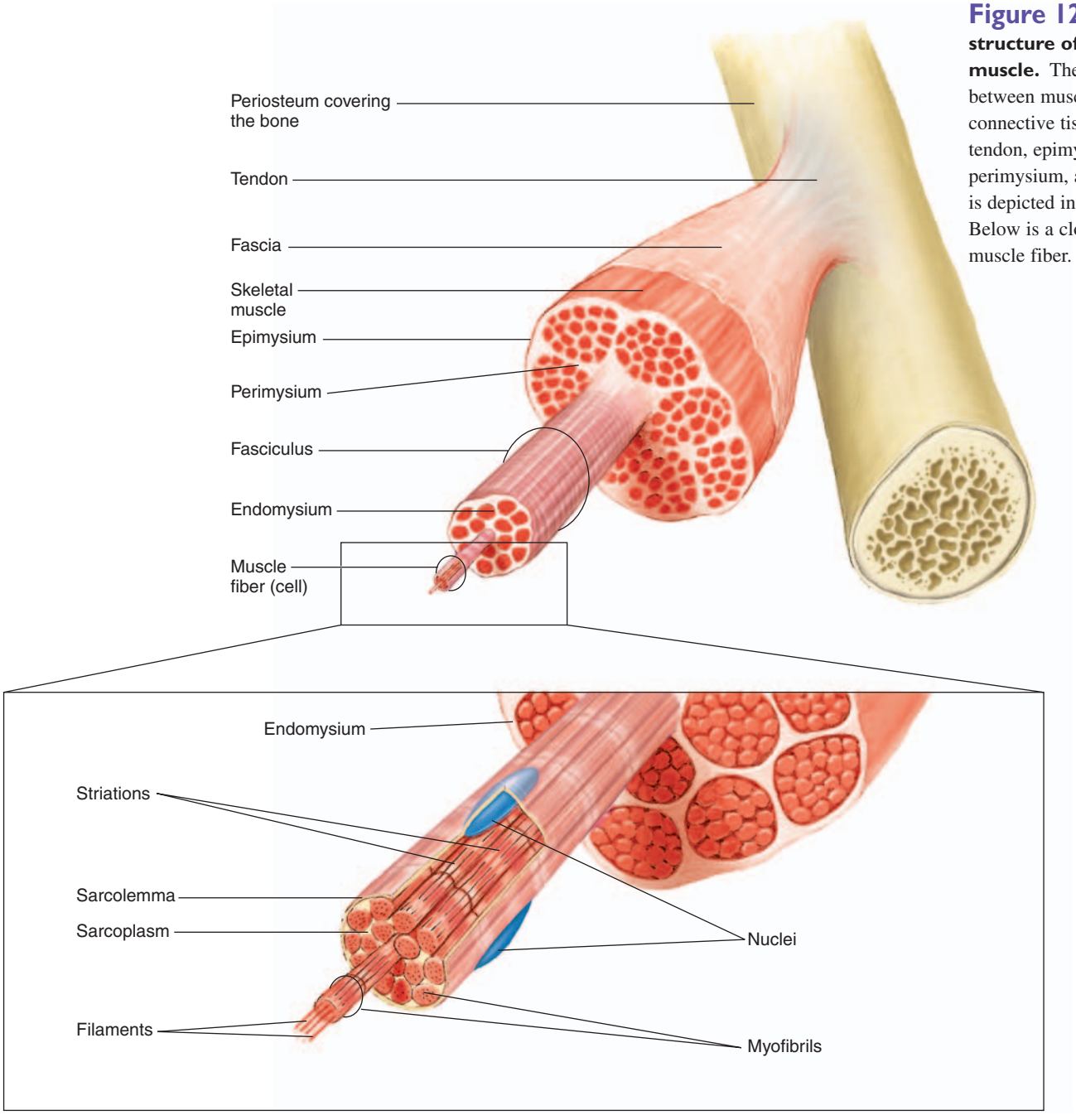


Figure 12.1 **The structure of a skeletal muscle.** The relationship between muscle fibers and the connective tissues of the tendon, epimysium, perimysium, and endomysium is depicted in the upper figure. Below is a close-up of a single muscle fiber.

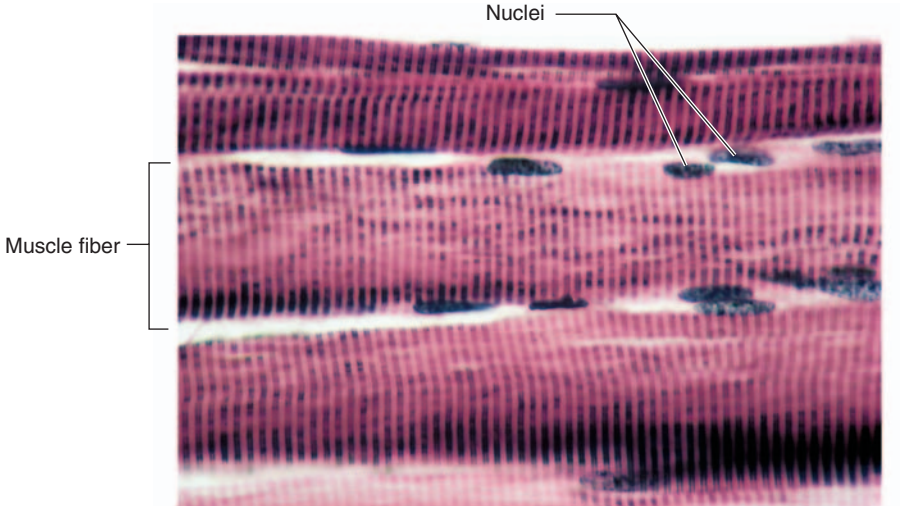


Figure 12.2 **The appearance of skeletal muscle fibers through the light microscope.** The striations are produced by alternating dark A bands and light I bands. (Note the peripheral location of the nuclei.)

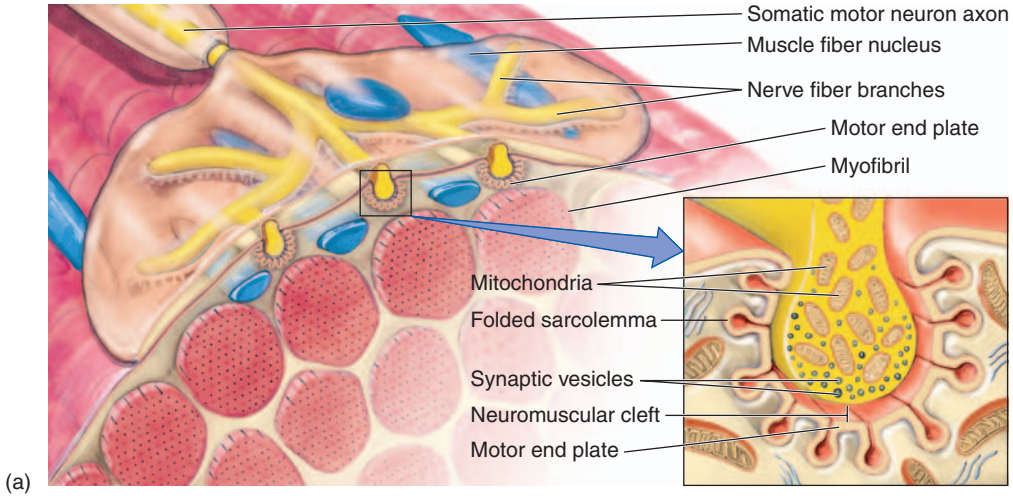
The dark bands are called **A bands,** and the light bands are called **I bands.** At high magnification in an electron microscope, thin dark lines can be seen in the middle of the I bands. These are called **Z lines** (see fig. 12.6). The labels A, I, and Z—derived in the course of early muscle research—are useful for describing the functional architecture of muscle fibers. The letters *A* and *I* stand for *anisotropic* and *isotropic,* respectively, which indicate the behavior of polarized light as it passes through these regions; the letter Z comes from the German word *Zwischenscheibe,* which translates to "between disc." These derivations are of historical interest only.

Motor Units

In vivo, each muscle fiber receives a single axon terminal from a somatic motor neuron. The motor neuron stimulates the muscle fiber to contract by liberating acetylcholine at the neuromuscular junction (described in chapter 7). The specialized region of the sarcolemma of the muscle fiber at the neuromuscular junction is known as a **motor end plate** (fig. 12.3).

CLINICAL

The acetylcholine (ACh) released by the axon terminals diffuses across the synaptic cleft and binds to ACh receptors in the plasma membrane of the end plate, thereby stimulating the muscle fiber. Prior to its release, the ACh is contained in synaptic vesicles that dock and fuse with the plasma membrane of the axon terminal and undergo exocytosis (see chapter 7, fig. 7.22). The potentially deadly **botulinum toxin,** produced by the bacteria *Clostridium botulinum,* is selectively taken into cholinergic nerve endings and cleaves the proteins needed for the exocytosis of the synaptic vesicles. This blocks nerve stimulation of the muscles, producing a flaccid paralysis. Interestingly, botulinum toxin is now used medically in certain cases to relieve muscle spasms due to excessive nerve stimulation. For example, it is injected into an affected extraocular muscle in order to help correct *strabismus* (deviation of the eye). Intramuscular injections of **Botox** (a brand name for botulinum toxin) are also given for the temporary cosmetic treatment of skin wrinkles.



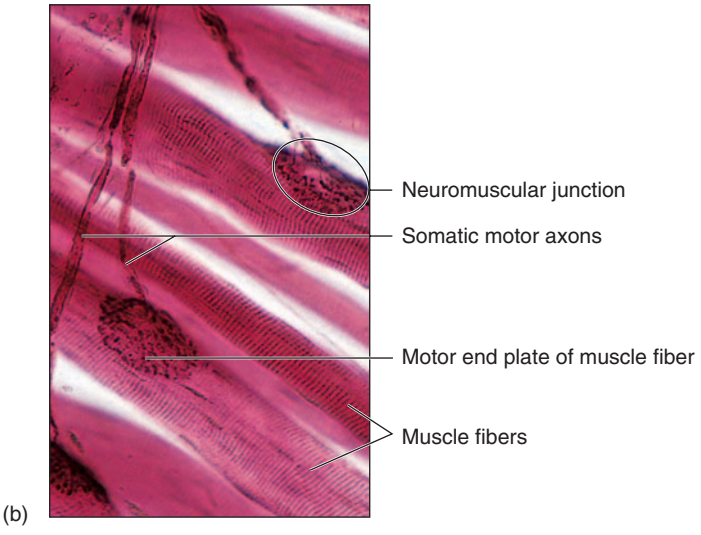


Figure 12.3 Motor end plates at the neuromuscular junction. The neuromuscular junction is the synapse between the nerve fiber and muscle fiber. The motor end plate is the specialized portion of the sarcolemma of a muscle fiber surrounding the terminal end of the axon. (*a*) An illustration of the neuromuscular junction. Notice the slight gap between the membrane of the axon and that of the muscle fiber. (*b*) A photomicrograph of muscle fibers and neuromuscular junctions.

The cell body of a somatic motor neuron is located in the ventral horn of the gray matter of the spinal cord and gives rise to a single axon that emerges in the ventral root of a spinal nerve (chapter 8). Each axon, however, can produce a number of collateral branches to innervate an equal number of muscle fibers. Each somatic motor neuron, together with all of the muscle fibers that it innervates, is known as a **motor unit** (fig. 12.4).

Whenever a somatic motor neuron is activated, all of the muscle fibers that it innervates are stimulated to contract. In vivo, graded contractions of whole muscles are produced by variations in the number of motor units that are activated. In order for these graded contractions to be smooth and sustained, different motor units must be activated by rapid, asynchronous stimulation.

Fine neural control over the strength of muscle contraction is optimal when there are many small motor units involved. In the extraocular muscles that position the eyes, for example, the *innervation ratio* (motor neuron:muscle fibers) of an average motor unit is one neuron per twenty-three muscle fibers. This affords a fine degree of control. The innervation ratio of the gastrocnemius, by contrast, averages one neuron per thousand muscle fibers. Stimulation of these motor units results in more powerful contractions at the expense of finer gradations in contraction strength.

All of the motor units controlling the gastrocnemius, however, are not the same size. Innervation ratios vary from 1:100 to 1:2,000. A neuron that innervates fewer muscle fibers has a smaller cell body and is stimulated by lower levels of excitatory input than a larger neuron that innervates a greater number of muscle fibers. The smaller motor units, as a result, are the ones that are used most often. When contractions of greater strength are required, larger and larger motor units are activated in a process known as **recruitment** of motor units.

Test Yourself Before You Continue

1. Describe the actions of muscles when they contract, and define the terms *agonist* and *antagonist* in muscle action.
2. Describe the different levels of muscle structure, explaining how the muscle and its substructures are packaged in connective tissues.
3. Define the terms *motor unit* and *innervation ratio* as they relate to muscle function, and draw a simple diagram of a motor unit with a 1:5 innervation ratio.
4. Using the concept of recruitment, explain how muscle contraction can be graded in its strength.

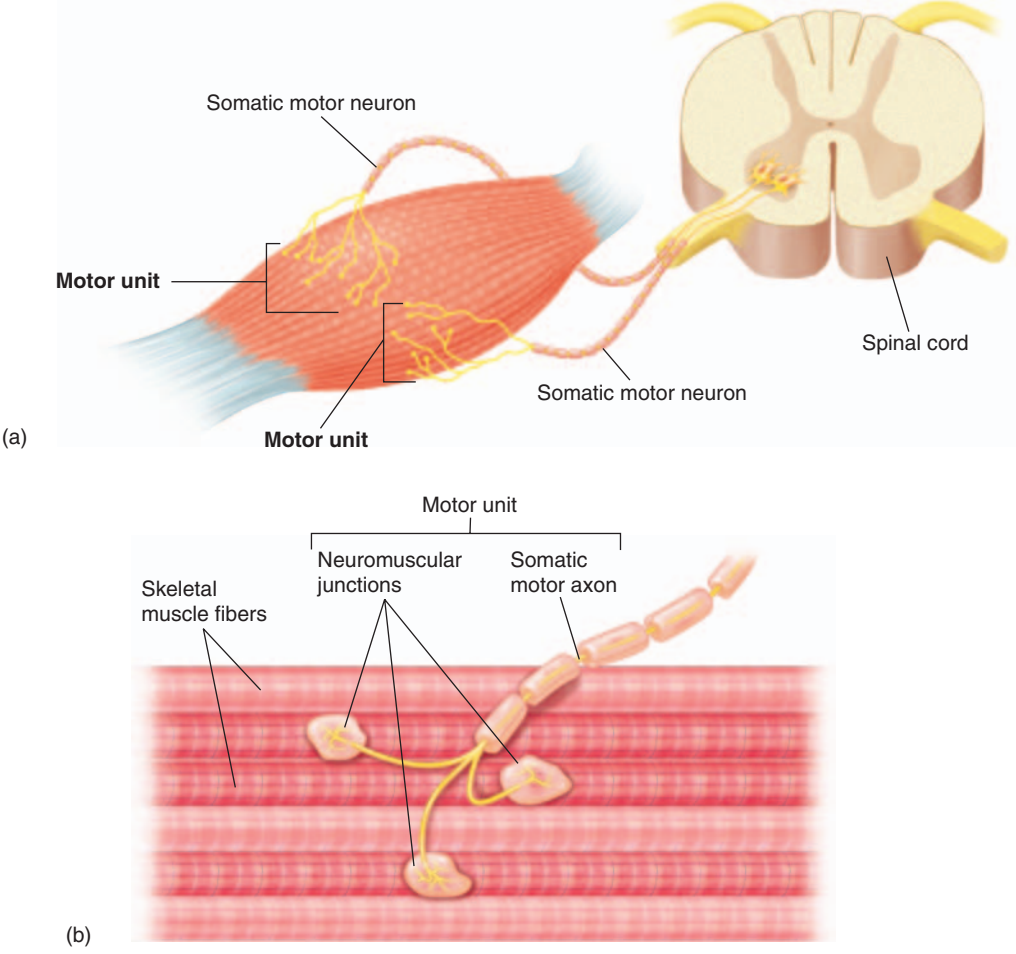


Figure 12.4 Motor units. A motor unit consists of a somatic motor neuron and the muscle fibers it innervates. (*a*) Illustration of a muscle containing two motor units. In reality, a muscle would contain many hundreds of motor units, and each motor unit would contain many more muscle fibers than are shown here. (*b*) A single motor unit consisting of a branched motor axon and the three muscle fibers it innervates (the fibers that are highlighted) is depicted. The other muscle fibers would be part of different motor units and would be innervated by different neurons (not shown).

Mechanisms of Contraction

The A bands within each muscle fiber are composed of thick filaments and the I bands contain thin filaments. Movement of cross bridges that extend from the thick to the thin filaments causes sliding of the filaments, and thus muscle tension and shortening.The activity of the cross bridges is regulated by the availability of Ca^{2+}, which is increased by electrical stimulation of the muscle fiber. Electrical stimulation produces contraction of the muscle through the binding of Ca^{2+} to regulatory proteins within the thin filaments.

When muscle cells are viewed in the electron microscope, which can produce images at several thousand times the magnification possible in an ordinary light microscope, each cell is seen to be composed of many subunits known as **myofibrils** (*fibrils* = little fibers) (fig. 12.5). These myofibrils are approximately 1 micrometer (1 μm) in diameter and extend in parallel rows from one end of the muscle fiber to the other. The myofibrils are so densely packed that other organelles, such as mitochondria and intracellular membranes, are restricted to the narrow cytoplasmic spaces that remain between adjacent myofibrils.

With the electron microscope, it can be seen that the muscle fiber does not have striations that extend from one side of the fiber to the other. It is the myofibrils that are striated with dark *A bands* and light *I bands* (fig. 12.6). The striated appearance of the entire muscle fiber when seen with a light microscope is an illusion created by the alignment of the dark and light bands of the myofibrils from one side of the fiber to the other. Since the separate myofibrils are not clearly seen at low magnification, the dark and light bands appear to be continuous across the width of the fiber.

Each myofibril contains even smaller structures called **myofilaments,** or simply **filaments.** When a myofibril is observed at high magnification in longitudinal section (side view), the A bands are seen to contain **thick filaments.** These are about 110 angstroms thick (110 Å, where 1 Å = 10^{-10} m) and are stacked in register. It is these thick filaments that give the A band its dark appearance. The lighter I band, by contrast, contains **thin filaments** (from 50 to 60 Å thick). The thick filaments are primarily composed of the protein **myosin,** and the thin filaments are primarily composed of the protein **actin.**

The I bands within a myofibril are the lighter areas that extend from the edge of one stack of thick filaments to the edge of the next stack of thick filaments. They are light in appearance because they contain only thin filaments. The thin filaments, however, do not end at the edges of the I bands. Instead, each thin filament extends partway into the A bands on each side (between the stack of thick filaments on each side of an I band). Since thick and thin filaments overlap at the edges of each A band, the edges of the A band are darker in appearance than the central region. These central lighter regions of the A bands are called the *H bands* (for *helle,* a German word meaning "bright"). The central H bands thus contain only thick filaments that are not overlapped by thin filaments.

In the center of each I band is a thin dark Z line. The arrangement of thick and thin filaments between a pair of Z lines forms a repeating pattern that serves as the basic subunit of striated muscle contraction. These subunits, from Z to Z, are known as **sarcomeres** (fig. 12.7*a*). A longitudinal section of a myofibril thus presents a side view of successive sarcomeres.

This side view is, in a sense, misleading; there are numerous sarcomeres within each myofibril that are out of the plane of the section (and out of the picture). A better appreciation of the three-dimensional structure of a myofibril can be obtained by viewing the myofibril in cross section. In this view, it can be seen that the Z lines are actually **Z discs,** and that the thin filaments

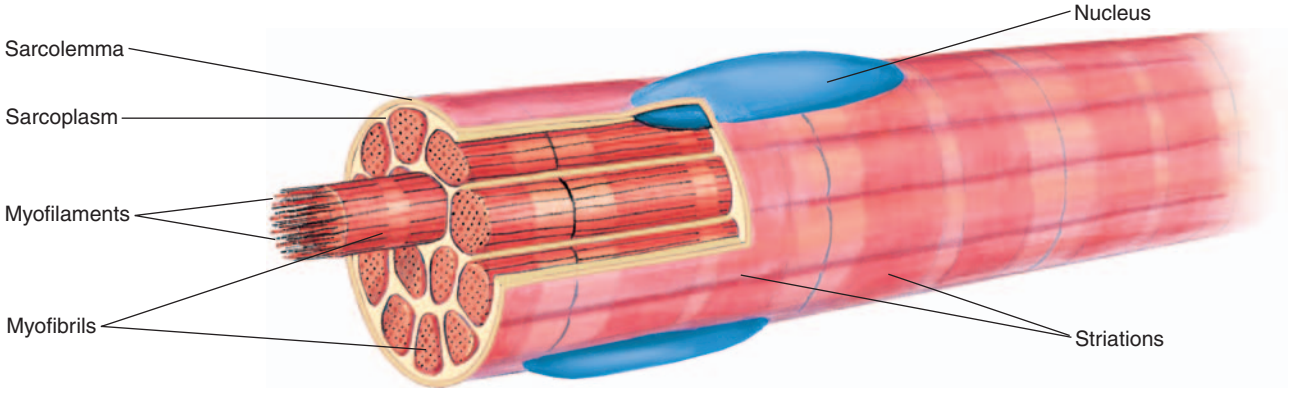


Figure 12.5 **The components of a skeletal muscle fiber.** A skeletal muscle fiber is composed of numerous myofibrils that contain myofilaments of actin and myosin. Overlapping of the myofilaments produces a striated appearance. Each skeletal muscle fiber is multinucleated.

that penetrate these Z discs surround the thick filaments in a hexagonal arrangement (fig. 12.7*b, right*). If we concentrate on a single row of dark thick filaments in this cross section, the alternating pattern of thick and thin filaments seen in longitudinal section becomes apparent.

Figure 12.8 indicates two structures not shown in the previous sarcomere figures. The **M lines** are produced by protein filaments located at the center of the thick filaments (and thus the A band) in a sarcomere. These serve to anchor the thick filaments, helping them to stay together during a contraction. Also shown are filaments of **titin,** a type of elastic protein that runs through the thick filaments from the M lines to the Z discs. Because of its elastic properties, titin is believed to contribute to the elastic recoil of muscles that helps them to return to their resting length during muscle relaxation.

Sliding Filament Theory of Contraction

When a muscle contracts it decreases in length as a result of the shortening of its individual fibers. Shortening of the muscle fibers, in turn, is produced by shortening of their myofibrils, which occurs as a result of the shortening of the distance from Z line to Z line. As the sarcomeres shorten in length, however, the A bands do *not* shorten but instead move closer together. The I bands—which represent the distance between A bands of successive sarcomeres—decrease in length (table 12.2).

The thin filaments composing the I band, however, do not shorten. Close examination reveals that the thick and thin filaments remain the same length during muscle contraction.

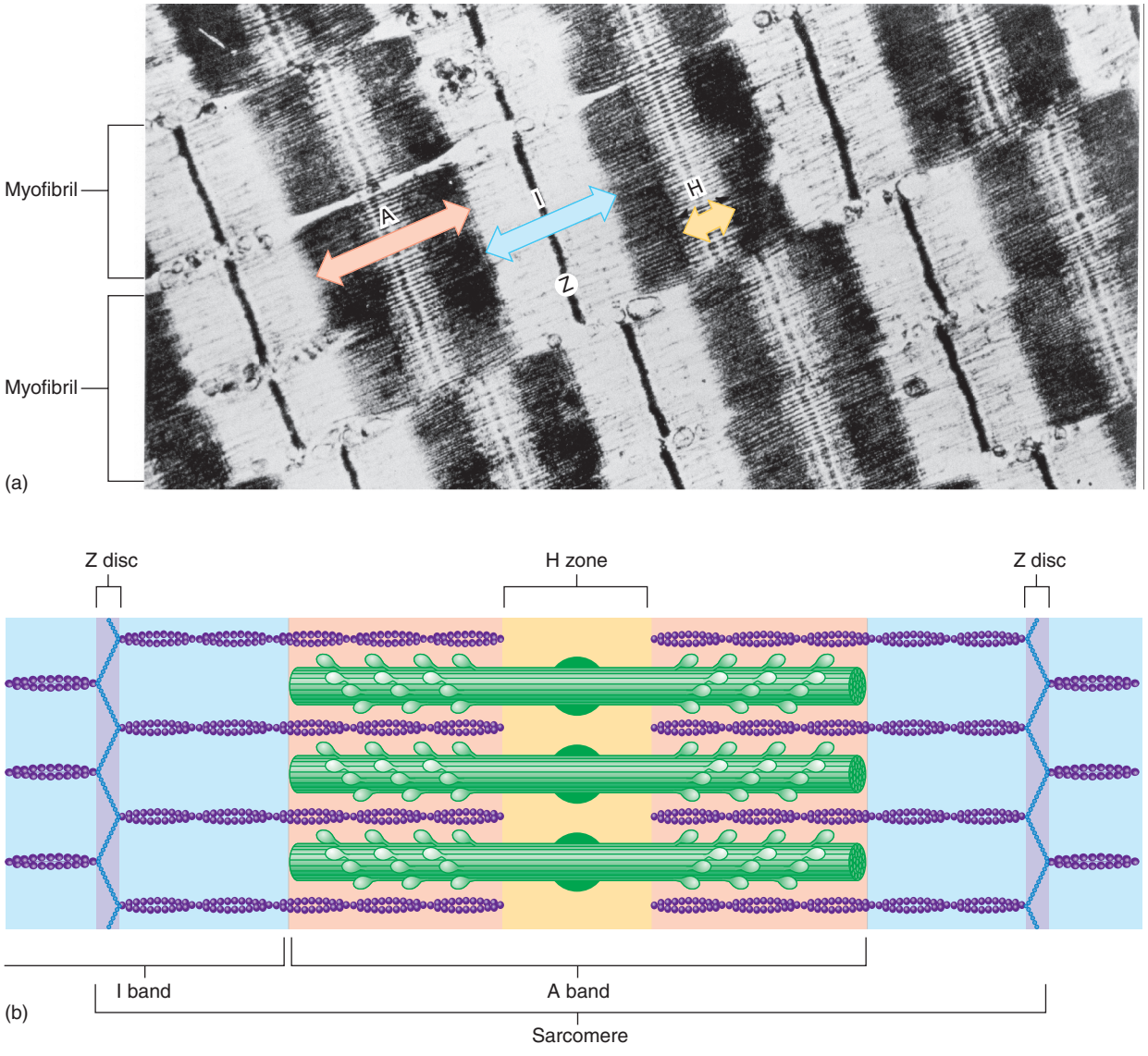


Figure 12.6 **The striations of skeletal muscles are produced by thick and thin filaments.** (*a*) Electron micrograph of a longitudinal section of myofibrils, showing the banding pattern characteristic of striated muscle. (*b*) Illustration of the arrangement of thick and thin filaments that produces the banding pattern. The colors used in (*a*) to depict different bands and structures correspond to the colors of (*b*).

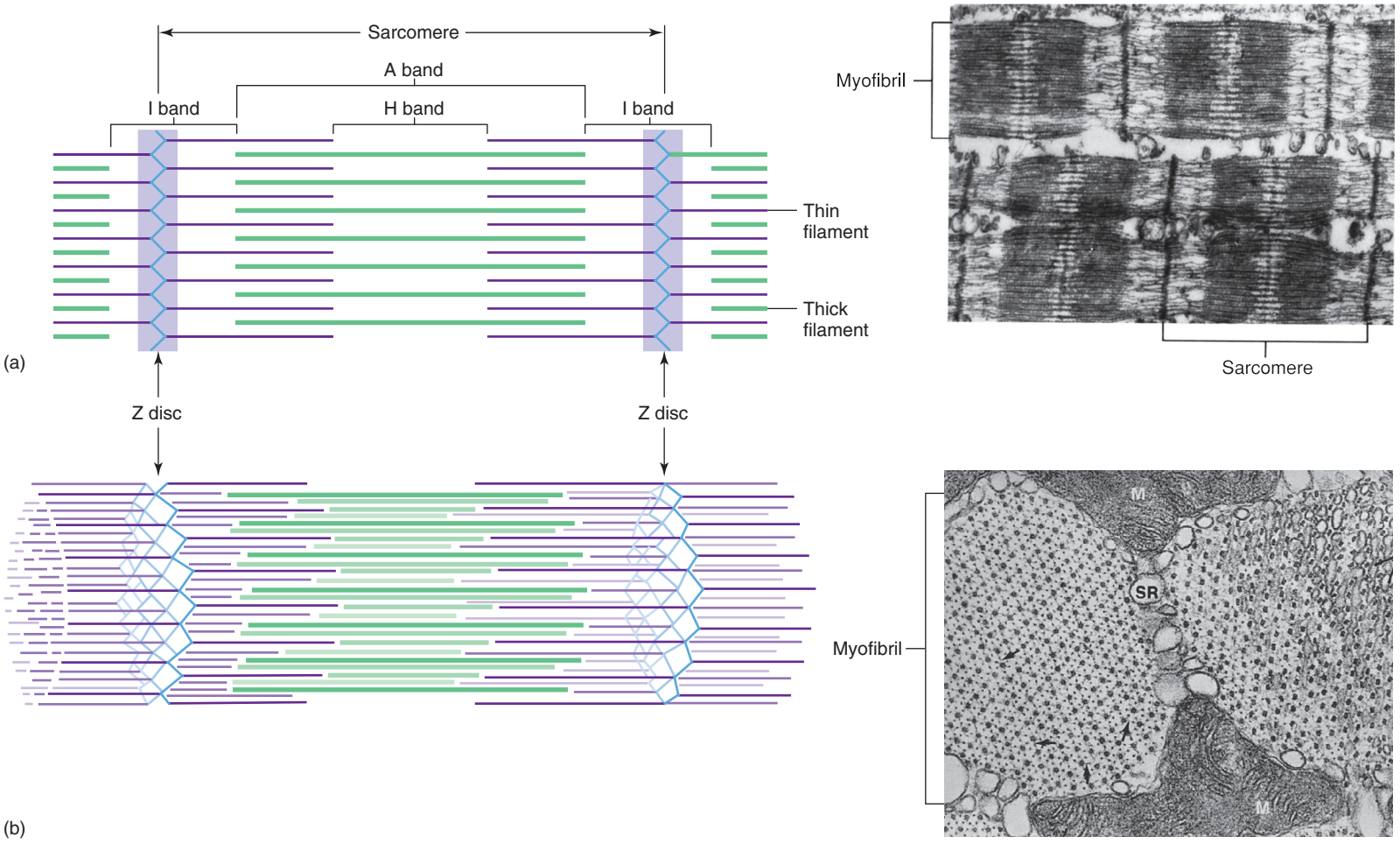


Figure 12.7 **Arrangement of thick and thin filaments in a striated muscle fiber.** *(a)* In a longitudinal section, the thick and thin filaments are seen to form repeating units called sarcomeres. The banding patterns of the sarcomeres are labeled I, A, and H, as shown. A corresponding electron micrograph (53,000×) is shown to the right of the illustration. *(b)* The three-dimensional structure of the sarcomeres is illustrated. This three-dimensional structure can be seen in a cross section of a myofibril taken through a region of overlapping thick and thin filaments. In the electron micrograph, the arrows point to cross bridges between the thick filaments (dark dots) and thin filaments (light dots). (SR = sarcoplasmic reticulum; M = mitochondria).

Electron micrographs (right) from R. G. Kessel and R. H. Kardon, *Tissues and Organs: A Test-Atlas of Scanning Electron Microscopy,* 1979, W. H. Freeman & Company.

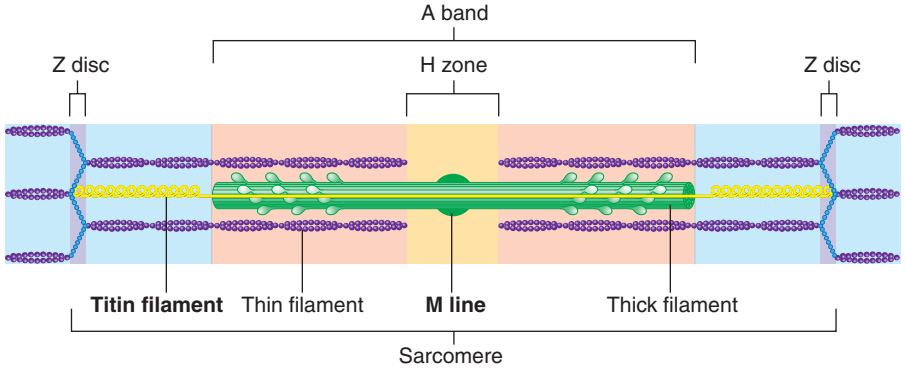


Figure 12.8 **Titin filaments and M lines.** The M lines are protein filaments in the middle of the A bands that join thick filaments together. Titin proteins are elastic proteins of extremely large size that run through the thick filaments, beginning at the M lines and ending at the Z discs. These stabilize the position of each thick filament within the sarcomere and serve as elastic elements that help muscles return to their resting length.

Table 12.2 Summary of the Sliding Filament Theory of Contraction

1. A myofiber, together with all its myofibrils, shortens by movement of the insertion toward the origin of the muscle.
2. Shortening of the myofibrils is caused by shortening of the sarcomeres— the distance between Z lines (or discs) is reduced.
3. Shortening of the sarcomeres is accomplished by sliding of the myofilaments— the length of each filament remains the same during contraction.
4. Sliding of the filaments is produced by asynchronous power strokes of myosin cross bridges, which pull the thin filaments (actin) over the thick filaments (myosin).
5. The A bands remain the same length during contraction, but are pulled toward the origin of the muscle.
6. Adjacent A bands are pulled closer together as the I bands between them shorten.
7. The H bands shorten during contraction as the thin filaments on the sides of the sarcomeres are pulled toward the middle.

Shortening of the sarcomeres is produced not by shortening of the filaments, but rather by the *sliding* of thin filaments over and between the thick filaments. In the process of contraction, the thin filaments on either side of each A band slide deeper and deeper toward the center, producing increasing amounts of overlap with the thick filaments. The I bands (containing only thin filaments) and H bands (containing only thick filaments) thus get shorter during contraction (fig. 12.9).

Cross Bridges

Sliding of the filaments is produced by the action of numerous **cross bridges** that extend out from the myosin toward the actin. These cross bridges are part of the myosin proteins that extend from the axis of the thick filaments to form "arms" that terminate in globular "heads" (fig. 12.10). A myosin protein has two globular heads that serve as cross bridges. The orientation of the myosin heads on one side of a sarcomere is opposite to that of the other side, so that, when the myosin heads form cross bridges by

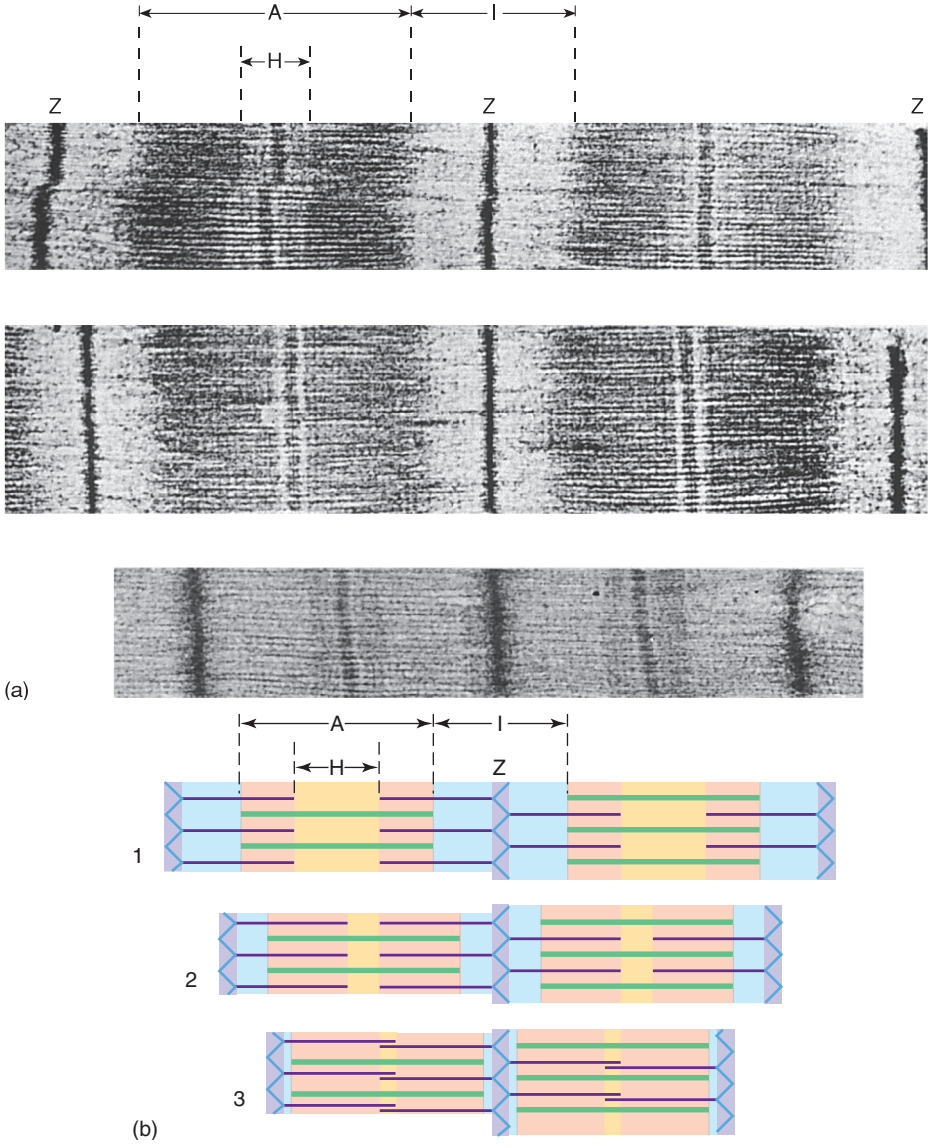


Figure 12.9 **The sliding filament model of muscle contraction.** (*a*) An electron micrograph and (*b*) a diagram of the sliding filament model of contraction. As the filaments slide, the Z lines are brought closer together and the sarcomeres get shorter. (*1*) Relaxed muscle; (*2*) partially contracted muscle; (*3*) fully contracted muscle.

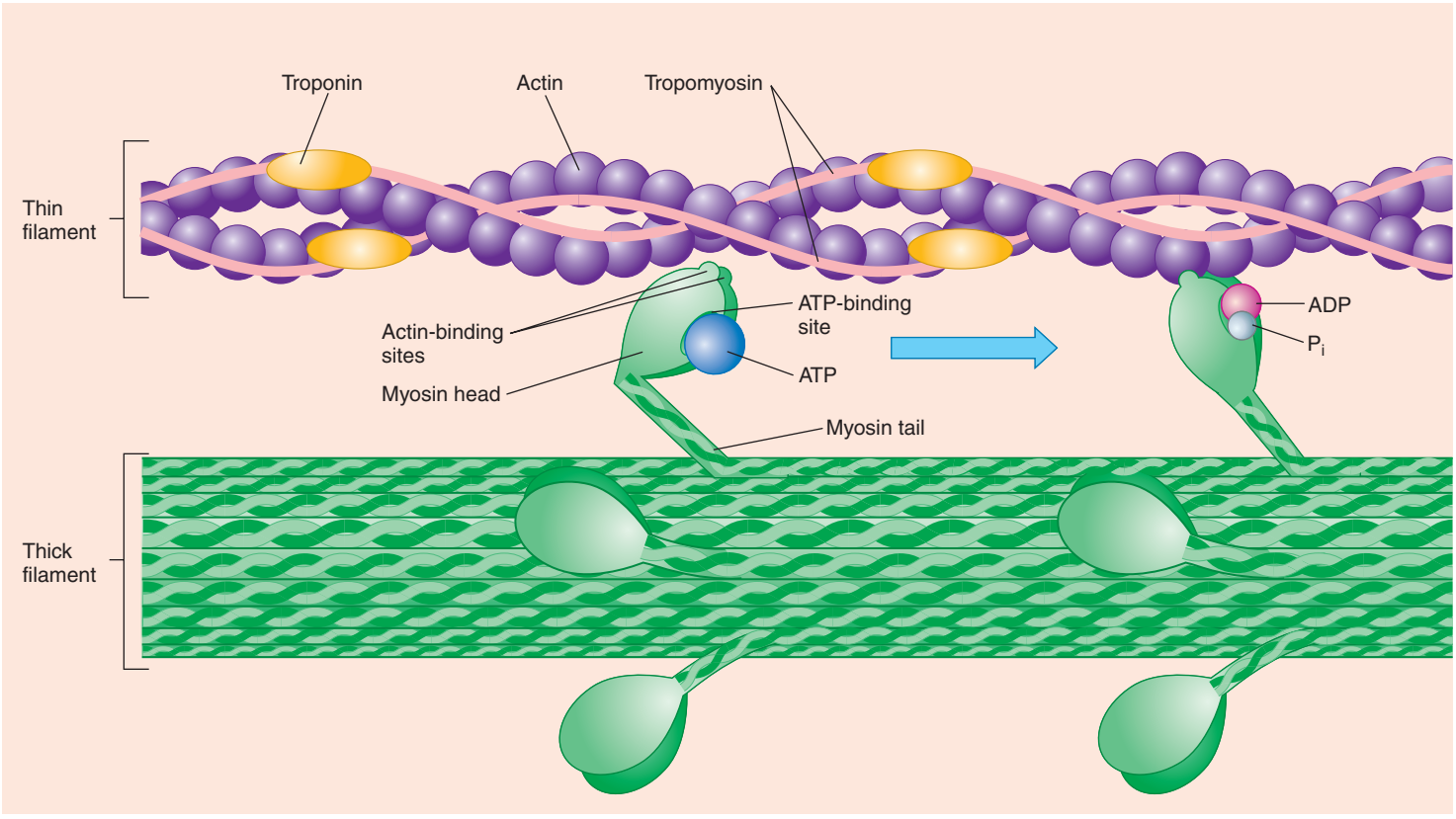


Figure 12.10 **The structure of myosin, showing its binding sites for ATP and actin.** Once the myosin head binds to ATP, it is hydrolyzed into ADP and inorganic phosphate (P_i). This activates the myosin head, "cocking it" to put it into position to bind to attachment sites in the actin molecules.

attaching to actin on each side of the sarcomere, they can pull the actin from each side toward the center.

Isolated muscles are easily stretched (although this is opposed in the body by the stretch reflex, described in a later section), demonstrating that the myosin heads are not attached to actin when the muscle is at rest. Each globular myosin head of a cross bridge contains an ATP-binding site closely associated with an actin-binding site (fig. 12.10, *left*). The globular heads function as **myosin ATPase** enzymes, splitting ATP into ADP and P_i.

This reaction must occur *before* the myosin heads can bind to actin. When ATP is hydrolyzed to ADP and P_i, the myosin head "cocks" (by analogy to the hammer of a gun), putting it into position to bind to actin (fig. 12.10, *right*).

Once the myosin head binds to actin, forming a cross bridge, the bound P_i is released. This results in a conformational change in the myosin, causing the cross bridge to produce a **power stroke** (fig. 12.11). This is the force that pulls the thin filaments toward the center of the A band.

After the power stroke, with the myosin head now in its flexed position, the bound ADP is released as a new ATP molecule binds to the myosin head. This release of ADP and binding to a new ATP is required in order for the myosin head to break its bond with actin after the power stroke is completed. If this process were prevented, the myosin heads would remain bound to the actin (see the Clinical box discussion of rigor mortis). The myosin head will then split ATP to ADP and P_i, and—if nothing prevents the binding of the myosin head to the actin—a new cross-bridge cycle will occur (fig. 12.12).

Note that the splitting of ATP is required *before* a cross bridge can attach to actin and undergo a power stroke, and that the attachment of a *new ATP* is needed for the cross bridge to release from actin at the end of a power stroke (fig. 12.12).

CLINICAL

The detachment of a cross bridge from actin at the end of a power stroke requires that a new ATP molecule bind to the myosin ATPase. The importance of this process is illustrated by the muscular contracture called **rigor mortis** that occurs due to lack of ATP when the muscle dies. Without ATP, the ADP remains bound to the cross bridges, and the cross bridges remain tightly bound to actin. This results in the formation of "rigor complexes" between myosin and actin that cannot detach. In rigor mortis, the muscles remain stiff until the myosin and actin begin to decompose.

Because the cross bridges are quite short, a single contraction cycle and power stroke of all the cross bridges in a muscle would shorten the muscle by only about 1% of its resting length. Since muscles can shorten up to 60% of their resting lengths, it is

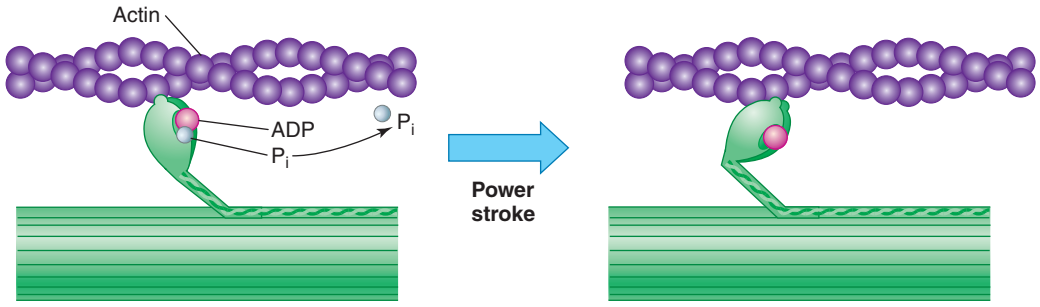


Figure 12.11 **The power stroke of the cross bridge.** After the myosin head binds to actin to form a cross bridge, inorganic phosphate (P_i) is released. This causes a conformational change in the myosin head, resulting in a power stroke that produces sliding of the thin filament over the thick filament.

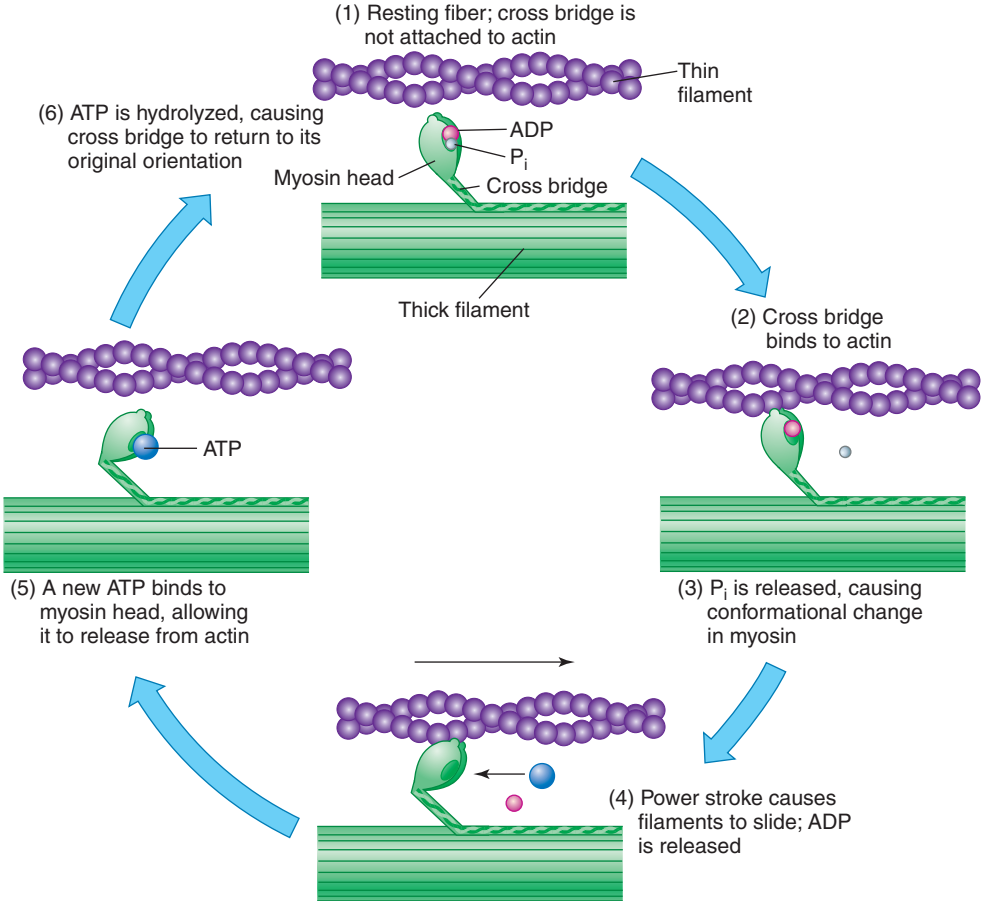


Figure 12.12 **The cross-bridge cycle that causes sliding of the filaments and muscle contraction.** Hydrolysis of ATP is required for activation of the cross bridge, and the binding of a new ATP is required for the cross bridge to release from the actin at the end of a cycle.

obvious that the contraction cycles must be repeated many times. In order for this to occur, the cross bridges must detach from the actin at the end of a power stroke, reassume their resting orientation, and then reattach to the actin and repeat the cycle.

During normal contraction, however, only a portion of the cross bridges are attached at any given time. The power strokes are thus not in synchrony, as the strokes of a competitive rowing team would be. Rather, they are like the actions of a team engaged in tug-of-war, where the pulling action of the members is asynchronous. Some cross bridges are engaged in power strokes at all times during the contraction.

Regulation of Contraction

When the cross bridges attach to actin, they undergo power strokes and cause muscle contraction. In order for a muscle to relax, therefore, the attachment of myosin cross bridges to actin must be prevented. The regulation of cross-bridge attachment to actin is a function of two proteins that are associated with actin in the thin filaments.

The actin filament—or *F-actin*—is a polymer formed of 300 to 400 globular subunits (*G-actin*), arranged in a double row and twisted to form a helix (fig. 12.13). A different type of protein,

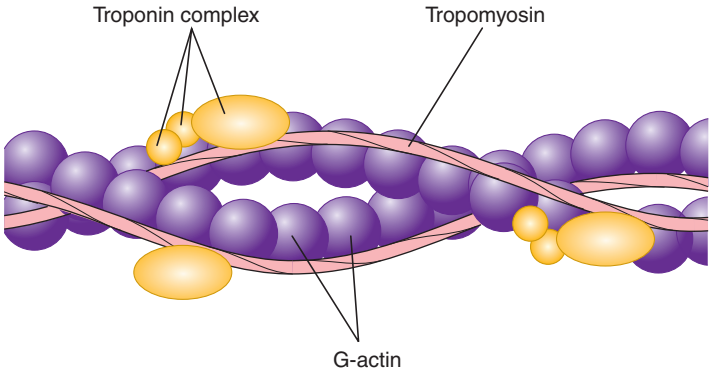


Figure 12.13 The structural relationship between troponin, tropomyosin, and actin. The tropomyosin is attached to actin, whereas the troponin complex of three subunits is attached to tropomyosin (not directly to actin).

known as **tropomyosin,** lies within the groove between the double row of G-actin monomers. There are forty to sixty tropomyosin molecules per thin filament, with each tropomyosin spanning a distance of approximately seven actin subunits.

Attached to the tropomyosin, rather than directly to the actin, is a third type of protein called **troponin.** Troponin is actually a complex of three proteins (see fig. 12.13). These are *troponin I* (which inhibits the binding of the cross bridges to actin); *troponin T* (which binds to tropomyosin); and *troponin C* (which binds Ca^{2+}). Troponin and tropomyosin work together to regulate the attachment of cross bridges to actin, and thus serve as a switch for muscle contraction and relaxation. In a relaxed muscle, the position of the tropomyosin in the thin filaments is such that it physically blocks the cross bridges from bonding to specific attachment sites in the actin. Thus, in order for the myosin cross bridges to attach to actin, the tropomyosin must be moved. This requires the interaction of troponin with Ca^{2+}.

Role of Ca^{2+} in Muscle Contraction

Scientists long thought that Ca^{2+} only served to form the calcium phosphate crystals that hardened bone, enamel, and dentin. In 1883, Sidney Ringer published the results of a surprisingly simple experiment that changed that idea. He isolated rat hearts and found that they beat well when placed in isotonic solutions made with the hard water from a London tap. When he made the isotonic solutions with distilled water, however, the hearts gradually stopped beating. This could be reversed, he found, if he added Ca^{2+} to the solutions. This demonstrated a role for Ca^{2+} in muscle contraction, a role that scientists now understand in some detail.

In a relaxed muscle, when tropomyosin blocks the attachment of cross bridges to actin, the concentration of Ca^{2+} in the sarcoplasm (cytoplasm of muscle cells) is very low. When the muscle cell is stimulated to contract, mechanisms that will be discussed shortly cause the concentration of Ca^{2+} in the sarcoplasm to quickly rise. Some of this Ca^{2+} attaches to troponin, causing a conformational change that moves the troponin complex *and* its attached tropomyosin out of the way so that the cross bridges can attach to actin (fig. 12.14). Once the attachment sites on the actin are exposed, the cross bridges can bind to actin, undergo power strokes, and produce muscle contraction.

The position of the troponin-tropomyosin complexes in the thin filaments is thus adjustable. When Ca^{2+} is not attached to troponin, the tropomyosin is in a position that inhibits attachment of cross bridges to actin, preventing muscle contraction. When Ca^{2+} attaches to troponin, the troponin-tropomyosin complexes shift position. The cross bridges can then attach to actin, produce a power stroke, and detach from actin. These contraction cycles can continue as long as Ca^{2+} is attached to troponin.

Clinical Investigation Clues

Remember that Maria has muscle pain and fatigue, and that her body seems stiff. Further, she has an elevated blood concentration of Ca^{2+}.

How might the high blood Ca^{2+} be related to Maria's symptoms?

What might cause an elevated blood Ca^{2+} (hint—see chapter 11 or 19).

Excitation-Contraction Coupling

Muscle contraction is turned on when sufficient amounts of Ca^{2+} bind to troponin. This occurs when the Ca^{2+} concentration of the sarcoplasm rises above 10^{-6} molar. In order for muscle relaxation to occur, therefore, the Ca^{2+} concentration of the sarcoplasm must be lowered to below this level. Muscle relaxation is produced by the active transport of Ca^{2+} out of the sarcoplasm into the **sarcoplasmic reticulum** (fig. 12.15). The sarcoplasmic reticulum is a modified endoplasmic reticulum, consisting of interconnected sacs and tubes that surround each myofibril within the muscle cell.

Most of the Ca^{2+} in a relaxed muscle fiber is stored within expanded portions of the sarcoplasmic reticulum known as *terminal cisternae.* When a muscle fiber is stimulated to contract by either a motor neuron *in vivo* or electric shocks *in vitro,* the stored Ca^{2+} is released from the sarcoplasmic reticulum by passive diffusion through membrane channels termed **calcium release channels** (fig. 12.16); these are also called *ryanodine receptors.* The Ca^{2+} can then bind to troponin and stimulate contraction. When a muscle fiber is no longer stimulated, the Ca^{2+} is actively transported back into the sarcoplasmic reticulum. Now, in order to understand how the release and uptake of Ca^{2+} is regulated, one more organelle within the muscle fiber must be described.

The terminal cisternae of the sarcoplasmic reticulum are separated only by a very narrow gap from **transverse tubules** (or **T tubules**). These are narrow membranous "tunnels" formed from and continuous with the sarcolemma (muscle plasma membrane). The transverse tubules thus open to the extracellular environment through pores in the cell surface and are able to conduct action potentials. The stage is now set to explain exactly how a motor neuron stimulates a muscle fiber to contract.

The release of acetylcholine from axon terminals at the neuromuscular junctions (motor end plates), as previously described, causes electrical activation of skeletal muscle fibers. End-plate potentials (analogous to EPSPs—chapter 7) are produced that generate action potentials. Action potentials in muscle cells, like those in nerve cells, are all-or-none events that

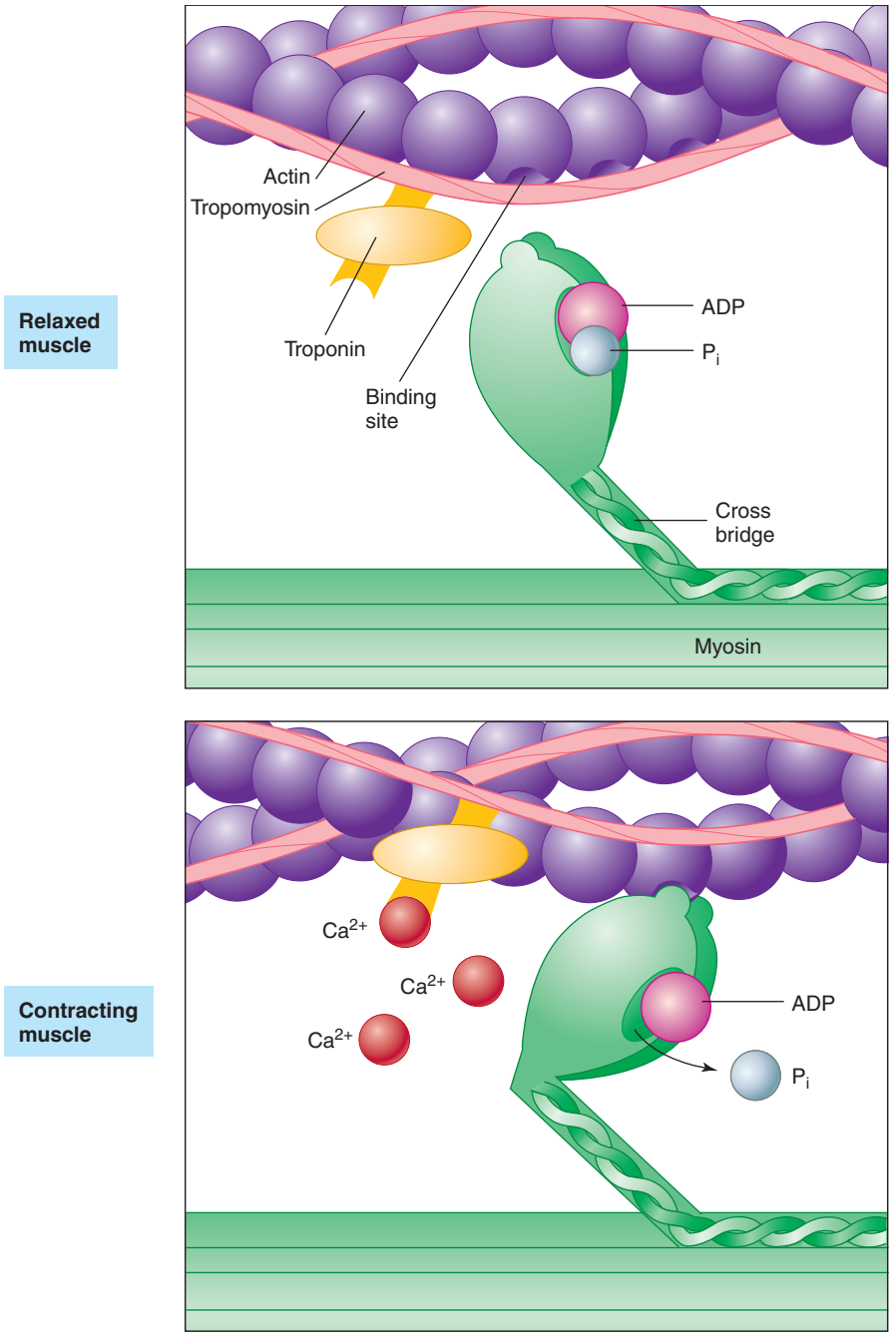


Figure 12.14 **The role of Ca^{2+} in muscle contraction.** The attachment of Ca^{2+} to troponin causes movement of the troponin-tropomyosin complex, which exposes binding sites on the actin. The myosin cross bridges can then attach to actin and undergo a power stroke.

are regenerated along the plasma membrane. It must be remembered that action potentials involve the flow of ions between the extracellular and intracellular environments across a plasma membrane that separates these two compartments. In muscle cells, therefore, action potentials can be conducted into the interior of the fiber across the membrane of the transverse tubules.

The transverse tubules contain **voltage-gated calcium channels,** also called *dihydropyridine (DHP) receptors.* These respond to membrane depolarization. When the transverse tubules conduct action potentials, the voltage-gated calcium channels undergo a conformational (shape) change. It is currently believed that there is a direct molecular coupling between these channels on the transverse tubules and the calcium release channels (ryanodine receptors) in the sarcoplasmic reticulum. The conformational change in the voltage-gated channels in the transverse tubules directly causes the calcium release channels in the sarcoplasmic reticulum to open. This releases Ca^{2+} into the cytoplasm, raising the cytoplasmic Ca^{2+} concentration and stimulating contraction (fig. 12.16). The process by which action potentials cause contraction is termed **excitation-contraction coupling** (table 12.3).

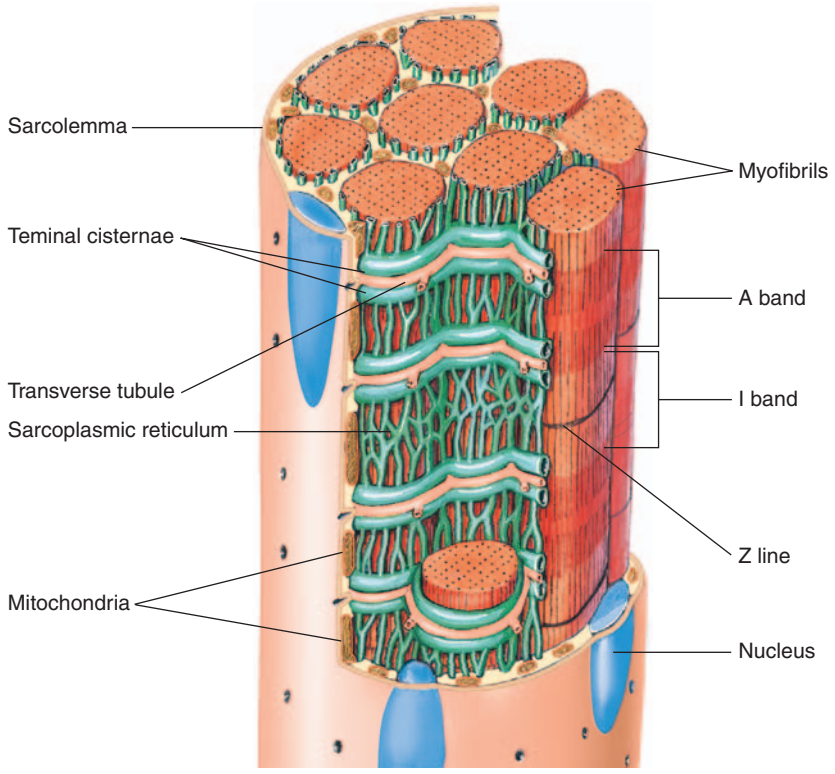


Figure 12.15 **The sarcoplasmic reticulum.** This figure depicts the relationship between myofibrils, the transverse tubules, and the sarcoplasmic reticulum. The sarcoplasmic reticulum (*green*) stores Ca^{2+} and is stimulated to release it by action potentials arriving in the transverse tubules.

This excitation-contraction coupling mechanism in skeletal muscle has been described as an *electromechanical release mechanism,* because the voltage-gated calcium channels (DHP receptors) and the calcium release channels (ryanodine receptors) are physically (mechanically) coupled. As a result, Ca^{2+} enters the cytoplasm from the sarcoplasmic reticulum, where it is stored. However, this electromechanical release mechanism is not the full story of how action potentials stimulate the contraction of skeletal muscles.

In addition to the ryanodine receptors, the membrane of the sarcoplasmic reticulum contains a different type of calcium release channel, a type that opens in response to the raised Ca^{2+} concentration of the cytoplasm. These calcium release channels are thus regulated by a *Ca^{2+}-induced Ca^{2+} release mechanism.* This mechanism contributes significantly to excitation-contraction coupling in skeletal muscle, and in cardiac muscle it is the mechanism most responsible for excitation-contraction coupling.

Muscle Relaxation

As long as action potentials continue to be produced—which is as long as neural simulation of the muscle is maintained—the calcium release channels in the sarcoplasmic reticulum will remain open, Ca^{2+} will passively diffuse out of the sarcoplasmic reticulum, and the Ca^{2+} concentration of the sarcoplasm will remain high. Thus, Ca^{2+} will remain attached to troponin, and the cross-bridge cycle will continue to maintain contraction.

To stop this action, the production of action potentials must cease, causing the calcium release channels to close. When this occurs, the effects of other transport proteins in the sarcoplasmic reticulum become unmasked. These are active transport pumps for Ca^{2+}—termed **Ca^{2+}-ATPase pumps,** which move Ca^{2+} from the sarcoplasm into the sarcoplasmic reticulum. Since these active transport pumps are powered by the hydrolysis of ATP, ATP is needed for muscle relaxation as well as for muscle contraction.

Test Yourself Before You Continue

1. With reference to the sliding filament theory, explain how the lengths of the A, I, and H bands change during contraction.
2. Describe a cycle of cross-bridge activity during contraction and discuss the role of ATP in this cycle.
3. Draw a sarcomere in a relaxed muscle and a sarcomere in a contracted muscle and label the bands in each. What is the significance of the differences in your drawings?
4. Describe the molecular structure of myosin and actin. How are tropomyosin and troponin positioned in the thin filaments and how do they function in the contraction cycle?
5. Use a flowchart to show the sequence of events from the time ACh is released from a nerve ending to the time Ca^{2+} is released from the sarcoplasmic reticulum.
6. Explain the requirements for Ca^{2+} and ATP in muscle contraction and relaxation.

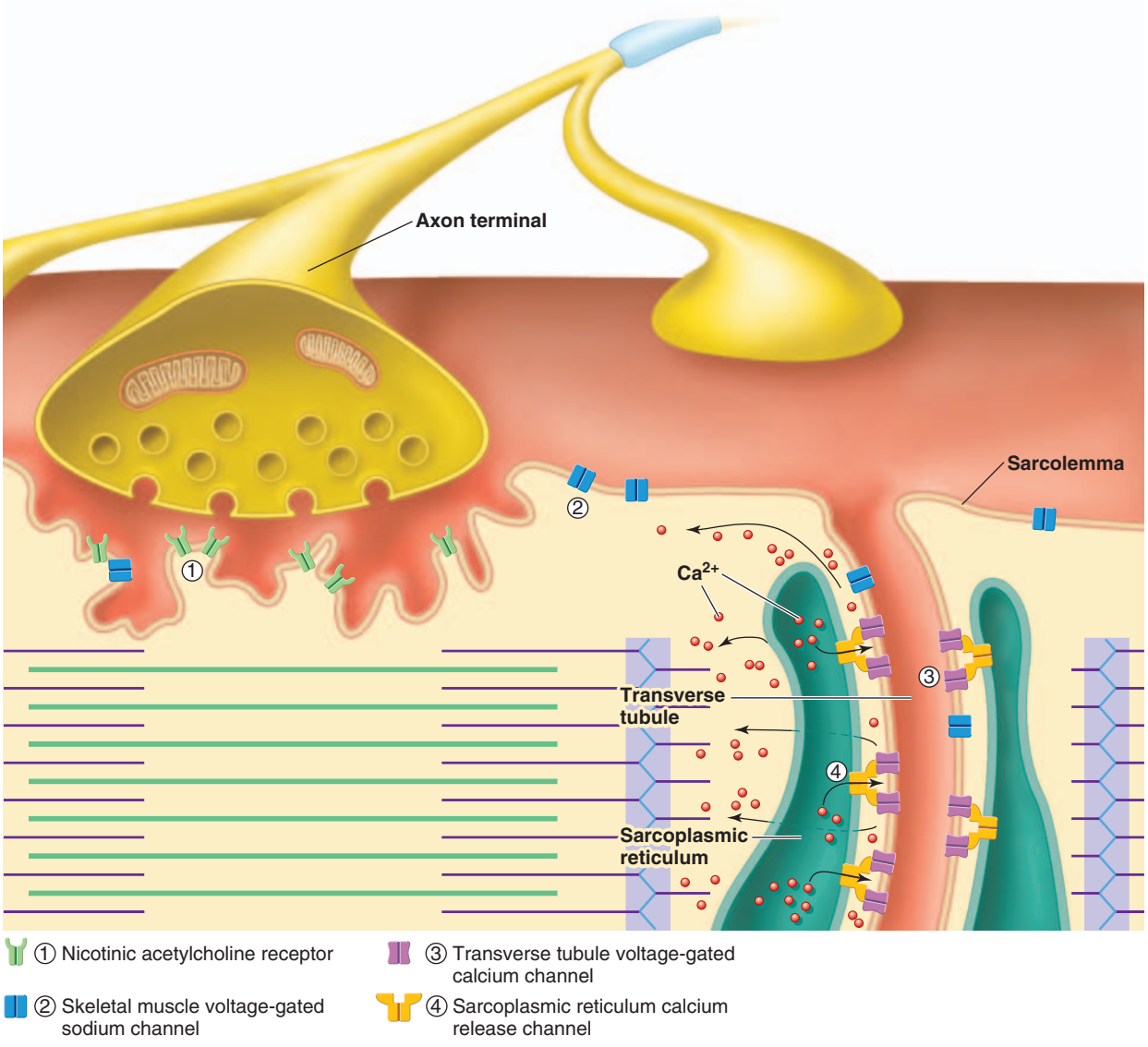


Figure 12.16 **The structures involved in excitation-contraction coupling.** The acetylcholine released from the axon binds to its nicotinic receptors in the motor end plate. This stimulates the production of a depolarization, which causes the opening of voltage-gated Na^+ channels and the resulting production of action potentials along the sarcolemma. The spread of action potentials into the transverse tubules stimulates the opening of their voltage-gated Ca^{2+} channels, which (directly or indirectly) causes the opening of voltage-gated Ca^{2+} channels in the sarcoplasmic reticulum. Calcium diffuses out of the sarcoplasmic reticulum, binds to troponin, and stimulates contraction.

Table 12.3 Summary of Events in Excitation-Contraction Coupling

1. Action potentials in a somatic motor neuron cause the release of acetylcholine neurotransmitter at the myoneural junction (one myoneural junction per myofiber).
2. Acetylcholine, through its interaction with receptors in the muscle cell membrane (sarcolemma), produces action potentials that are regenerated across the sarcolemma.
3. The membranes of the transverse tubules (T tubules) are continuous with the sarcolemma and conduct action potentials deep into the muscle fiber.
4. Action potentials in the T tubules, acting through a mechanism that is incompletely understood, stimulate the release of Ca^{2+} from the terminal cisternae of the sarcoplasmic reticulum.
5. Ca^{2+} released into the sarcoplasm attaches to troponin, causing a change in its structure.
6. The shape change in troponin causes its attached tropomyosin to shift position in the actin filament, thus exposing binding sites for the myosin cross bridges.
7. Myosin cross bridges, previously activated by the hydrolysis of ATP, attach to actin.
8. Once the previously activated cross bridges attach to actin, they undergo a power stroke and pull the thin filaments over the thick filaments.
9. Attachment of fresh ATP allows the cross bridges to detach from actin and repeat the contraction cycle as long as Ca^{2+} remains attached to troponin.
10. When action potentials stop being produced, the sarcoplasmic reticulum actively accumulates Ca^{2+} and tropomyosin returns to its inhibitory position.

Contractions of Skeletal Muscles

Contraction of muscles generates tension, which allows muscles to shorten and thereby perform work. The contraction strength of skeletal muscles must be sufficiently great to overcome the load on a muscle in order for that muscle to shorten.

The contractions of skeletal muscles generally produce movements of bones at joints, which act as levers to move the loads against which the muscle's force is exerted. The contractile behavior of the muscle, however, is more easily studied *in vitro* (outside the body) than *in vivo* (within the body). When a muscle—for example, the gastrocnemius (calf muscle) of a frog—is studied *in vitro,* it is usually mounted so that one end is fixed and the other is movable. The mechanical force of the muscle contraction is transduced (changed) into an electric current, which can be amplified and displayed on a recording device (fig. 12.17). In this way, the contractile behavior of the whole muscle in response to experimentally administered electric shocks can be studied.

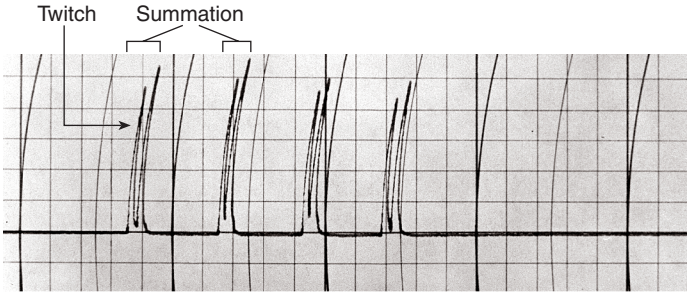


Figure 12.17 **Recording muscle contractions.** Recorder tracings demonstrating twitch and summation of an isolated frog gastrocnemius muscle.

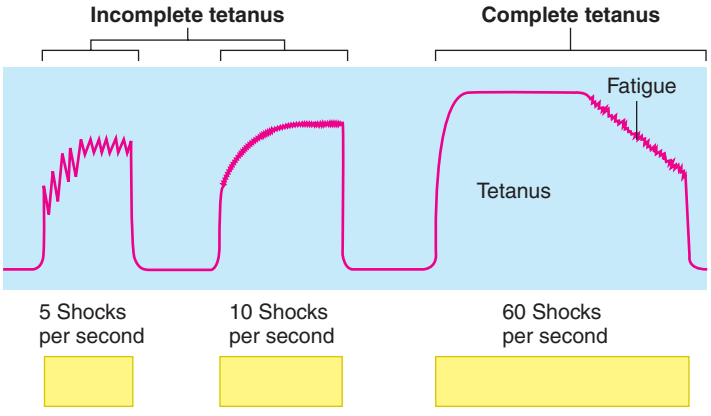


Figure 12.18 **Incomplete and complete tetanus.** When an isolated muscle is shocked repeatedly, the separate twitches summate to produce a sustained contraction. At a relatively slow rate of stimulation (5 or 10 per second), the separate muscle twitches can still be observed. This is incomplete tetanus. When the frequency of stimulation increases to 60 shocks per second, however, complete tetanus—a smooth, sustained contraction—is observed. If the stimulation is continued, the muscle will demonstrate fatigue.

Twitch, Summation, and Tetanus

When the muscle is stimulated with a single electric shock of sufficient voltage, it quickly contracts and relaxes. This response is called a **twitch** (fig. 12.17). Increasing the stimulus voltage increases the strength of the twitch, up to a maximum. The strength of a muscle contraction can thus be *graded,* or varied—an obvious requirement for the proper control of skeletal movements. If a second electric shock is delivered immediately after the first, it will produce a second twitch that may partially "ride piggyback" on the first. This response is called **summation** (fig. 12.17).

Stimulation of fibers within a muscle *in vitro* with an electric stimulator, or *in vivo* by motor axons, usually results in the full contraction of the individual fibers. Stronger muscle contractions are produced by the stimulation of greater numbers of muscle fibers. Skeletal muscles can thus produce **graded contractions,** the strength of which depends on the number of fibers stimulated rather than on the strength of the contractions of individual muscle fibers.

If the stimulator is set to deliver an increasing frequency of electric shocks automatically, the relaxation time between successive twitches will get shorter and shorter as the strength of contraction increases in amplitude. This effect is known as **incomplete tetanus** (fig. 12.18). Finally, at a particular "fusion frequency" of stimulation, there is no visible relaxation between successive twitches. Contraction is smooth and sustained, as it is during normal muscle contraction *in vivo.* This smooth, sustained contraction is called **complete tetanus.** (The term *tetanus* should not be confused with the disease of the same name, which is accompanied by a painful state of muscle contracture, or *tetany.*) The tetanus produced *in vitro* by the asynchronous twitches of muscle fibers simulates the normal, smooth contraction produced *in vivo* by the asynchronous activation of motors units.

Treppe

If the voltage of the electrical shocks delivered to an isolated muscle *in vitro* is gradually increased from zero, the strength of the muscle twitches will increase accordingly, up to a maximal value at which all of the muscle fibers are stimulated. This demonstrates the graded nature of the muscle contraction. If a series of electrical shocks at this maximal voltage is given to a fresh muscle so that each shock produces a separate twitch, each of the twitches evoked will be successively stronger, up to a higher maximum. This demonstrates **treppe,** or the *staircase effect.* Treppe may represent a warmup effect, and is believed to be due to an increase in intracellular Ca^{2+}, which is needed for muscle contraction.

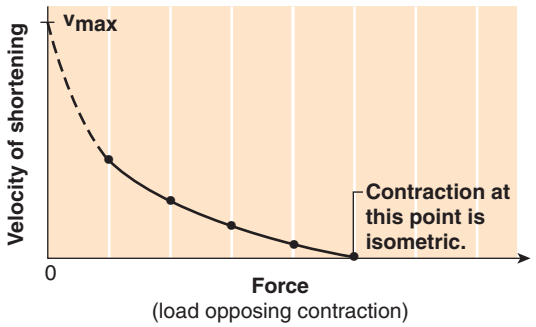


Figure 12.19 **Force-velocity curve.** This graph illustrates the inverse relationship between the force opposing muscle contraction (the load against which the muscle must work) and the velocity of muscle shortening. A force that is sufficiently great prevents muscle shortening, so that the contraction is isometric. If there is no force acting against the muscle contraction, the velocity of shortening is maximal (V_{max}). Since this cannot be measured (because there will always be some load), the estimated position of the curve is shown with a dashed line.

Types of Muscle Contractions

In order for muscle fibers to shorten when they contract, they must generate a force that is greater than the opposing forces that act to prevent movement of the muscle's insertion. When you lift a weight by flexing your elbow joint, for example, the force produced by contraction of your biceps brachii muscle is greater than the force of gravity on the object being lifted. The tension produced by the contraction of each muscle fiber separately is insufficient to overcome the opposing force, but the combined contractions of numerous muscle fibers may be sufficient to overcome the opposing force and flex your forearm. In this case, the muscle and all of its fibers shorten in length.

This process can be seen by examining the **force-velocity curve.** This graph shows the inverse relationship between the force opposing muscle contraction (the load against which the muscle must work) and the velocity of muscle shortening (fig. 12.19). The tension produced by the shortening muscle is just greater than the force (load) at each value, causing the muscle to shorten. Under these controlled experimental conditions, the contraction strength is constant at each load; this muscle contraction during shortening is thus called an **isotonic contraction** (*iso* = same; *tonic* = strength).

If the load is zero, a muscle contracts and shortens with its maximum velocity. As the load increases, the velocity of muscle shortening decreases. When the force opposing contraction (the load) becomes sufficiently great, the muscle is unable to shorten when it exerts a given tension. That is, its velocity of shortening is zero. At this point, where muscle tension does not cause muscle shortening, the contraction is called an **isometric** (literally, "same length") **contraction.**

Isometric contraction can be voluntarily produced, for example, by lifting a weight and maintaining the forearm in a partially flexed position. We can then increase the amount of muscle tension produced by recruiting more muscle fibers until the muscle begins to shorten; at this point, isometric contraction is converted to isotonic contraction.

When a muscle contracts, it exerts tension on its attachments. If this tension is equal to the opposing force (load), the muscle stays the same length and produces an isometric contraction. If the muscle tension is greater than the load, the muscle shortens when it contracts. This may be an isotonic contraction, but can be described more generally as a **concentric** (or **shortening**) **contraction.** When a force exerted on a muscle to stretch it is greater than the force of muscle contraction, the muscle will be stretched by that force. In other words, the muscle will lengthen *despite* its contraction. This is known as an **eccentric** (or **lengthening**) **contraction.** For example, when you do a "curl" with a dumbbell, your biceps brachii muscle produces a concentric contraction as you flex your forearm. When you gently lower the dumbbell back to the resting position, your biceps produces an eccentric contraction. The force of contraction of your biceps in this example allows the dumbbell to be lowered gently against the force of gravity as your biceps lengthens.

Another example of eccentric muscle contractions occurs when you jump from a height and land in a flexed-leg position. In this case, the extensor muscles of your legs (the quadriceps femoris group) contract eccentrically to absorb some of the shock. In this case, most of the energy absorbed by the muscles is dissipated as heat. Less dramatically (and somewhat less painfully), these muscles also contract eccentrically when you jog downhill or hike down a steep mountain trail.

Series-Elastic Component

In order for a muscle to shorten when it contracts, and thus to move its insertion toward its origin, the noncontractile parts of the muscle and the connective tissue of its tendons must first be pulled tight. These structures, particularly the tendons, have elasticity—they resist distension, and when the distending force is released, they tend to spring back to their resting lengths. Tendons provide what is called a **series-elastic component** because they are somewhat elastic and in line (in series) with the force of muscle contraction. The series-elastic component absorbs some of the tension as a muscle contracts, and it must be pulled tight before muscle contraction can result in muscle shortening.

When the gastrocnemius muscle was stimulated with a single electric shock as described earlier, the amplitude of the twitch was reduced because some of the force of contraction was used to stretch the series-elastic component. Quick delivery of a second shock thus produced a greater degree of muscle shortening than the first shock, culminating at the fusion frequency of stimulation with complete tetanus, in which the strength of contraction was much greater than that of individual twitches.

Some of the energy used to stretch the series-elastic component during muscle contraction is released by elastic recoil when the muscle relaxes. This elastic recoil, which helps the muscles return to their resting length, is of particular importance for the muscles involved in breathing. As we will see in chapter 16, inspiration is produced by muscle contraction and expiration is produced by the elastic recoil of the thoracic structures that were stretched during inspiration.

Length-Tension Relationship

The strength of a muscle's contraction is influenced by a variety of factors. These include the number of fibers within the muscle that are stimulated to contract, the frequency of stimulation, the thickness of each muscle fiber (thicker fibers have more myofibrils and thus can exert more power), and the initial length of the muscle fibers when they are at rest.

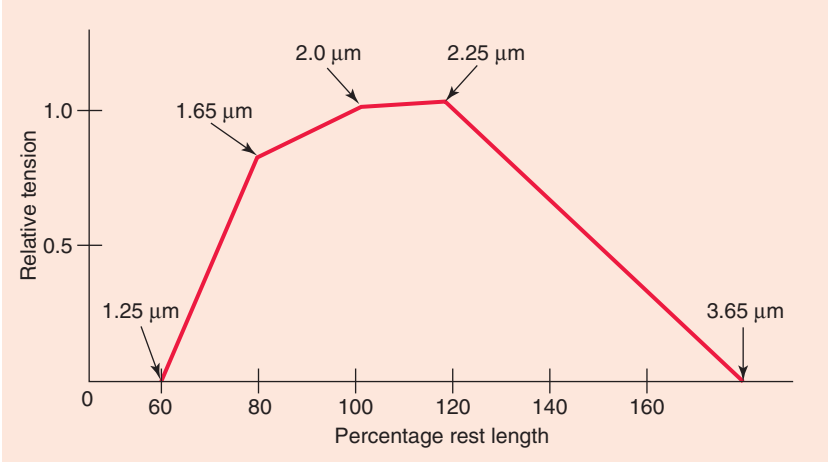
There is an "ideal" resting length for striated muscle fibers. This is the length at which they can generate maximum force. The force that the muscle generates when it contracts is usually measured as the force required to prevent it from shortening. The muscle is made to contract isometrically, and the force required to prevent it from shortening is measured as the *tension* produced. As illustrated in figure 12.20, this tension is maximal when the sarcomeres are at a length of 2.0 to 2.2 μm. As it turns out, this is the length of the sarcomeres when muscles are at their normal resting lengths. In the body, this normal resting length is maintained by reflex contractions in response to passive stretching, as described in a later section of this chapter.

When the sarcomere lengths are greater than about 2.2 μm, the tension produced by the muscle contraction decreases with increasing sarcomere length. This is because there are fewer interactions of myosin cross bridges with actin. When the sarcomeres reach a length of about 3.6 μm, there is no overlap of thick and thin filaments, and no interactions can occur between myosin and actin. Therefore, the muscle produces zero tension (fig. 12.20).

When the sarcomere length is shorter than 2.0 μm, the force generated by muscle contraction declines with decreasing sarcomere length (fig. 12.20). This is believed to result from interference with cross-bridge action, in part because of increasing distance between thick and thin filaments as the muscle fiber gets shorter and thicker. Also, as the muscle fiber gets shorter and thicker, opposing forces (such as fluid pressure of the sarcoplasm) develop. The double overlapping of thin filaments (see the left sarcomere in fig. 12.20) may further interfere with the action of cross-bridges. The force of muscle contraction declines still further when the thick filaments abut against the Z discs at a sarcomere length of 1.7 μm. This may be due to deformation of the myosin. At a sarcomere length of 1.25 μm, the muscle produces zero force (fig. 12.20).

Test Yourself Before You Continue

1. Explain how graded contractions and smooth, sustained contractions can be produced *in vitro* and *in vivo*.
2. Distinguish among isotonic, isometric, and eccentric contractions, and describe what factors determine if a contraction will be isometric or isotonic.
3. Identify the nature and physiological significance of the series-elastic component of muscle contraction.
4. Describe the relationship between the resting muscle length and the strength of its contraction.



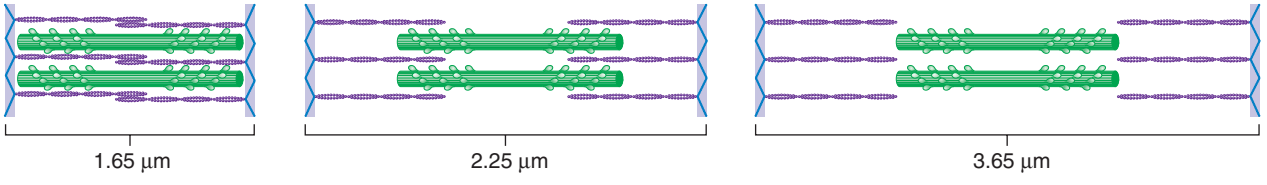


Figure 12.20 **The length-tension relationship in skeletal muscles.** Maximum relative tension (1.0 on the *y* axis) is achieved when the muscle is 100% to 120% of its resting length (sarcomere lengths from 2.0 to 2.25 μm). Increases or decreases in muscle (and sarcomere) lengths result in rapid decreases in tension.

Energy Requirements of Skeletal Muscles

Skeletal muscles generate ATP through aerobic and anaerobic respiration and through the use of phosphate groups donated by creatine phosphate.The aerobic and anaerobic abilities of skeletal muscle fibers differ according to muscle fiber type, which are described according to their speed of contraction, color, and major mode of energy metabolism.

Skeletal muscles at rest obtain most of their energy from the aerobic respiration of fatty acids. During exercise, muscle glycogen and blood glucose are also used as energy sources (fig. 12.21). Energy obtained by cell respiration is used to make ATP, which serves as the immediate source of energy for (1) the movement of the cross bridges for muscle contraction and (2) the pumping of Ca^{2+} into the sarcoplasmic reticulum for muscle relaxation.

Metabolism of Skeletal Muscles

Skeletal muscles respire anaerobically for the first 45 to 90 seconds of moderate-to-heavy exercises because the cardiopulmonary system requires this amount of time to sufficiently increase the oxygen supply to the exercising muscles. If exercise is moderate, aerobic respiration contributes the major portion of the skeletal muscle energy requirements following the first 2 minutes of exercise.

Maximal Oxygen Uptake

Whether exercise is light, moderate, or heavy for a given person depends on that person's maximal capacity for aerobic exercise. The maximum rate of oxygen consumption (by aerobic respiration) in the body is called the **maximal oxygen uptake,** or the **aerobic capacity,** and is often expressed in abbreviated form as the $\dot{V}_{O_2}$ max. The maximal oxygen uptake is determined primarily by a person's age, size, and sex. It is from 15% to 20% higher for males than for females and highest at age 20 for both sexes. The $\dot{V}_{O_2}$ max ranges from about 12 ml of O_2 per minute per kilogram body weight for older, sedentary people to about 84 ml per minute per kilogram for young, elite male athletes. Some world-class athletes

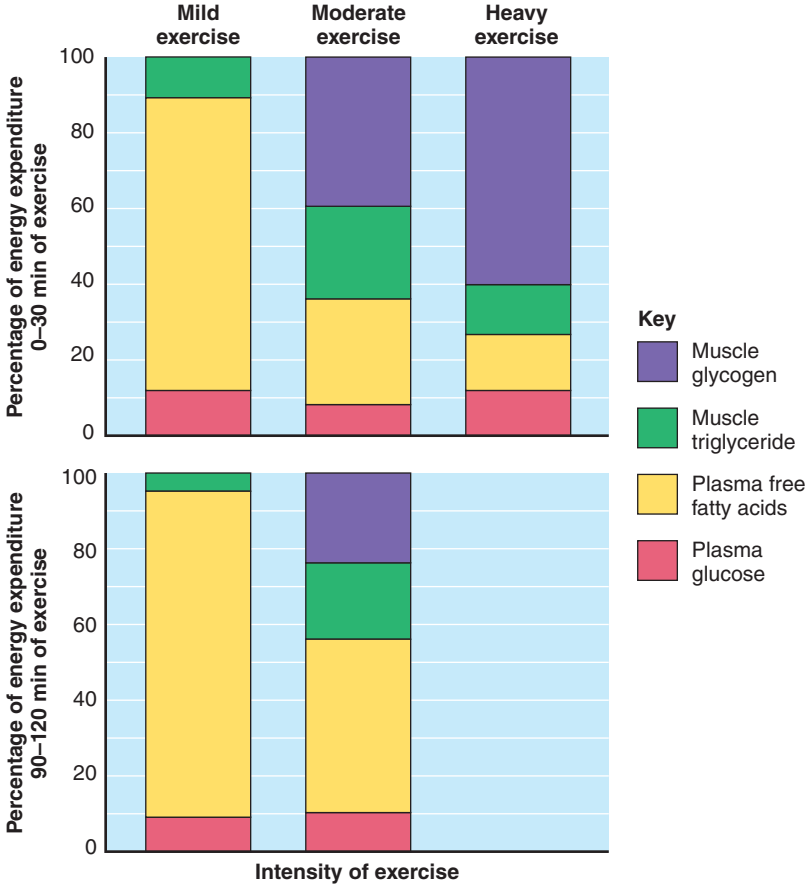


Figure 12.21 **Muscle fuel consumption during exercise.** The relative contributions of plasma glucose, plasma free fatty acids, muscle glycogen, and muscle triglycerides to the energy consumption of exercising muscles. These are shown during mild exercise (25% of $\dot{V}_{O_2}$ max), moderate exercise (65% of $\dot{V}_{O_2}$ max), and heavy exercise (85% of $\dot{V}_{O_2}$ max). Data for heavy exercise performed at 90 to 120 minutes are not available.

have maximal oxygen uptakes that are twice the average for their age and sex—this appears to be due largely to genetic factors, but training can increase the maximum oxygen uptake by about 20%.

The intensity of exercise can also be defined by the **lactate** (or **anaerobic**) **threshold.** This is the percentage of the maximal oxygen uptake at which a significant rise in blood lactate levels occurs. For average healthy people, for example, a significant amount of blood lactate appears when exercise is performed at about 50% to 70% of the $\dot{V}_{O_2}$ max.

During light exercise (at about 25% of the $\dot{V}_{O_2}$ max), most of the exercising muscle's energy is derived from the aerobic respiration of fatty acids. These are derived mainly from stored fat in adipose tissue, and to a lesser extent from triglycerides stored in the muscle (fig. 12.21). When a person exercises just below the lactate threshold, where the exercise can be described as moderately intense (at 50% to 70% of the $\dot{V}_{O_2}$ max), the energy is derived almost equally from fatty acids and glucose (obtained from stored muscle glycogen and the blood plasma). By contrast, glucose from these sources supplies two-thirds of the energy for muscles during heavy exercise above the lactate threshold.

During exercise, the carrier protein for the facilitated diffusion of glucose (GLUT4—chapter 6) is moved into the muscle fiber's plasma membrane, so that the cell can take up an increasing amount of blood glucose. The uptake of plasma glucose contributes 15% to 30% of the muscle's energy needs during moderate exercise and up to 40% of the energy needs during very heavy exercise. This would produce hypoglycemia if the liver failed to increase its output of glucose. The liver increases its output of glucose primarily through hydrolysis of its stored glycogen, but gluconeogenesis (the production of glucose from amino acids, lactate, and glycerol) contributes increasingly to the liver's glucose production as exercise is prolonged.

Clinical Investigation Clue

Remember that Maria has a high maximal oxygen uptake, consistent with her athletic lifestyle.

Is it possible, likely, or unlikely that Maria's muscle pain and fatigue are caused by her playing softball?

Oxygen Debt

When a person stops exercising, the rate of oxygen uptake does not immediately return to pre-exercise levels; it returns slowly (the person continues to breathe heavily for some time afterward). This extra oxygen is used to repay the **oxygen debt** incurred during exercise. The oxygen debt includes oxygen that was withdrawn from savings deposits—hemoglobin in blood and myoglobin in muscle (see chapter 16); the extra oxygen required for metabolism by tissues warmed during exercise; and the oxygen needed for the metabolism of the lactic acid produced during anaerobic respiration.

Phosphocreatine

During sustained muscle activity, ATP may be used faster than it can be produced through cell respiration. At these times, the rapid renewal of ATP is extremely important. This is accomplished by combining ADP with phosphate derived from another high-energy phosphate compound called **phosphocreatine,** or **creatine phosphate.**

Within muscle cells, the phosphocreatine concentration is more than three times the concentration of ATP and represents a ready reserve of high-energy phosphate that can be donated directly to ADP (fig. 12.22). Production of ATP from ADP and phosphocreatine is so efficient that, even though the rate of ATP breakdown rapidly increases from rest to heavy exercise, muscle ATP concentrations hardly change! During times of rest, the depleted reserve of phosphocreatine can be restored by the reverse reaction—phosphorylation of creatine with phosphate derived from ATP.

Creatine is produced by the liver and kidneys, and a small amount can be obtained by eating meat and fish. In addition, some athletes take creatine monohydrate dietary supplements, which have been found to increase muscle phosphocreatine by 15% to 40%. Most studies indicate that this can improve muscle mass, strength and performance, particularly of high-intensity exercise. Studies of the long-term effects of creatine supplements in rodents suggest possible damaging effects to the liver and kidneys, but the health implications of these studies to long-term creatine supplementation in humans are not established.

CLINICAL

The enzyme that transfers phosphate between creatine and ATP is called **creatine kinase,** or **creatine phosphokinase.** Skeletal muscle and heart muscle have two different forms of this enzyme (they have different isoenzymes, as described in chapter 4). The skeletal muscle isoenzyme is found to be elevated in the blood of people with muscular dystrophy (degenerative disease of skeletal muscles). The plasma concentration of the isoenzyme characteristic of heart muscle is elevated as a result of myocardial infarction (damage to heart muscle), and measurements of this enzyme are thus used as a means of diagnosing heart disease.

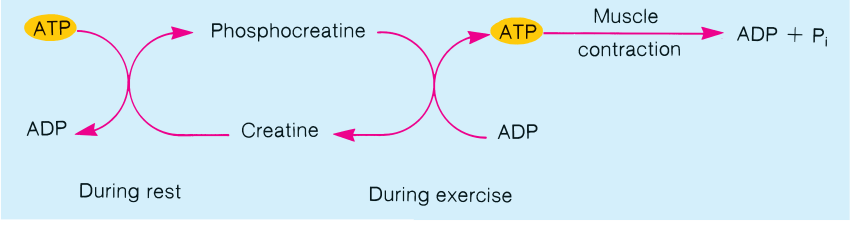


Figure 12.22 **The production and utilization of phosphocreatine in muscles.** Phosphocreatine serves as a muscle reserve of high-energy phosphate, used for the rapid formation of ATP.

Clinical Investigation Clue

Remember that Maria had a normal blood level of creatine phosphokinase.

What does this suggest about the health of her muscles and heart?

Slow- and Fast-Twitch Fibers

Skeletal muscle fibers can be divided on the basis of their contraction speed (time required to reach maximum tension) into **slow-twitch,** or **type I, fibers,** and **fast-twitch,** or **type II, fibers.** These differences are associated with different myosin ATPase isoenzymes, which can also be designated as "slow" and "fast." The two fiber types can be distinguished by their ATPase isoenzyme when they are appropriately stained (fig. 12.23). The extraocular muscles that position the eyes, for example, have a high proportion of fast-twitch fibers and reach maximum tension in about 7.3 msec (milliseconds—thousandths of a second). The soleus muscle in the leg, by contrast, has a high proportion of slow-twitch fibers and requires about 100 msec to reach maximum tension (fig. 12.24).

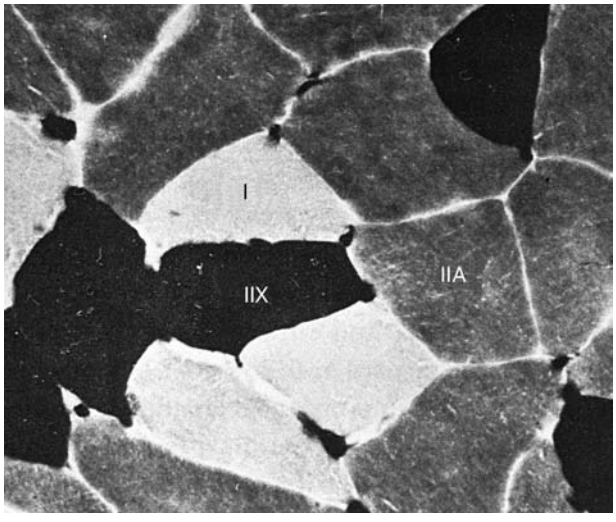


Figure 12.23 Skeletal muscle stained to indicate activity of myosin ATPase. ATPase activity is greater in the type II (fast-twitch) fibers than in the type I (slow-twitch) fibers. Among the fast-twitch fibers, ATPase activity is greatest in the fast-glycolytic (IIX) fibers. The fast-oxidative (IIA) fibers show an intermediate level of activity.

Muscles like the soleus are *postural muscles;* they are able to sustain a contraction for a long period of time without fatigue. The resistance to fatigue demonstrated by these muscles is aided by other characteristics of slow-twitch (type I) fibers that endow them with a high oxidative capacity for aerobic respiration. Hence, the type I fibers are often referred to as **slow oxidative fibers.** These fibers have a rich capillary supply, numerous mitochondria and aerobic respiratory enzymes, and a high concentration of *myoglobin.* Myoglobin is a red pigment, similar to the hemoglobin in red blood cells, that improves the delivery of oxygen to the slow-twitch fibers. Because of their high myoglobin content, slow-twitch fibers are also called **red fibers.**

The thicker, fast-twitch (type II) fibers have fewer capillaries and mitochondria than slow-twitch fibers and not as much myoglobin; hence, these fibers are also called **white fibers.** Fast-twitch fibers are adapted to respire anaerobically by a large store of glycogen and a high concentration of glycolytic enzymes.

In addition to the type I (slow-twitch) and type II (fast-twitch) fibers, human muscles have an intermediate fiber type. These intermediate fibers are fast-twitch but also have a high oxidative capacity; therefore, they are relatively resistant to fatigue. They are called type **IIA fibers,** or **fast oxidative fibers,** because of their aerobic ability. The other fast-twitch fibers are anaerobically adapted; these are called **fast glycolytic fibers** because of their high rate of glycolysis. Not all fast glycolytic fibers are alike, however. There are different fibers in this class, which vary in their contraction speeds and glycolytic abilities. In some animals, the extreme fast glycolytic fibers are of the type designated **type IIB fibers.** In humans, these fast glycolytic fibers are currently designated **type IIX fibers.** The three major fiber types in humans are compared in table 12.4.

People vary tremendously in the proportion of fast- and slow-twitch fibers in their muscles (fig. 12.25). The percent of slow-twitch, type I fibers in the quadriceps femoris muscles of the legs, for example, can vary from under 20% (in people who are excellent sprinters) to as high as 95% (in people who are good marathon runners). These differences are believed to be primarily the result of differences in genetics, although physical training is also an important factor.

A muscle such as the gastrocnemius contains both fast- and slow-twitch fibers, although fast-twitch fibers predominate. A given somatic motor axon, however, innervates muscle fibers of one type only. The sizes of these motor units differ; the motors units composed of slow-twitch fibers tend to be smaller (have fewer fibers) than the motor units of fast-twitch fibers. As

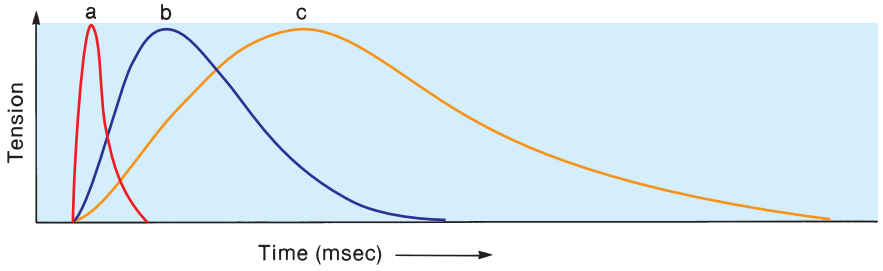


Figure 12.24 A comparison of the rates at which maximum tension is developed in three muscles. These are *(a)* the relatively fast-twitch extraocular and *(b)* gastrocnemius muscles, and *(c)* the slow-twitch soleus muscle.

Table 12.4 Characteristics of Muscle Fiber Types

Feature	Slow Oxidative/Red (Type I)	Fast Oxidative/White (Type IIA)	Fast Glycolytic/White (Type IIX)
Diameter	Small	Intermediate	Large
Z-line thickness	Wide	Intermediate	Narrow
Glycogen content	Low	Intermediate	High
Resistance to fatigue	High	Intermediate	Low
Capillaries	Many	Many	Few
Myoglobin content	High	High	Low
Respiration	Aerobic	Aerobic	Anaerobic
Oxidative capacity	High	High	Low
Glycolytic ability	Low	High	High
Twitch rate	Slow	Fast	Fast
Myosin ATPase content	Low	High	High

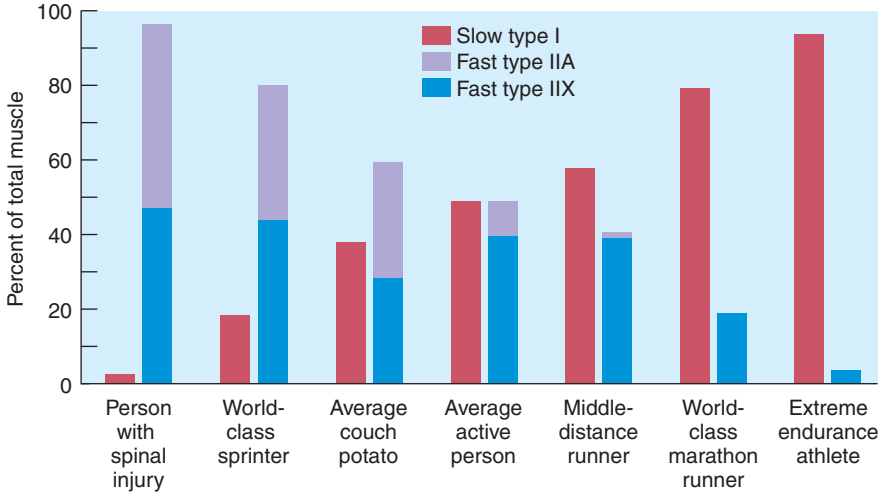


Figure 12.25 Relative abundance of different muscle fiber types in different people. The percent of slow type I fibers, fast type IIX fibers, and intermediate fast type IIA fibers in the muscles of different people varies tremendously. This is due to differences in genetics and to the effects of physical training.

mentioned earlier, motor units are recruited from smaller to larger when increasing effort is required; thus, the smaller motor units with slow-twitch fibers would be used most often in routine activities. Larger motor units with fast-twitch fibers, which can exert a great deal of force but which respire anaerobically and thus fatigue quickly, would be used relatively infrequently and for only short periods of time.

Muscle Fatigue

Muscle fatigue may be defined as any exercise-induced reduction in the ability of a muscle to generate force or power. Fatigue during a sustained maximal contraction, when all the motor units are used and the rate of neural firing is maximal—as when lifting an extremely heavy weight—appears to be due to an accumulation of extracellular K^+. (Remember that K^+ leaves axons and muscle fibers during the repolarization phase of action potentials.) This reduces the membrane potential of muscle fibers and interferes with their ability to produce action potentials. Fatigue under these circumstances lasts only a short time, and maximal tension can again be produced after less than a minute's rest.

Muscle fatigue that occurs during most types of exercise, however, appears to have different causes. Chiefly, there is depletion of muscle glycogen and a reduced ability of the sarcoplasmic reticulum to release Ca^{2+}, leading to failure of excitation-contraction coupling. Although failure of excitation-contraction coupling is known to produce muscle fatigue, the reasons for that failure—despite nearly a century of study—are incompletely understood.

It has been known from the early twentieth century that fatigue occurs when lactic acid accumulates, and that restoring aerobic respiration allows muscle glycogen and contractile ability to recover. This led to the widespread belief that the lowered pH caused by lactic acid interferes with excitation-contraction coupling. Ongoing research, however, suggests that other changes that occur during exercise may be important causes of fatigue. Among these are (1) depletion of intracellular K^+ and accumula-

tion of extracellular K^+; and (2) the accumulation of cytoplasmic P_i derived from the breakdown of phosphocreatine. Recent evidence suggests that these changes contribute to muscle fatigue by reducing the ability of the sarcoplasmic reticulum to release Ca^{2+}.

The foregoing is a description of the reasons that muscle tissue can fatigue during exercise. When humans exercise, however, we often experience fatigue *before* our muscles themselves have fatigued sufficiently to limit exercise. Put another way, our maximum voluntary muscle force is often less than the maximum force that our muscle is itself capable of producing. This demonstrates **central fatigue**—muscle fatigue caused by changes in the CNS rather than by fatigue of the muscles themselves. During exercise, a progressive reduction in the voluntary activation of muscles demonstrates central fatigue.

Evidence suggests that central fatigue is complex. In part, it involves a reduced ability of the "upper motoneurons" (interneurons in the brain devoted to motor control) to drive the "lower motoneurons" (in the spinal cord). Muscle fatigue thus has two major components: a peripheral component (fatigue in the muscles themselves) and a central component (fatigue in the activation of muscles by motoneurons).

Adaptations of Muscles to Exercise Training

The maximal oxygen uptake, obtained during very strenuous exercise, averages 50 ml of O_2 per minute per kilogram body weight in males between the ages of 20 and 25 (females average 25% lower). For trained endurance athletes (such as swimmers and long-distance runners), maximal oxygen uptakes can be as high as 86 ml of O_2 per minute per kilogram. These considerable differences affect the lactate threshold, and thus the amount of exercise that can be performed before lactic acid production contributes to muscle fatigue. In addition to having a higher aerobic capacity, well-trained athletes also have a lactate threshold that is a higher percentage of their $\dot{V}_{O_2}$ max. The lactate threshold of an untrained person, for example, might be 60% of the $\dot{V}_{O_2}$ max, whereas the lactate threshold of a trained athlete can be up to 80% of the $\dot{V}_{O_2}$ max. These athletes thus produce less lactic acid at a given level of exercise than the average person, and therefore they are less subject to fatigue than the average person.

Since the depletion of muscle glycogen places a limit on exercise, any adaptation that spares muscle glycogen will improve physical endurance. This is achieved in trained athletes by an increased proportion of energy that is derived from the aerobic respiration of fatty acids, resulting in a slower depletion of their muscle glycogen. The greater the level of physical training, the higher the proportion of energy derived from the oxidation of fatty acids during exercise below the $\dot{V}_{O_2}$ max.

All fiber types adapt to endurance training by an increase in mitochondria, and thus in aerobic respiratory enzymes. In fact, the maximal oxygen uptake can be increased by as much as 20% through endurance training. There is a decrease in type IIX (fast glycolytic) fibers, which have a low oxidative capacity, accompanied by an increase in type IIA (fast oxidative) fibers, which have a high oxidative capacity. Although the type IIA fibers are still classified as fast-twitch, they show an increase in the slow myosin ATPase isoenzyme form, indicating that they are in a transitional state between the type II and type I fibers. A summary of the changes that occur as a result of endurance training is presented in table 12.5.

Table 12.5 Effects of Endurance Training on Skeletal Muscles

1. Improved ability to obtain ATP from oxidative phosphorylation
2. Increased size and number of mitochondria
3. Less lactic acid produced per given amount of exercise
4. Increased myoglobin content
5. Increased intramuscular triglyceride content
6. Increased lipoprotein lipase (enzyme needed to utilize lipids from blood)
7. Increased proportion of energy derived from fat; less from carbohydrates
8. Lower rate of glycogen depletion during exercise
9. Improved efficiency in extracting oxygen from blood
10. Decreased number of type IIX (fast glycolytic) fibers; increased number of type IIA (fast oxidative) fibers

Endurance training does not increase the size of muscles. Muscle enlargement is produced only by frequent periods of high-intensity exercise in which muscles work against a high resistance, as in weightlifting. As a result of resistance training, type II muscle fibers become thicker, and the muscle therefore grows by hypertrophy (an increase in cell size rather than number of cells). This happens first because the myofibrils within a muscle fiber thicken because of the synthesis of actin and myosin proteins and the addition of new sarcomeres. Then, after a myofibril has attained a certain thickness, it may split into two myofibrils, each of which may become thicker as a result of the addition of sarcomeres. Muscle hypertrophy, in short, is associated with an increase in the size of the myofibrils, and then in the number of myofibrils within the muscle fibers.

The decline in physical strength of older people is associated with a reduced muscle mass, which is due to a loss of muscle fibers and to a decrease in the size of fast-twitch muscle fibers. Aging is also associated with a reduced density of blood capillaries surrounding the muscle fibers, leading to a decrease in oxidative capacity. Resistance training can cause the surviving muscle fibers to hypertrophy and become stronger, partially compensating for the decline in the number of muscle fibers in elderly people. Endurance training can increase the density of blood capillaries in the muscles, improving the ability of the blood to deliver oxygen to the muscles. The muscle glycogen of older people can also be increased by endurance training, but it cannot be raised to the levels present in youth.

Muscle Damage and Repair

Destruction of striated muscle fibers is particularly damaging because the remaining healthy fibers cannot divide to replace the damaged ones. However, skeletal muscles have stem cells known

as **satellite cells,** located outside of a variable proportion of muscle fibers. The satellite cells can proliferate after injury and form myotubes, which fuse to form muscle fibers. This permits muscles to repair and regenerate themselves to some degree after damage. However, for unknown reasons, the ability of satellite cells to repair damaged skeletal muscles is incomplete and declines with age. This decline may be related to the observed decline in the number of satellite cells and their declining ability to proliferate and function with age.

When muscles *hypertrophy*, or grow larger as a result of increased fiber size, the number of nuclei in each fiber must increase in proportion to the larger volume of the fiber. These new nuclei are provided by the satellite cells. The muscle atrophy that usually occurs with age may be related to the decline in satellite cell numbers and function with age.

Myostatin is a recently discovered paracrine regulator in skeletal muscles that is able to inhibit satellite cell function and muscle growth. Consistent with these ideas, recent studies suggest that elderly people with declining muscle mass have elevated levels of myostatin. Lowering myostatin might thus be expected to increase muscle mass. Indeed, mice and cattle with the gene for producing myostatin "knocked out" have greatly increased muscle mass. The functions of myostatin, and the mechanisms that regulate satellite cell proliferation and formation of myotubes, have many potential health applications and are currently active areas of research.

FITNESS

Muscle atrophy (reduction in size) and accompanying declines in muscle strength occur in the weight-bearing muscles of the legs when astronauts experience *microgravity* (weightlessness) for long periods. For example, reductions in muscle volume and performance were measured in the United States *Skylab* missions. However, in *Skylab 4* (which lasted 84 days), adjustments in the diet and the exercise program were able to significantly compensate for the effects of microgravity on tested muscles. Like the effects of weightlessness in astronauts, weight-bearing muscles are similarly "unloaded" in bedridden people and in people with a leg immobilized by a cast. In prolonged bed rest of two to three weeks, the calf and leg muscles experience declines in size and strength comparable to those seen in space flights. Perhaps surprisingly, immobilization of the leg in a cast results in more rapid declines in muscle performance and size than those observed for similar time periods in bed rest or the microgravity of space.

Test Yourself Before You Continue

1. Draw a figure illustrating the relationship between ATP and creatine phosphate, and explain the physiological significance of this relationship.
2. Describe the characteristics of slow- and fast-twitch fibers (including intermediate fibers). Explain how the fiber types are determined and list the functions of different fiber types.
3. Explain the different causes of muscle fatigue with reference to the various fiber types.
4. Describe the effects of endurance training and resistance training on the fiber characteristics of muscles.

Neural Control of Skeletal Muscles

Skeletal muscles contain stretch receptors called muscle spindles that stimulate the production of impulses in sensory neurons when a muscle is stretched. These sensory neurons can synapse with alpha motoneurons, which stimulate the muscle to contract in response to the stretch. Other motor neurons, called gamma motoneurons, stimulate the tightening of the spindles and thus increase their sensitivity.

Motor neurons in the spinal cord, or **lower motor neurons** (often shortened to *motoneurons*), are those previously described that have cell bodies in the spinal cord and axons within nerves that stimulate muscle contraction (table 12.6). The activity of these neurons is influenced by (1) sensory feedback from the muscles and tendons and (2) facilitory and inhibitory effects from **upper motor neurons,** which are interneurons in the brain that contribute axons to descending motor tracts. Lower motor neurons are thus said to be the *final common pathway* by which sensory stimuli and higher brain centers exert control over skeletal movements.

CLINICAL

The disease known as **amyotrophic lateral sclerosis (ALS)** involves degeneration of the lower motor neurons, leading to skeletal muscle atrophy and paralysis. This disease is sometimes called *Lou Gehrig's disease,* after the baseball player who suffered from it, and also includes the famous physicist Steven Hawking among its victims. Scientists have recently learned that the inherited form of this disease is caused by a defect in the gene for a specific enzyme—*superoxide dismutase*. This enzyme is responsible for eliminating superoxide free radicals, which are highly toxic products that can damage the motor neurons. The mutant gene produces an enzyme that has a different, and in fact destructive, action.

The cell bodies of lower motor neurons are located in the ventral horn of the gray matter of the spinal cord (chapter 8). Axons from these cell bodies leave the ventral side of the spinal cord to form the *ventral roots* of spinal nerves (see fig. 8.28). The *dorsal roots* of spinal nerves contain sensory fibers whose cell bodies are located in the *dorsal root ganglia.* Both sensory (*afferent*)

Table 12.6 A Partial Listing of Terms Used to Describe the Neural Control of Skeletal Muscles

Term	Description
1. Lower motoneurons	Neurons whose axons innervate skeletal muscles—also called the "final common pathway" in the control of skeletal muscles
2. Higher motoneurons	Neurons in the brain that are involved in the control of skeletal movements and that act by facilitating or inhibiting (usually by way of interneurons) the activity of the lower motoneurons
3. Alpha motoneurons	Lower motoneurons whose fibers innervate ordinary (extrafusal) muscle fibers
4. Gamma motoneurons	Lower motoneurons whose fibers innervate the muscle spindle fibers (intrafusal fibers)
5. Agonist/antagonist	A pair of muscles or muscle groups that insert on the same bone, the agonist being the muscle of reference
6. Synergist	A muscle whose action facilitates the action of the agonist
7. Ipsilateral/contralateral	Ipsilateral—located on the same side, or the side of reference; contralateral—located on the opposite side
8. Afferent/efferent	Afferent neurons—sensory; efferent neurons—motor

and motor (*efferent*) fibers join in a common connective tissue sheath to form the spinal nerves at each segment of the spinal cord. In the lumbar region there are about 12,000 sensory and 6,000 motor fibers per spinal nerve.

About 375,000 cell bodies have been counted in a lumbar segment—a number far larger than can be accounted for by the number of motor neurons. Most of these neurons do not contribute fibers to the spinal nerve. Rather, they serve as *interneurons,* whose fibers conduct impulses up, down, and across the central nervous system. Those fibers that conduct impulses to higher spinal cord segments and the brain form *ascending tracts,* and those that conduct to lower spinal segments contribute to *descending tracts.* Those fibers that cross the midline of the CNS to synapse on the opposite side are part of *commissural tracts.* Interneurons can thus conduct impulses up and down on the same, or *ipsilateral,* side, and can affect neurons on the opposite, or *contralateral,* side of the central nervous system.

Muscle Spindle Apparatus

In order for the nervous system to control skeletal movements properly, it must receive continuous sensory feedback information concerning the effects of its actions. This sensory information includes (1) the tension that the muscle exerts on its tendons, provided by the **Golgi tendon organs,** and (2) muscle length, provided by the **muscle spindle apparatus.** The spindle apparatus, so called because it is wider in the center and tapers toward the ends, functions as a length detector. Muscles that require the finest degree of control, such as the muscles of the hand, have the highest density of spindles.

Each spindle apparatus contains several thin muscle cells, called *intrafusal fibers* (*fusus* = spindle), packaged within a connective tissue sheath. Like the stronger and more numerous "ordinary" muscle fibers outside the spindles—the *extrafusal fibers*—the spindles insert into tendons on each end of the muscle. Spindles are therefore said to be in parallel with the extrafusal fibers.

Unlike the extrafusal fibers, which contain myofibrils along their entire length, the contractile apparatus is absent from the central regions of the intrafusal fibers. The central, noncontracting part of an intrafusal fiber contains nuclei. There are two types of intrafusal fibers. One type, the *nuclear bag fibers,* have their nuclei arranged in a loose aggregate in the central regions of the fibers. The other type of intrafusal fibers, called *nuclear chain fibers,* have their nuclei arranged in rows. Two types of sensory neurons serve these intrafusal fibers. **Primary,** or **annulospiral, sensory endings** wrap around the central regions of the nuclear bag and chain fibers (fig. 12.26), and **secondary,** or **flower-spray, endings** are located over the contracting poles of the nuclear chain fibers.

Since the spindles are arranged in parallel with the extrafusal muscle fibers, stretching a muscle causes its spindles to stretch. This stimulates both the primary and secondary sensory endings. The spindle apparatus thus serves as a length detector because the frequency of impulses produced in the primary and secondary endings is proportional to the length of the muscle. The primary endings, however, are most stimulated at the onset of stretch, whereas the secondary endings respond in a more tonic (sustained) fashion as stretch is maintained. Sudden, rapid stretching of a muscle activates both types of sensory endings, and is thus a more powerful stimulus for the muscle spindles than a slower, more gradual stretching that has less of an effect on the primary sensory endings. Since the activation of the sensory endings in muscle spindles produces a reflex contraction, the force of this reflex contraction is greater in response to rapid stretch than to gradual stretch.

FITNESS

Rapid stretching of skeletal muscles produces very forceful muscle contractions as a result of the activation of primary and secondary endings in the muscle spindles and the monosynaptic stretch reflex. This can result in painful muscle spasms, as may occur, for example, when muscles are forcefully pulled in the process of setting broken bones. Painful muscle spasms may be avoided in physical exercise by stretching slowly and thereby stimulating mainly the secondary endings in the muscle spindles. A slower rate of stretch also allows time for the inhibitory Golgi tendon organ reflex to occur and promote muscle relaxation.

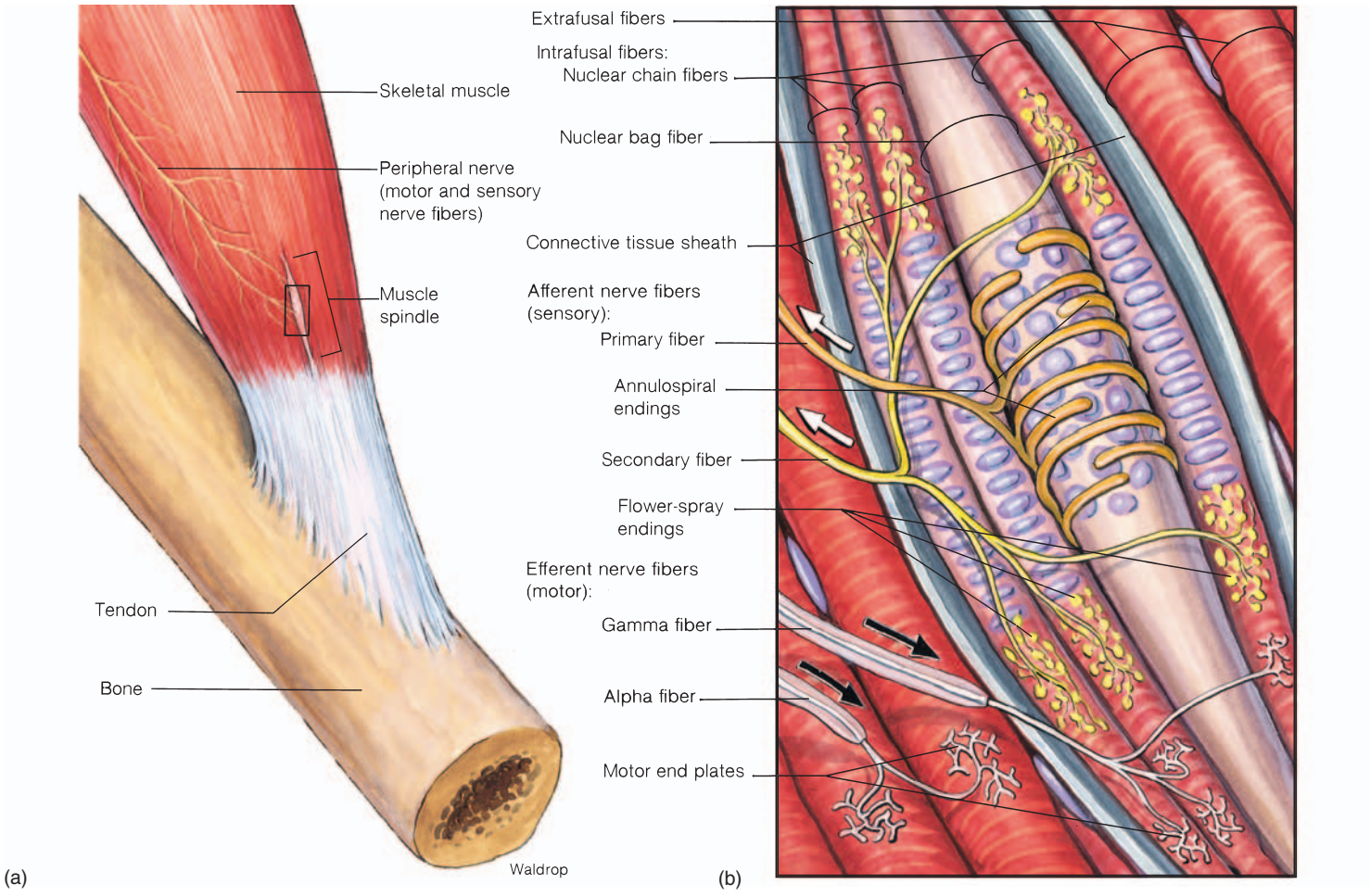


Figure 12.26 **The location and structure of a muscle spindle.** *(a)* A muscle spindle within a skeletal muscle. *(b)* The structure and innervation of a muscle spindle.

Alpha and Gamma Motoneurons

In the spinal cord, two types of lower motor neurons innervate skeletal muscles. The motor neurons that innervate the extrafusal muscle fibers are called **alpha motoneurons;** those that innervate the intrafusal fibers are called **gamma motoneurons** (fig. 12.26). The alpha motoneurons are faster conducting (60 to 90 meters per second) than the thinner gamma motoneurons (10 to 40 meters per second). Since only the extrafusal muscle fibers are sufficiently strong and numerous to cause a muscle to shorten, only stimulation by the alpha motoneurons can cause muscle contraction that results in skeletal movements.

The intrafusal fibers of the muscle spindle are stimulated to contract by gamma motoneurons, which represent one-third of all efferent fibers in spinal nerves. However, because the intrafusal fibers are too few in number and their contraction too weak to cause a muscle to shorten, stimulation by gamma motoneurons results only in isometric contraction of the spindles. Since myofibrils are present in the poles but absent in the central regions of intrafusal fibers, the more distensible central region of the intrafusal fiber is pulled toward the ends in response to stimulation by gamma motoneurons. As a result, the spindle is tightened. This effect of gamma motoneurons, which is sometimes termed *active stretch* of the spindles, serves to increase the sensitivity of the spindles when the entire muscle is passively stretched by external forces. The activation of gamma motoneurons thus enhances the stretch reflex and is an important factor in the voluntary control of skeletal movements.

Coactivation of Alpha and Gamma Motoneurons

Most of the fibers in the descending motor tracts synapse with interneurons in the spinal cord; only about 10% of the descending fibers synapse directly with the lower motor neurons. It is likely that very rapid movements are produced by direct synapses with the lower motor neurons, whereas most other movements are produced indirectly via synapses with spinal interneurons, which in turn stimulate the motor neurons.

Upper motor neurons—interneurons in the brain that contribute fibers to descending motor tracts—usually stimulate alpha and gamma motoneurons simultaneously. Such stimulation is known as **coactivation.** Stimulation of alpha motoneurons results in muscle contraction and shortening; activation of gamma motoneurons stimulates contraction of the intrafusal fibers, and thus

Table 12.7 Summary of Events in a Monosynaptic Stretch Reflex

1. Passive stretch of a muscle (produced by tapping its tendon) stretches the spindle (intrafusal) fibers.
2. Stretching of a spindle distorts its central (bag or chain) region, which stimulates dendritic endings of sensory nerves.
3. Action potentials are conducted by afferent (sensory) nerve fibers into the spinal cord on the dorsal roots of spinal nerves.
4. Axons of sensory neurons synapse with dendrites and cell bodies of somatic motor neurons located in the ventral horn gray matter of the spinal cord.
5. Efferent nerve impulses in the axons of somatic motor neurons (which form the ventral roots of spinal nerves) are conducted to the ordinary (extrafusal) muscle fibers. These neurons are alpha motoneurons.
6. Release of acetylcholine from the endings of alpha motoneurons stimulates the contraction of the extrafusal fibers, and thus of the whole muscle.
7. Contraction of the muscle relieves the stretch of its spindles, thus decreasing electrical activity in the spindle afferent nerve fibers.

"takes out the slack" that would otherwise be present in the spindles as the muscles shorten. In this way, the spindles remain under tension and provide information about the length of the muscle even while the muscle is shortening.

Under normal conditions, the activity of gamma motoneurons is maintained at the level needed to keep the muscle spindles under proper tension while the muscles are relaxed. Undue relaxation of the muscles is prevented by stretch and activation of the spindles, which in turn elicits a reflex contraction (described in the next section). This mechanism produces a normal resting muscle length and state of tension, or **muscle tone.**

Skeletal Muscle Reflexes

Although skeletal muscles are often called voluntary muscles because they are controlled by descending motor pathways that are under conscious control, they often contract in an unconscious, reflex fashion in response to particular stimuli. In the simplest type of reflex, a skeletal muscle contracts in response to the stimulus of muscle stretch. More complex reflexes involve inhibition of antagonistic muscles and regulation of a number of muscles on both sides of the body.

The Monosynaptic Stretch Reflex

Reflex contraction of skeletal muscles occurs in response to sensory input and does not depend on the activation of upper motor neurons. The **reflex arc,** which describes the nerve impulse pathway from sensory to motor endings in such reflexes, involves only a few synapses within the CNS. The simplest of all reflexes—the *muscle stretch reflex*—consists of only one synapse within the CNS. The sensory neuron directly synapses with the motor neuron, without involving spinal cord interneurons. The stretch reflex is thus a **monosynaptic reflex** in terms of the individual reflex arcs (although, of course, many sensory neurons are activated at the same time, leading to the activation of many motor neurons). Resting skeletal muscles are maintained at an optimal length, as previously described under the heading "Length-Tension Relationship," by stretch reflexes.

The stretch reflex is present in all muscles, but it is most dramatic in the extensor muscles of the limbs. The **knee-jerk reflex**—the most commonly evoked stretch reflex—is initiated by striking the patellar ligament with a rubber mallet. This stretches the entire body of the muscle, and thus passively stretches the spindles within the muscle so that sensory nerves with primary (annulospiral) endings in the spindles are activated. Axons of these sensory neurons synapse within the ventral gray matter of the spinal cord with *alpha motoneurons.* These large, fast-conducting motor nerve fibers stimulate the extrafusal fibers of the extensor muscle, resulting in isotonic contraction and the knee jerk. This is an example of negative feedback—stretching of the muscles (and spindles) stimulates shortening of the muscles (and spindles). These events are summarized in table 12.7 and illustrated in figure 12.27.

Golgi Tendon Organs

The **Golgi tendon organs** continuously monitor tension in the tendons produced by muscle contraction or passive stretching of a muscle. Sensory neurons from these receptors synapse with interneurons in the spinal cord; these interneurons, in turn, have *inhibitory synapses* (via IPSPs and postsynaptic inhibition—chapter 7) with motor neurons that innervate the muscle (fig. 12.28). This inhibitory Golgi tendon organ reflex is called a **disynaptic reflex** (because two synapses are crossed in the CNS), and it helps to prevent excessive muscle contractions or excessive passive muscle stretching. Indeed, if a muscle is stretched extensively, it will actually relax as a result of the inhibitory effects produced by the Golgi tendon organs.

CLINICAL

Damage to spinal nerves, or to the cell bodies of lower motor neurons (by poliovirus, for example), produces a **flaccid paralysis,** characterized by reduced muscle tone, depressed stretch reflexes, and atrophy. Damage to upper motor neurons or descending motor tracts at first produces spinal shock in which there is a flaccid paralysis. This is followed in a few weeks by **spastic paralysis,** characterized by increased muscle tone, exaggerated stretch reflexes, and other signs of hyperactive lower motor neurons.

The appearance of spastic paralysis suggests that upper motor neurons normally exert an inhibitory effect on lower alpha and gamma motor neurons. When this inhibition is removed, the gamma motoneurons become hyperactive and the spindles thus become overly sensitive to stretch. This can be demonstrated dramatically by forcefully dorsiflecting the patient's foot (pushing it up) and then releasing it. Forced extension stretches the antagonistic flexor muscles, which contract and produce the opposite movement (plantar flexion). Alternative activation of antagonistic stretch reflexes produces a flapping motion known as *clonus.*

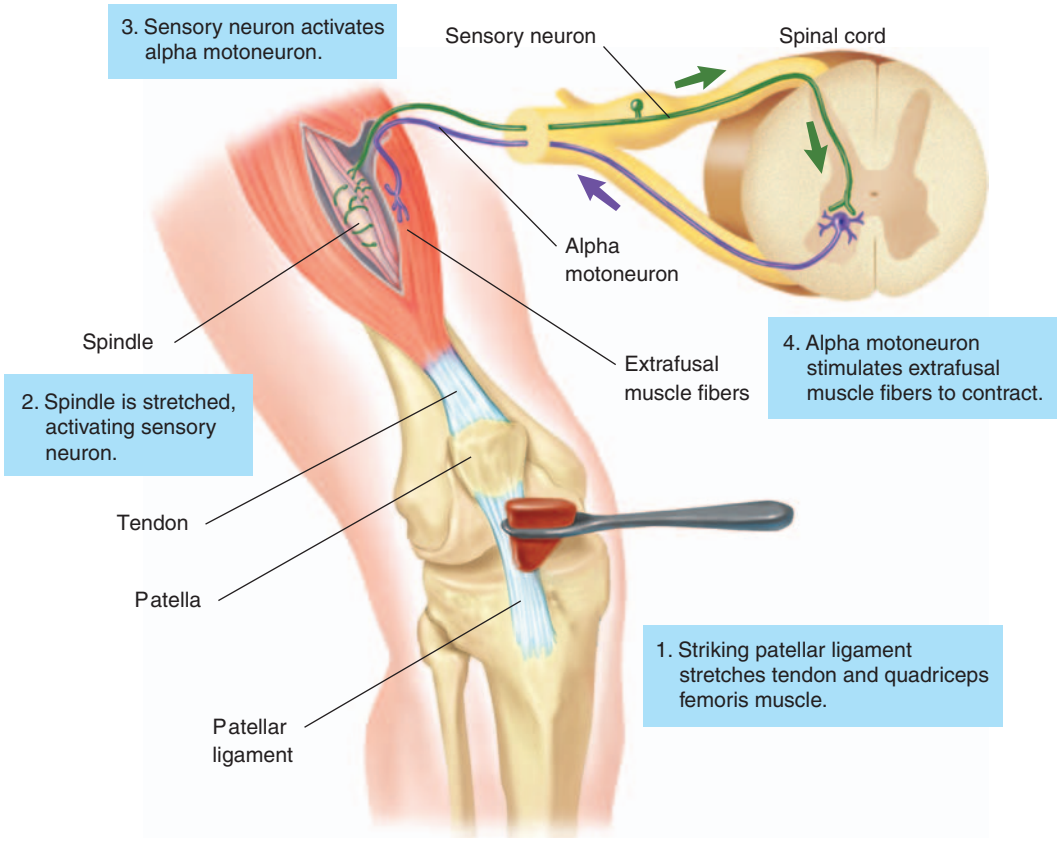


Figure 12.27 The knee-jerk reflex. This is an example of a monosynaptic stretch reflex.

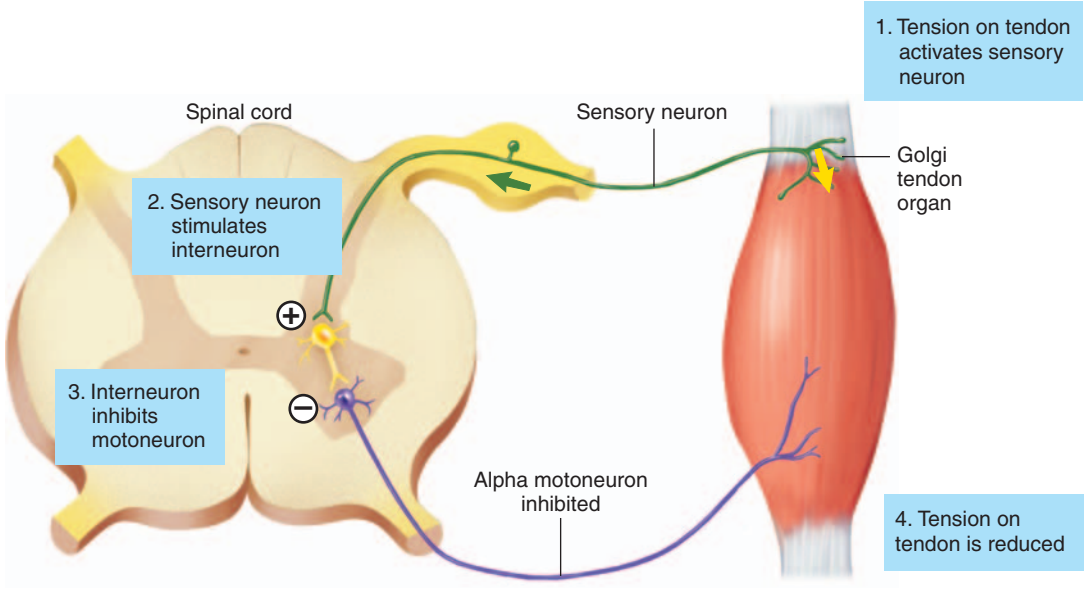


Figure 12.28 The action of the Golgi tendon organ. An increase in muscle tension stimulates the activity of sensory nerve endings in the Golgi tendon organ. This sensory input stimulates an interneuron, which in turn inhibits the activity of a motor neuron innervating that muscle. This is therefore a disynaptic reflex.

Reciprocal Innervation and the Crossed-Extensor Reflex

In the knee-jerk and other stretch reflexes, the sensory neuron that stimulates the motor neuron of a muscle also stimulates interneurons within the spinal cord via collateral branches. These interneurons inhibit the motor neurons of antagonist muscles via inhibitory postsynaptic potentials (IPSPs). This dual stimulatory and inhibitory activity is called **reciprocal innervation** (fig. 12.29).

When a limb is flexed, for example, the antagonistic extensor muscles are passively stretched. Extension of a limb similarly stretches the antagonistic flexor muscles. If the monosynaptic stretch reflexes were not inhibited, reflex contraction of the antagonistic muscles would always interfere with the intended movement. Fortunately, whenever the "intended," or agonist

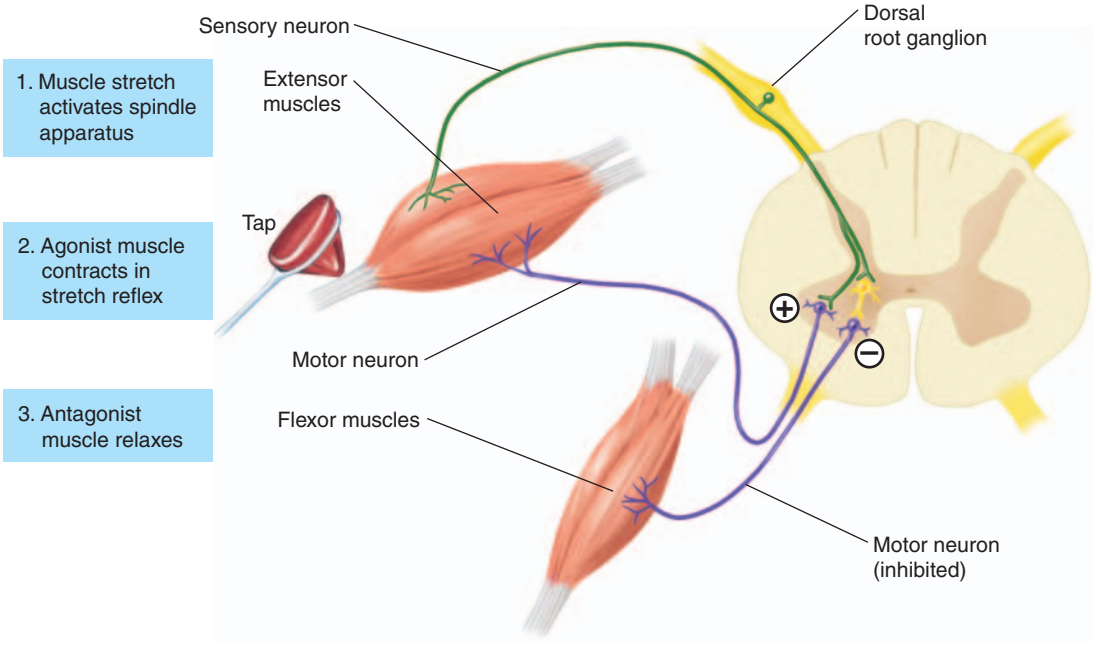


Figure 12.29 **A diagram of reciprocal innervation.** Afferent impulses from muscle spindles stimulates alpha motoneurons to the agonist muscle (the extensor) directly, but (via an inhibitory interneuron) they inhibit activity in the alpha motoneuron to the antagonist muscle.

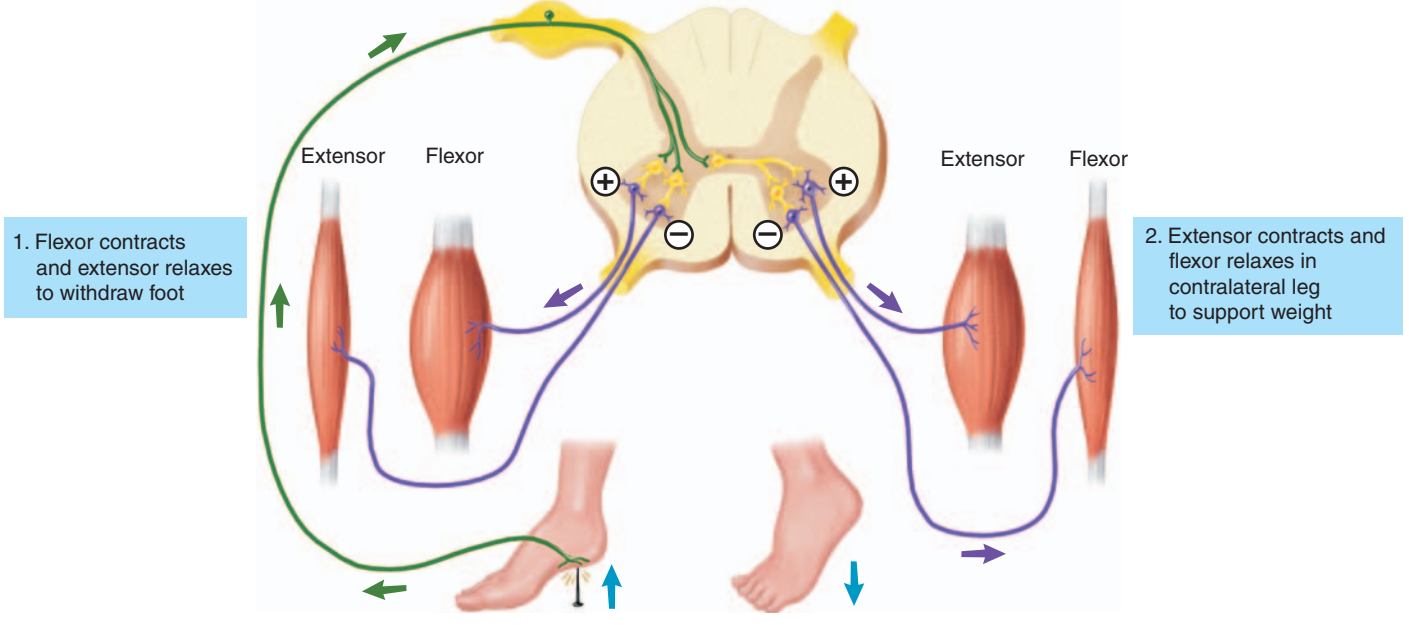


Figure 12.30 **The crossed-extensor reflex.** This complex reflex demonstrates double reciprocal innervation.

muscles, are stimulated to contract, the alpha and gamma motoneurons that stimulate the antagonist muscles are inhibited.

The stretch reflex, with its reciprocal innervations, involves the muscles of one limb only and is controlled by only one segment of the spinal cord. More complex reflexes involve muscles controlled by numerous spinal cord segments and affect muscles on the contralateral side of the cord. Such reflexes involve **double reciprocal innervation** of muscles.

Double reciprocal innervation is illustrated by the **crossed-extensor reflex.** If you step on a tack with your right foot, for example, this foot is withdrawn by contraction of the flexors and relaxation of the extensors of your right leg. The contralateral left leg, by contrast, extends to help support your body during this withdrawal reflex. The extensors of your left leg contract while its flexors relax. These events are illustrated in figure 12.30.

Upper Motor Neuron Control of Skeletal Muscles

As previously described, upper motor neurons are neurons in the brain that influence the control of skeletal muscle by lower motor neurons (alpha and gamma motoneurons). Neurons in the precentral gyrus of the cerebral cortex contribute axons that cross to the contralateral sides in the pyramids of the medulla oblongata; these tracts are thus called **pyramidal tracts** (chapter 8). The pyramidal tracts include the *lateral* and *ventral corticospinal tracts.* Neurons in other areas of the brain produce the **extrapyramidal tracts.** The major extrapyramidal tract is the *reticulospinal tract,* which originates in the reticular formation of the medulla oblongata and pons. Brain areas that influence the activity of extrapyramidal tracts are believed to produce the inhibition of lower motor neurons described in the preceding section.

Cerebellum

The **cerebellum,** like the cerebrum, receives sensory input from muscle spindles and Golgi tendon organs. It also receives fibers from areas of the cerebral cortex devoted to vision, hearing, and equilibrium.

There are no descending tracts from the cerebellum. The cerebellum can influence motor activity only indirectly, through its output to the vestibular nuclei, red nucleus, and basal nuclei. These structures, in turn, affect lower motor neurons via the vestibulospinal tract, rubrospinal tract, and reticulospinal tract. It is interesting that all output from the cerebellum is inhibitory; these inhibitory effects aid motor coordination by eliminating inappropriate neural activity. Damage to the cerebellum interferes with the ability to coordinate movements with spatial judgment. Under- or overreaching for an object may occur, followed by *intention tremor,* in which the limb moves back and forth in a pendulum-like motion.

Basal Nuclei

The **basal nuclei,** sometimes called the **basal ganglia,** include the *caudate nucleus, putamen,* and *globus pallidus* (chapter 8; see fig. 8.12). Often included in this group are other nuclei of the *thalamus, subthalamus, substantia nigra,* and *red nucleus.* Acting directly via the rubrospinal tract and indirectly via synapses in the reticular formation and thalamus, the basal nuclei have profound effects on the activity of lower motor neurons.

In particular, through their synapses in the reticular formation (see fig. 8.12), the basal nuclei exert an inhibitory influence on the activity of lower motor neurons. Damage to the basal nuclei thus results in increased muscle tone, as previously described. People with such damage display *akinesia,* lack of desire to use the affected limb, and *chorea,* sudden and uncontrolled random movements (table 12.8).

Table 12.8 Symptoms of Upper Motor Neuron Damage

Babinski's reflex—Extension of the great toe when the sole of the foot is stroked along the lateral border
Spastic paralysis—High muscle tone and hyperactive stretch reflexes; flexion of arms and extension of legs
Hemiplegia—Paralysis of upper and lower limbs on one side—commonly produced by damage to motor tracts as they pass through internal capsule (such as by cerebrovascular accident—stroke)
Paraplegia—Paralysis of the lower limbs on both sides as a result of lower spinal cord damage
Quadriplegia—Paralysis of upper and lower limbs on both sides as a result of damage to the upper region of the spinal cord or brain
Chorea—Random uncontrolled contractions of different muscle groups (as in Saint Vitus' dance) as a result of damage to basal nuclei
Resting tremor—Shaking of limbs at rest; disappears during voluntary movements; produced by damage to basal nuclei
Intention tremor—Oscillations of the arm following voluntary reaching movements; produced by damage to cerebellum

CLINICAL

Parkinson's disease (or *paralysis agitans*) is a disorder of the basal nuclei involving degeneration of fibers from the substantia nigra. These fibers, which use dopamine as a neurotransmitter, are required to antagonize the effects of other fibers that use acetylcholine (ACh) as a transmitter. The relative deficiency of dopamine compared to ACh is believed to produce the symptoms of Parkinson's disease, including resting tremor. This "shaking" of the limbs tends to disappear during voluntary movements and then reappear when the limb is again at rest.

Test Yourself Before You Continue

1. Draw a muscle spindle surrounded by a few extrafusal fibers. Indicate the location of primary and secondary sensory endings and explain how these endings respond to muscle stretch.
2. Describe all of the events that occur from the time the patellar tendon is struck with a mallet to the time the leg kicks.
3. Explain how a Golgi tendon organ is stimulated and describe the disynaptic reflex that occurs.
4. Explain the significance of reciprocal innervation and double reciprocal innervation in muscle reflexes.
5. Describe the functions of gamma motoneurons and explain why they are stimulated at the same time as alpha motoneurons during voluntary muscle contractions.
6. Explain how a person with spinal cord damage might develop clonus.

Cardiac and Smooth Muscles

Cardiac muscle, like skeletal muscle, is striated and contains sarcomeres that shorten by sliding of thin and thick filaments. But while skeletal muscle requires nervous stimulation to contract, cardiac muscle can produce impulses and contract spontaneously. Smooth muscles lack sarcomeres, but they do contain actin and myosin that produce contractions in response to a unique regulatory mechanism.

Unlike skeletal muscles, which are voluntary effectors regulated by somatic motor neurons, cardiac and smooth muscles are involuntary effectors regulated by autonomic motor neurons. Although there are important differences between skeletal muscle and cardiac and smooth muscle, there are also significant similarities. All types of muscle are believed to contract by means of sliding of thin filaments over thick filaments. The sliding of the filaments is produced by the action of myosin cross bridges in all types of muscles, and excitation-contraction coupling in all types of muscles involves Ca^{2+}.

Cardiac Muscle

Like skeletal muscle cells, cardiac (heart) muscle cells, or **myocardial cells,** are striated; they contain actin and myosin filaments arranged in the form of sarcomeres, and they contract by means of the sliding filament mechanism. The long, fibrous skeletal muscle cells, however, are structurally and functionally separated from each other, whereas the myocardial cells are short, branched, and interconnected. Each myocardial cell is tubular in structure and joined to adjacent myocardial cells by electrical synapses, or **gap junctions** (see chapter 7, fig. 7.20).

The gap junctions are concentrated at the ends of each myocardial cell (fig. 12.31), which permits electrical impulses to be conducted primarily along the long axis from cell to cell. Gap junctions in cardiac muscle have an affinity for stain that makes them appear as dark lines between adjacent cells when viewed in the light microscope. These dark-staining lines are known as *intercalated discs* (fig. 12.32).

Electrical impulses that originate at any point in a mass of myocardial cells, called a **myocardium,** can spread to all cells in the mass that are joined by gap junctions. Because all cells in a myocardium are electrically joined, a myocardium behaves as a single functional unit. Thus, unlike skeletal muscles that produce contractions that are graded depending on the number of cells stimulated, a myocardium contracts to its full extent each time because all of its cells contribute to the contraction. The ability of the myocardial cells to contract, however, can be increased by the hormone epinephrine and by stretching of the heart chambers. The heart contains two distinct myocardia (atria and ventricles), as will be described in chapter 13.

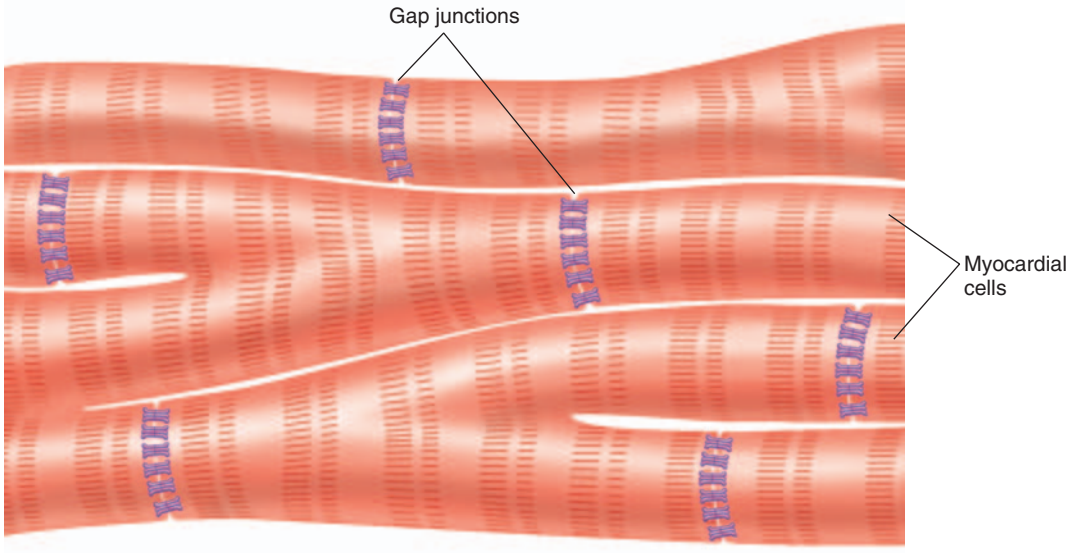


Figure 12.31 **Myocardial cells are interconnected by gap junctions.** The gap junctions are fluid-filled channels through the plasma membrane of adjacent cells that permit the conduction of impulses from one cell to the next. The gap junctions are concentrated at the ends of each myocardial cell, and each gap junction is composed of connexin proteins (also see chapter 7, fig. 7.20).

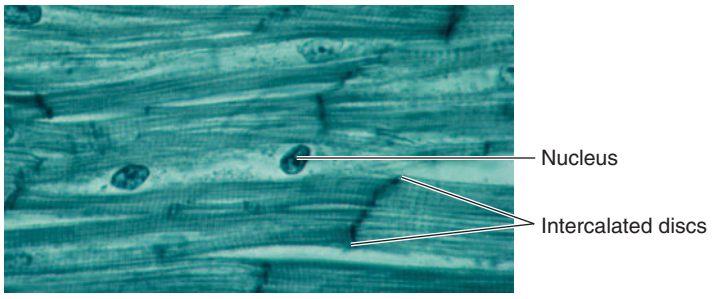


Figure 12.32 **Cardiac muscle.** Notice that the cells are short, branched, and striated and that they are interconnected by intercalated discs.

CLINICAL

Cardiac muscle, like skeletal muscle, contains the troponin complex of three proteins (see fig. 12.13). **Troponin I** helps inhibit the binding of the myosin cross-bridges to actin; **troponin T** binds to tropomyosin in the thin filaments, and **troponin C** binds to Ca^{2+} for muscle contraction. Damage to myocardial cells, which occurs in **myocardial infarction,** causes troponins to be released into the blood. Fortunately for clinical diagnosis, troponins T and I are slightly different in cardiac muscle than in skeletal muscle. Thus, troponins T and I released by damaged myocardial cells can be distinguished and measured by laboratory tests using specific antibodies. Such tests are now an important tool in the diagnosis of myocardial infarction.

Unlike skeletal muscles, which require external stimulation by somatic motor nerves before they can produce action potentials and contract, cardiac muscle is able to produce action potentials automatically. Cardiac action potentials normally originate in a specialized group of cells called the *pacemaker.* However, the rate of this spontaneous depolarization, and thus the rate of the heartbeat, are regulated by autonomic innervation. Regulation of the cardiac rate is described more fully in chapter 14.

Smooth Muscle

Smooth (visceral) muscles are arranged in circular layers in the walls of blood vessels and bronchioles (small air passages in the lungs). Both circular and longitudinal smooth muscle layers occur in the tubular digestive tract, the ureters (which transport urine), the ductus deferentia (which transport sperm cells), and the uterine tubes (which transport ova). The alternate contraction of circular and longitudinal smooth muscle layers in the intestine produces **peristaltic waves,** which propel the contents of these tubes in one direction.

Although smooth muscle cells do not contain sarcomeres (which produce striations in skeletal and cardiac muscle), they do contain a great deal of actin and some myosin, which produces a ratio of thin to thick filaments of about 16 to 1 (in striated muscles the ratio is 2 to 1). Unlike striated muscles, in which the thin filaments are relatively short (extending from a Z disc into a sarcomere), the thin filaments of smooth muscle cells are quite long. They attach either to regions of the plasma membrane of the smooth muscle cell or to cytoplasmic protein structures called **dense bodies,** which are analogous to the Z discs of striated muscle (fig. 12.33*b*).

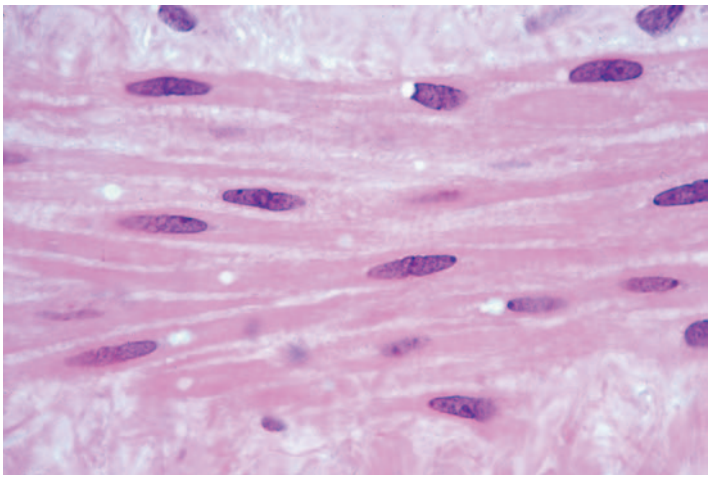
In smooth muscle, the myosin proteins of the thick filaments are stacked vertically so that their long axis is perpendicular to the long axis of the thick filament (fig. 12.33*c*). In this way, the myosin heads can form cross bridges with actin all along the length of the thick filaments. This is different from the horizontal arrangement of myosin proteins in the thick filaments of striated muscles (see fig. 12.10), which is required to cause the shortening of sarcomeres.

The arrangement of the contractile apparatus in smooth muscle cells, and the fact that it is not organized into sarcomeres, is required for proper smooth muscle function. Smooth muscles must be able to contract even when greatly stretched—in the urinary bladder, for example, the smooth muscle cells may be stretched up to two and a half times their resting length. The smooth muscle cells of the uterus may be stretched up to eight times their original length by the end of pregnancy. Striated muscles, because of their structure, lose their ability to contract when the sarcomeres are stretched to the point where actin and myosin no longer overlap (as shown in fig. 12.20).

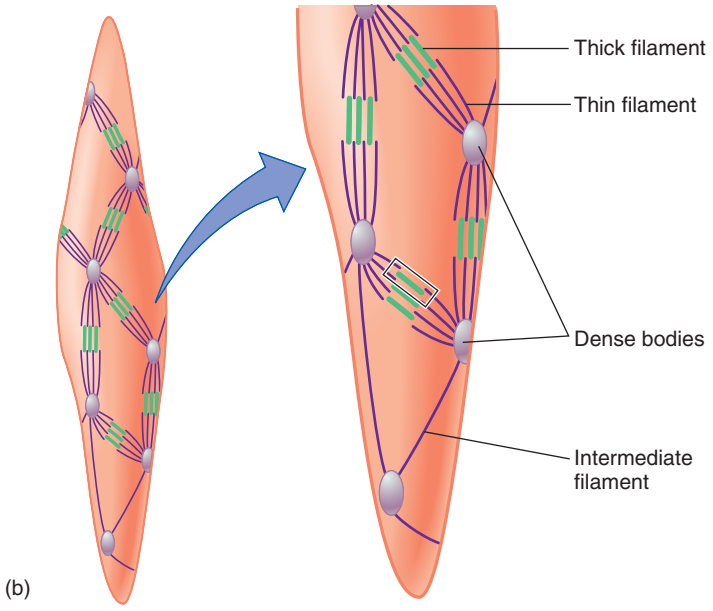
Excitation-Contraction Coupling in Smooth Muscles

As in striated muscles, the contraction of smooth muscles is triggered by a sharp rise in the Ca^{2+} concentration within the cytoplasm of the muscle cells. However, the sarcoplasmic reticulum of smooth muscles is less developed than that of skeletal muscles, and Ca^{2+} released from this organelle may account for only the initial phase of smooth muscle contraction. Extracellular Ca^{2+} diffusing into the smooth muscle cell through its plasma membrane is responsible for sustained contractions. This Ca^{2+} enters primarily through voltage-regulated Ca^{2+} channels in the plasma membrane. The opening of these channels is graded by the amount of depolarization; the greater the depolarization, the more Ca^{2+} will enter the cell and the stronger will be the smooth muscle contraction.

The events that follow the entry of Ca^{2+} into the cytoplasm are somewhat different in smooth muscles than in striated muscles. In striated muscles, Ca^{2+} combines with troponin. Troponin, however, is not present in smooth muscle cells. In smooth muscles, Ca^{2+} combines with a protein in the cytoplasm called **calmodulin,** which is structurally similar to troponin. Calmodulin was previously discussed in relation to the function of Ca^{2+} as a second messenger in hormone action (chapter 11). The calmodulin-Ca^{2+} complex thus formed combines with and activates **myosin light-chain kinase (MLCK),** an enzyme that catalyzes the phosphorylation (addition of phosphate groups) of *myosin light chains,* a component of the myosin cross bridges. In



(a)



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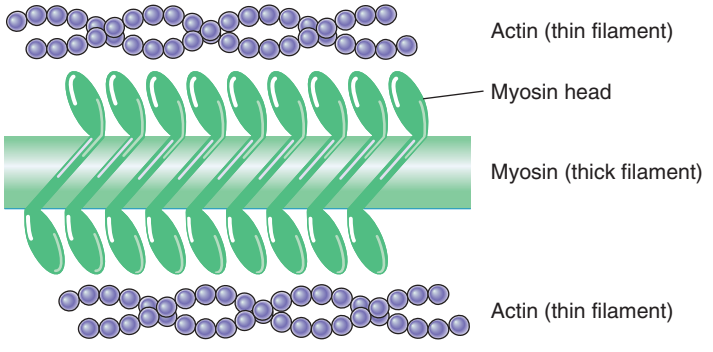


(c)

Figure 12.33 **Smooth muscle and its contractile apparatus.** *(a)* A photomicrograph of smooth muscle cells in the wall of a blood vessel. *(b)* Arrangement of thick and thin filaments in smooth muscles. Note that dense bodies are also interconnected by intermediate fibers. *(c)* The myosin proteins are stacked in a different arrangement in smooth muscles than in striated muscles.

smooth muscle (unlike striated muscle), the phosphorylation of myosin cross bridges is the regulatory event that permits them to bind to actin and thereby produce a contraction (fig. 12.34).

Unlike the situation in striated muscle cells, which produce all-or-none action potentials, smooth muscle cells can produce graded depolarizations and contractions without producing action potentials. Indeed, only these graded depolarizations are conducted from cell to cell in many smooth muscles. The greater the depolarization of a smooth muscle cell, the more Ca^{2+} will enter, and the more MLCK enzymes will be activated. With more MLCK enzymes activated, more cross bridges will become phosphorylated and able to bind to actin. In this way, a stronger depolarization of the smooth muscle cell leads to a stronger contraction.

Relaxation of the smooth muscle follows the closing of the Ca^{2+} channels and lowering of the cytoplasmic Ca^{2+} concentrations by the action of Ca^{2+}-ATPase active transport pumps.

Under these conditions, calmodulin dissociates from the myosin light-chain kinase, thereby inactivating this enzyme. The phosphate groups that were added to the myosin are then removed by a different enzyme, a *myosin phosphatase* (fig. 12.34). Dephosphorylation inhibits the cross bridge from binding to actin and producing another power stroke.

In addition to being graded, the contractions of smooth muscle cells are slow and sustained. The slowness of contraction is related to the fact that myosin ATPase in smooth muscle is slower in its action (splitting ATP for the cross-bridge cycle) than it is in striated muscle. The sustained nature of smooth muscle contraction is explained by the theory that cross bridges in smooth muscles can enter a *latch state.*

The latch state allows smooth muscle to maintain its contraction in a very energy-efficient manner, hydrolyzing less ATP than would otherwise be required. This ability is obviously important for smooth muscles, given that they encircle the walls of hollow organs and must sustain contractions for long periods of time. The mechanisms by which the latch state is produced, however, are complex and poorly understood.

The three muscle types—skeletal, cardiac, and smooth—are compared in table 12.9.

CLINICAL

Drugs such as *nifedipine (Procardia)* and related newer compounds are **calcium channel blockers.** These drugs block Ca^{2+} channels in the membrane of smooth muscle cells within the walls of blood vessels, causing the muscles to relax and the vessels to dilate. This effect, called vasodilation, may be helpful in treating some cases of hypertension (high blood pressure). Calcium-channel-blocking drugs are also used when spasm of the coronary arteries (vasospasm) produces angina pectoris, which is pain caused by insufficient blood flow to the heart.

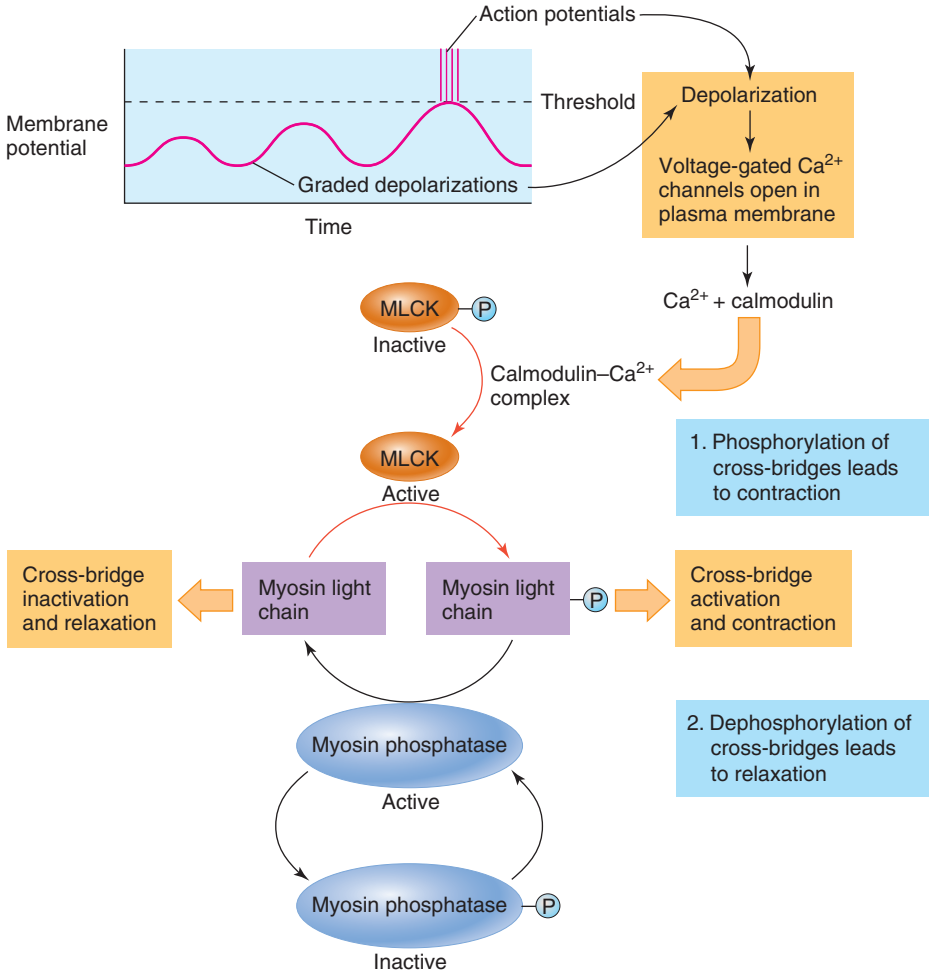


Figure 12.34 **Excitation-contraction coupling in smooth muscle.** When Ca^{2+} passes through voltage-gated channels in the plasma membrane it enters the cytoplasm and binds to calmodulin. The calmodulin-Ca^{2+} complex then activates myosin light-chain kinase (MLCK) by removing a phosphate group. The activated MLCK, in turn, phosphorylates the myosin light chains, thereby activating the cross bridges to cause contraction. Contraction is ended when myosin phosphatase becomes activated. Upon its activation, myosin phosphatase removes the phosphates from the myosin light chains and thereby inactivates the cross bridges.

Table 12.9 Comparison of Skeletal, Cardiac, and Smooth Muscle

Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Striated; actin and myosin arranged in sarcomeres	Striated; actin and myosin arranged in sarcomeres	Not striated; more actin than myosin; actin inserts into dense bodies and cell membrane
Well-developed sarcoplasmic reticulum and transverse tubules	Moderately developed sarcoplasmic reticulum and transverse tubules	Poorly developed sarcoplasmic reticulum; no transverse tubules
Contains troponin in the thin filaments	Contains troponin in the thin filaments	Contains calmodulin, a protein that, when bound to Ca^{2+}, activates the enzyme myosin light-chain kinase
Ca^{2+} released into cytoplasm from sarcoplasmic reticulum	Ca^{2+} enters cytoplasm from sarcoplasmic reticulum and extracellular fluid	Ca^{2+} enters cytoplasm from extracellular fluid, sarcoplasmic reticulum, and perhaps mitochondria
Cannot contract without nerve stimulation; denervation results in muscle atrophy	Can contract without nerve stimulation; action potentials originate in pacemaker cells of heart	Maintains tone in absence of nerve stimulation; visceral smooth muscle produces pacemaker potentials; denervation results in hypersensitivity to stimulation
Muscle fibers stimulated independently; no gap junctions	Gap junctions present as intercalated discs	Gap junctions generally present

Clinical Investigation Clues

Remember that Maria was taking a calcium-channel-blocking drug to treat her hypertension.

How do such drugs help to lower blood pressure? Is it likely that this drug contributed to Maria's skeletal muscle pain and fatigue?

Could it raise her blood Ca^{2+} levels?

If not, what could raise her blood Ca^{2+}?

Single-Unit and Multiunit Smooth Muscles

Smooth muscles are often grouped into two functional categories: **single-unit** and **multiunit** (fig. 12.35). Single-unit smooth muscles have numerous gap junctions (electrical synapses) between adjacent cells that weld them together electrically; they thus behave as a single unit, much like cardiac muscle. Most smooth muscles—including those in the digestive tract and uterus—are single-unit.

Only some cells of single-unit smooth muscles receive autonomic innervation, but the ACh released by the axon can diffuse to other smooth muscle cells. Binding of ACh to its muscarinic receptors causes depolarization by closing K^+ channels, as described in chapter 9 (see fig. 9.11). Such stimulation, however, only modifies the automatic behavior of single-unit smooth muscles. Single-unit smooth muscles display *pacemaker* activity, in which certain cells stimulate others in the mass. This is similar to the situation in cardiac muscle. Single-unit smooth muscles also display intrinsic, or *myogenic,* electrical activity and contraction in response to stretch. For example, the stretch induced by an increase in the volume of a ureter or a section of the digestive tract can stimulate myogenic contraction. Such contraction does not require stimulation by autonomic nerves.

Contraction of multiunit smooth muscles, by contrast, requires nerve stimulation. Multiunit smooth muscles have few, if any, gap junctions. The cells must thus be stimulated individually by nerve fibers. Examples of multiunit smooth muscles are the arrector pili muscles in the skin and the ciliary muscles attached to the lens of the eye.

Autonomic Innervation of Smooth Muscles

The neural control of skeletal muscles differs significantly from that of smooth muscles. A skeletal muscle fiber has only one junction with a somatic nerve fiber, and the receptors for the neurotransmitter are located only at the neuromuscular junction. By contrast, the entire surface of smooth muscle cells contains neurotransmitter receptor proteins. Neurotransmitter molecules are released along a stretch of an autonomic nerve fiber that is located some distance from the smooth muscle cells. The regions of the autonomic fiber that release transmitters appear as bulges, or *varicosities,* and the neurotransmitters released from these varicosities stimulate a number of smooth muscle cells. Since there are numerous varicosities along a stretch of an autonomic nerve ending, they form synapses "in passing"—or *synapses en passant*—with the smooth muscle cells. This was described in chapter 9 (see fig. 9.9) and is shown in figure 12.35.

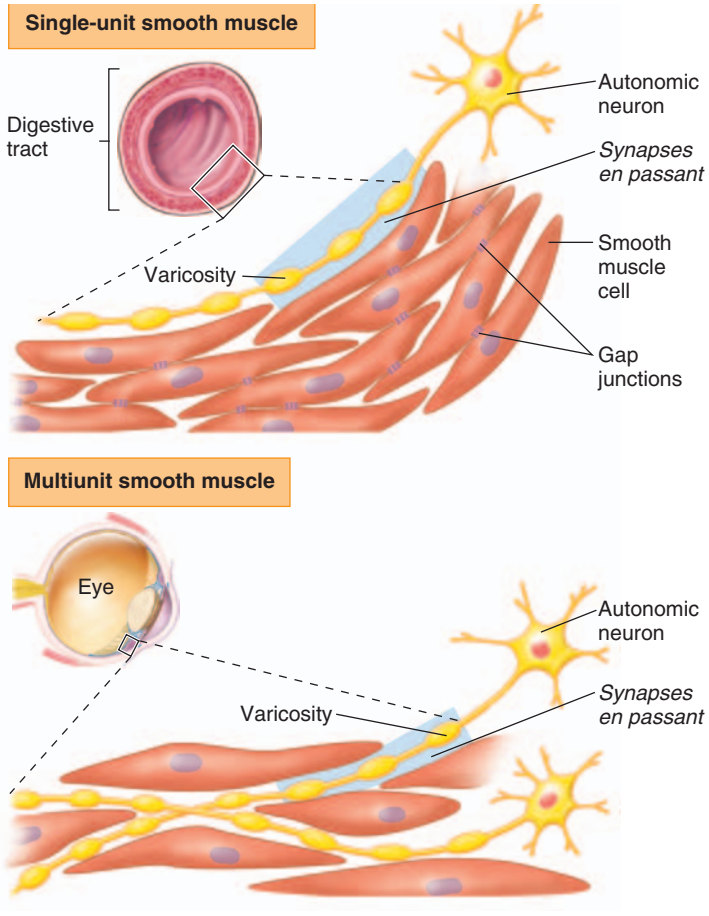


Figure 12.35 **Single-unit and multiunit smooth muscle.** In single-unit smooth muscle, the individual smooth muscle cells are electrically joined by gap junctions, so that depolarizations can spread from one cell to the next. In multiunit smooth muscle, each smooth muscle cell must be stimulated by an axon. The axons of autonomic neurons have varicosities, which release neurotransmitters, and which form *synapses en passant* with the smooth muscle cells.

Test Yourself Before You Continue

1. Explain how cardiac muscle differs from skeletal muscle in its structure and regulation of contraction.
2. Contrast the structure of a smooth muscle cell with that of a skeletal muscle fiber and discuss the advantages of each type of structure.
3. Describe the events by which depolarization of a smooth muscle cell results in contraction and explain why smooth muscle contractions are slow and sustained.
4. Distinguish between single-unit and multiunit smooth muscles.

Interactions

HPer Links of the Muscular System with Other Body Systems

Integumentary System

- The skin helps to protect all organs of the body from invasion by pathogens (p. 466)
- The smooth muscles of cutaneous blood vessels are needed for the regulation of cutaneous blood flow (p. 446)
- The arrector pili muscles in the skin produce goose bumps (p. 18)

Skeletal System

- Bones store calcium, which is needed for the control of muscle contraction (p. 652)
- The skeleton provides attachment sites for muscles (p. 340)
- Joints of the skeleton provide levers for movement (p. 340)
- Muscle contractions maintain the health and strength of bone (p. 653)

Nervous System

- Somatic motor neurons stimulate contraction of skeletal muscles (p. 156)
- Autonomic neurons stimulate smooth muscle contraction or relaxation (p. 228)
- Autonomic nerves increase cardiac output during exercise (p. 443)
- Sensory neurons from muscles monitor muscle length and tension (p. 362)

Endocrine System

- Sex hormones promote muscle development and maintenance (p. 638)
- Parathyroid hormone and other hormones regulate blood calcium and phosphate concentrations (p. 653)
- Epinephrine and norepinephrine influence contractions of cardiac muscle and smooth muscles (p. 236)
- Insulin promotes glucose entry into skeletal muscles (p. 640)
- Adipose tissue secretes hormones that regulate the sensitivity of muscles to insulin (p. 634)

Circulatory System

- Blood transports O_2 and nutrients to muscles and removes CO_2 and lactic acid (p. 382)
- Contractions of skeletal muscles serve as a pump to assist blood movement within veins (p. 410)
- Cardiac muscle enables the heart to function as a pump (p. 394)
- Smooth muscle enables blood vessels to constrict and dilate (p. 406)

Respiratory System

- The lungs provide oxygen for muscle metabolism and eliminate carbon dioxide (p. 502)
- Respiratory muscles enable ventilation of the lungs (p. 511)

Urinary System

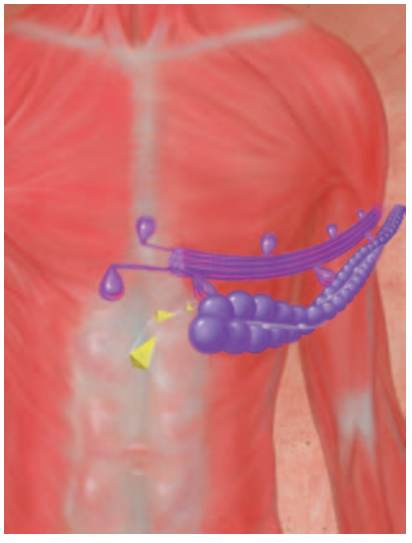
- The kidneys eliminate creatinine and other metabolic wastes from muscle (p. 550)
- The kidneys help to regulate the blood calcium and phosphate concentrations (p. 653)
- Muscles of the urinary tract are needed for the control of urination (p. 552)

Digestive System

- The GI tract provides nutrients for all body organs, including muscles (p. 587)
- Smooth muscle contractions push digestion products along the GI tract (p. 590)
- Muscular sphincters of the GI tract help to regulate the passage of food (p. 591)

Reproductive System

- Testicular androgen promotes growth of skeletal muscle (p. 672)
- Muscle contractions contribute to orgasm in both sexes (p. 673)
- Uterine muscle contractions are required for vaginal delivery of a fetus (p. 706)



Summary

Skeletal Muscles 340

I. Skeletal muscles are attached to bones by tendons.
- **A.** Skeletal muscles are composed of separate cells, or fibers, that are attached in parallel to the tendons.
- **B.** Individual muscle fibers are covered by the endomysium; bundles of fibers, called fascicles, are covered by the perimysium; and the entire muscle is covered by the epimysium.
- **C.** Skeletal muscle fibers are striated.
  1. The dark striations are called A bands, and the light regions are called I bands.
  2. Z lines are located in the middle of each I band.

II. The contraction of muscle fibers *in vivo* is stimulated by somatic motor neurons.
- **A.** Each somatic motor axon branches to innervate numerous muscle fibers.
- **B.** The motor neuron and the muscle fibers it innervates are called a motor unit.
  1. When a muscle is composed of a relatively large number of motor units (such as in the hand), there is fine control of muscle contraction.
  2. The large muscles of the leg have relatively few motor units, which are correspondingly large in size.
  3. Sustained contractions are produced by the asynchronous stimulation of different motor units.

Mechanisms of Contraction 344

I. Skeletal muscle cells, or fibers, contain structures called myofibrils.
- **A.** Each myofibril is striated with dark (A) and light (I) bands. In the middle of each I band are Z lines.
- **B.** The A bands contain thick filaments, composed primarily of myosin.
  1. The edges of each A band also contain thin filaments, which overlap the thick filaments.
  2. The central regions of the A bands contain only thick filaments—these regions are the H bands.
- **C.** The I bands contain only thin filaments, composed primarily of actin.
- **D.** Thin filaments are composed of globular actin subunits known as G-actin. A protein known as tropomyosin is also located at intervals in the thin filaments. Another protein—troponin—is attached to the tropomyosin.

II. Myosin cross bridges extend out from the thick filaments to the thin filaments.
- **A.** At rest, the cross bridges are not attached to actin.
  1. The cross-bridge heads function as ATPase enzymes.
  2. ATP is split into ADP and P_i, activating the cross bridge.
- **B.** When the activated cross bridges attach to actin, they release P_i and undergo a power stroke.
- **C.** At the end of a power stroke, the cross bridge releases the ADP and binds to a new ATP.
  1. This allows the cross bridge to detach from actin and repeat the cycle.
  2. Rigor mortis is caused by the inability of cross bridges to detach from actin because of a lack of ATP.

III. The activity of the cross bridges causes the thin filaments to slide toward the centers of the sarcomeres.
- **A.** The filaments slide—they do not shorten—during muscle contraction.
- **B.** The lengths of the H and I bands decrease, whereas the A bands stay the same length during contraction.

IV. When a muscle is at rest, the Ca^{2+} concentration of the sarcoplasm is very low and cross bridges are prevented from attaching to actin.
- **A.** The Ca^{2+} is actively transported into the sarcoplasmic reticulum.
- **B.** The sarcoplasmic reticulum is a modified endoplasmic reticulum that surrounds the myofibrils.

V. Action potentials are conducted by transverse tubules into the muscle fiber.
- **A.** Transverse tubules are invaginations of the cell membrane that almost touch the sarcoplasmic reticulum.
- **B.** Action potentials in the transverse tubules stimulate the opening of Ca^{2+}-release channels in the sarcoplasmic reticulum, causing Ca^{2+} to diffuse into the sarcoplasm and stimulate contractions.

VI. When action potentials cease, the Ca^{2+}-release channels in the sarcoplasmic reticulum close.
- **A.** This allows the active transport Ca^{2+}-ATPase pumps in the sarcoplasmic reticulum to accumulate Ca, removing it from the sarcoplasm and sarcomeres.
- **B.** As a result of the removal of Ca^{2+} from troponin, the muscle relaxes.

Contractions of Skeletal Muscles 354

I. Muscles *in vitro* can exhibit twitch, summation, and tetanus.
- **A.** The rapid contraction and relaxation of muscle fibers is called a twitch.
- **B.** A whole muscle also produces a twitch in response to a single electrical pulse *in vitro*.
  1. The stronger the electric shock, the stronger the muscle twitch—whole muscles can produce graded contractions.
  2. The graded contraction of whole muscles is due to different numbers of fibers participating in the contraction.

C. The summation of fiber twitches can occur so rapidly that the muscle produces a smooth, sustained contraction known as tetanus.

D. When a muscle exerts tension without shortening, the contraction is termed isometric; when shortening does occur, the contraction is isotonic.

E. When a muscle contracts but, despite its contraction, is made to lengthen due to the application of an external force, the contraction is said to be eccentric.

II. The series-elastic component refers to the elastic composition of the muscle and its associated structures, which must be stretched tight before the tension exerted by the muscle can cause movement.

III. The strength of a muscle contraction is dependent upon its resting length.

A. If the muscle is too short or too long prior to stimulation, the filaments in the sarcomeres will not have an optimum amount of overlap.

B. At its normal resting length *in vivo,* a muscle is at its optimum length for contraction.

Energy Requirements of Skeletal Muscles 357

I. Aerobic cell respiration is ultimately required for the production of ATP needed for cross-bridge activity.

A. Resting muscles and muscles performing light exercise obtain most of their energy from fatty acids.

B. During moderate exercise, just below the lactate threshold, energy is obtained about equally from fatty acids and glucose.

C. Glucose, from the muscle's stored glycogen and from blood plasma, becomes an increasingly important energy source during heavy exercise.

D. New ATP can be quickly produced from the combination of ADP with phosphate derived from phosphocreatine.

E. Muscle fibers are of three types.

1. Slow-twitch red fibers are adapted for aerobic respiration and are resistant to fatigue.

2. Fast-twitch white fibers are adapted for anaerobic respiration.

3. Intermediate fibers are fast-twitch but adapted for aerobic respiration.

II. Muscle fatigue may be caused by a number of mechanisms.

A. Fatigue during sustained maximal contraction may be produced by the accumulation of extracellular K^+ as a result of high levels of nerve activity.

B. Fatigue during moderate exercise is primarily a result of anaerobic respiration by fast-twitch fibers.

1. The productions of lactic acid and consequent fall in pH, the depletion of muscle glycogen, and other metabolic changes interfere with the release of Ca^{2+} from the sarcoplasmic reticulum.

2. Interference with excitation contraction coupling, rather than depletion of ATP, appears to be responsible for muscle fatigue.

C. In human exercise, however, fatigue is often caused by changes in the CNS before the muscles themselves fatigue; this central fatigue reduces the force of voluntary contractions.

III. Physical training affects the characteristics of the muscle fibers.

A. Endurance training increases the aerobic capacity of muscle fibers and their use of fatty acids for energy, so that their reliance on glycogen and anaerobic respiration—and thus their susceptibility to fatigue—is reduced.

B. Resistance training causes hypertrophy of muscle fibers because of an increase in the size and number of myofibrils.

Neural Control of Skeletal Muscles 362

I. The somatic motor neurons that innervate the muscles are called lower motor neurons.

A. Alpha motoneurons innervate the ordinary, or extrafusal, muscle fibers. These are the fibers that produce muscle shortening during contraction.

B. Gamma motoneurons innervate the intrafusal fibers of the muscle spindles.

II. Muscle spindles function as length detectors in muscles.

A. Spindles consist of several intrafusal fibers wrapped together. The spindles are in parallel with the extrafusal fibers.

B. Stretching of the muscle stretches the spindles, which excites sensory endings in the spindle apparatus.

1. Impulses in the sensory neurons travel into the spinal cord in the dorsal roots of spinal nerves.

2. The sensory neuron synapses directly with an alpha motoneuron within the spinal cord, which produces a monosynaptic reflex.

3. The alpha motoneuron stimulates the extrafusal muscle fibers to contract, thus relieving the stretch. This is called the stretch reflex.

C. The activity of gamma motoneurons tightens the spindles, thus making them more sensitive to stretch and better able to monitor the length of the muscle, even during muscle shortening.

III. The Golgi tendon organs monitor the tension that the muscle exerts on its tendons.

A. As the tension increases, sensory neurons from Golgi tendon organs inhibit the activity of alpha motoneurons.

B. This is a disynaptic reflex because the sensory neurons synapse with interneurons, which in turn make inhibitory synapses with motoneurons.

IV. A crossed-extensor reflex occurs when a foot steps on a tack.

A. Sensory input from the injured foot causes stimulation of flexor muscles and inhibition of the antagonistic extensor muscles.

B. The sensory input also crosses the spinal cord to cause stimulation of extensor and inhibition of flexor muscles in the contralateral leg.

V. Most of the fibers of descending tracts synapse with spinal interneurons, which in turn synapse with the lower motor neurons.

A. Alpha and gamma motoneurons are usually stimulated at the same time, or coactivated.

B. The stimulation of gamma motoneurons keeps the muscle spindles under tension and sensitive to stretch.

C. Upper motor neurons, primarily in the basal nuclei, also exert inhibitory effects on gamma motoneurons.

VI. Neurons in the brain that affect the lower motor neurons are called upper motor neurons.

A. The fibers of neurons in the precentral gyrus, or motor cortex, descend to the lower motor neurons as the lateral and ventral corticospinal tracts.

1. Most of these fibers cross to the contralateral side in the brain stem, forming structures called the pyramids; therefore, this system is called the pyramidal system.

2. The left side of the brain thus controls the musculature on the right side, and vice versa.

B. Other descending motor tracts are part of the extrapyramidal system.

1. The neurons of the extrapyramidal system make numerous synapses in different areas of the brain, including the midbrain, brain stem, basal nuclei, and cerebellum.

2. Damage to the cerebellum produces intention tremor, and degeneration of dopaminergic neurons in the basal nuclei produces Parkinson's disease.

Cardiac and Smooth Muscles 369

I. Cardiac muscle is striated and contains sarcomeres.

A. In contrast to skeletal muscles, which require neural stimulation to contract, action potentials in the heart originate in myocardial cells; stimulation by neurons is not required.

B. Also unlike the situation in skeletal muscles, action potentials can cross from one myocardial cell to another.

II. The thin and thick filaments in smooth muscles are not organized into sarcomeres.

A. The thin filaments extend from the plasma membrane and from dense bodies in the cytoplasm.

B. The myosin proteins are stacked perpendicular to the long axis of the thick filaments, so they can bind to actin all along the length of the thick filament.

C. Depolarizations are graded and conducted from one smooth muscle cell to the next.

1. The depolarizations stimulate the entry of Ca^{2+}, which binds to calmodulin; this complex then activates myosin light-chain kinase, which phosphorylates the myosin heads.

2. Phosphorylation of the myosin heads is needed for them to be able to bind to actin and produce contractions.

D. Smooth muscles are classified as single-unit, if they are interconnected by gap junctions, and as multiunit if they are not so connected.

E. Autonomic neurons have varicosities that release neurotransmitter all along their length of contact with the smooth muscle cells, making *synapses en passant.*

Review Activities

Test Your Knowledge of Terms and Facts

1. A graded whole muscle contraction is produced *in vivo* primarily by variations in

a. the strength of the fiber's contraction.

b. the number of fibers that are contracting.

c. both of these.

d. neither of these.

2. The series-elastic component of muscle contraction is responsible for

a. increased muscle shortening to successive twitches.

b. a time delay between contraction and shortening.

c. the lengthening of muscle after contraction has ceased.

d. all of these.

3. Which of these muscles have motor units with the highest innervation ratio?

a. leg muscles

b. arm muscles

c. muscles that move the fingers

d. muscles of the trunk

4. The stimulation of gamma motoneurons produces

a. isotonic contraction of intrafusal fibers.

b. isometric contraction of intrafusal fibers.

c. either isotonic or isometric contraction of intrafusal fibers.

d. contraction of extrafusal fibers.

5. In a single reflex arc involved in the knee-jerk reflex, how many synapses are activated within the spinal cord?

a. thousands

b. hundreds

c. dozens

d. two

e. one

6. Spastic paralysis may occur when there is damage to

a. the lower motor neurons.

b. the upper motor neurons.

c. either the lower or the upper motor neurons.

7. When a skeletal muscle shortens during contraction, which of these statements is *false?*
   - **a.** The A bands shorten.
   - **b.** The H bands shorten.
   - **c.** The I bands shorten.
   - **d.** The sarcomeres shorten.
8. Electrical excitation of a muscle fiber *most directly* causes
   - **a.** movement of tropomyosin.
   - **b.** attachment of the cross bridges to action.
   - **c.** release of Ca^{2+} from the sarcoplasmic reticulum.
   - **d.** splitting of ATP.
9. The energy for muscle contraction is *most directly* obtained from
   - **a.** phosphocreatine.
   - **b.** ATP.
   - **c.** anaerobic respiration.
   - **d.** aerobic respiration.
10. Which of these statements about cross bridges is *false?*
    - **a.** They are composed of myosin.
    - **b.** They bind to ATP after they detach from actin.
    - **c.** They contain an ATPase.
    - **d.** They split ATP before they attach to actin.
11. When a muscle is stimulated to contract, Ca^{2+} binds to
    - **a.** myosin.
    - **b.** tropomyosin.
    - **c.** actin.
    - **d.** troponin.
12. Which of these statements about muscle fatigue is *false?*
    - **a.** It may result when ATP is no longer available for the crossbridge cycle.
    - **b.** It may be caused by a loss of muscle cell Ca^{2+}.
    - **c.** It may be caused by the accumulation of extracellular K^{+}.
    - **d.** It may be a result of lactic acid production.
13. Which of these types of muscle cells are *not* capable of spontaneous depolarization?
    - **a.** single-unit smooth muscle
    - **b.** multiunit smooth muscle
    - **c.** cardiac muscle
    - **d.** skeletal muscle
    - **e.** both *b* and *d*
    - **f.** both *a* and *c*
14. Which of these muscle types is striated and contains gap junctions?
    - **a.** single-unit smooth muscle
    - **b.** multiunit smooth muscle
    - **c.** cardiac muscle
    - **d.** skeletal muscle
15. In an isotonic muscle contraction,
    - **a.** the length of the muscle remains constant.
    - **b.** the muscle tension remains constant.
    - **c.** both muscle length and tension are changed.
    - **d.** movement of bones does not occur.

Test Your Understanding of Concepts and Principles

1. Using the concept of motor units, explain how skeletal muscles *in vivo* produce graded and sustained contractions.[1]
2. Describe how an isometric contraction can be converted into an isotonic contraction using the concepts of motor unit recruitment and the series-elastic component of muscles.
3. Beginning with the production of a depolarization in the muscle fiber, trace the sequence of events in which the cross bridges attach to the thin filaments when a muscle is stimulated by a nerve. Why don't the cross bridges attach to the thin filaments when a muscle is relaxed?
4. Using the sliding filament theory of contraction, explain why the contraction strength of a muscle is maximal at a particular muscle length.
5. Explain why muscle tone is first decreased and then increased when descending motor tracts are damaged. How is muscle tone maintained?
6. Explain the role of ATP in muscle contraction and muscle relaxation.
7. Why are all the muscle fibers of a given motor unit of the same type? Why are smaller motor units and slow-twitch muscle fibers used more frequently than larger motor units and fast-twitch fibers?
8. What changes occur in muscle metabolism as the intensity of exercise is increased? Describe the changes that occur as a result of endurance training and explain how these changes allow more strenuous exercise to be performed before the onset of muscle fatigue.
9. Compare the mechanism of excitation-coupling in striated muscle with that in smooth muscle.
10. Compare cardiac muscle, single-unit smooth muscle, and multiunit smooth muscle with respect to the regulation of their contraction.

[1]*Note:* This question is answered in the chapter 12 Study Guide found on the Online Learning Center at www.mhhe.com/fox9.

Test Your Ability to Analyze and Apply Your Knowledge

1. Your friend eats huge helpings of pasta for two days prior to a marathon, claiming such "carbo loading" is of benefit in the race. Is he right? What are some other things he can do to improve his performance?
2. Compare muscular dystrophy and amyotrophic lateral sclerosis (ALS) in terms of their causes and their effects on muscles.
3. Why is it important to have a large amount of stored high-energy phosphates in the form of creatine phosphate for the function of muscles during exercise? What might happen to a muscle in your body if it ever ran out of ATP?
4. How is electrical excitation of a skeletal muscle fiber coupled to muscle contraction? Speculate on why the exact mechanism of this coupling has been difficult to determine.
5. How would a rise in the extracellular Ca^{2+} concentration affect the beating of a heart? Explain the mechanisms involved. Lowering the blood Ca^{2+} concentration can cause muscle spasms. What might be responsible for this effect?

Related Websites

Check out the Links Library at www.mhhe.com/fox9 for links to sites containing resources related to the muscles. These links are monitored to ensure current URLs.