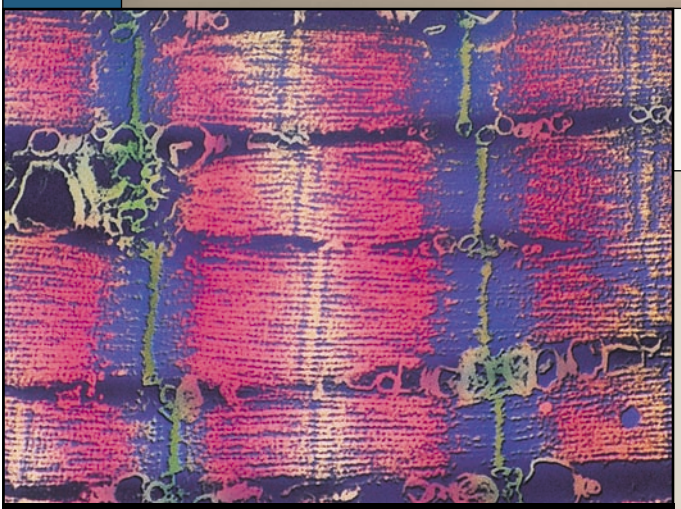

Color-enhanced electron microscope image of skeletal muscle sarcomeres

CHAPTER 9 NINE

MUSCLE

The ability to use chemical energy to produce force and movement is present to a limited extent in most cells, but in muscle cells it has become dominant. Muscles generate force and movements used in the regulation of the internal environment, and they also produce movements in the external environment. In humans, the ability to communicate, whether by speech, writing, or artistic expression, also depends on muscle contractions. Indeed, it is only by controlling the activity of muscles that the human mind ultimately expresses itself.

Three types of muscle tissue can be identified on the basis of structure, contractile properties, and control mechanisms: (1) skeletal muscle, (2) smooth muscle, and (3) cardiac muscle. Most skeletal muscle, as the name implies, is attached to bone, and its contraction is responsible for supporting and moving the skeleton. The contraction of skeletal muscle is initiated by impulses in the neurons to the muscle and is usually under voluntary control.

Sheets of smooth muscle surround various hollow organs and tubes, including the stomach, intestines, urinary bladder, uterus, blood vessels, and airways in the lungs. Contraction of the smooth muscle surrounding hollow organs may propel the luminal contents through the organ, or it may regulate internal flow by changing the tube diameter. In addition, small bundles of smooth muscle cells are attached to the hairs of the skin and iris of the eye. Smooth muscle contraction is controlled by the autonomic nervous system, hormones, autocrine/paracrine agents, and other local chemical signals. Some smooth muscles contract autonomously, however, even in the absence of such signals. In contrast to skeletal muscle, smooth muscle is not normally under voluntary control.

Cardiac muscle is the muscle of the heart. Its contraction propels blood through the circulatory system. Like smooth muscle, it is regulated by the autonomic nervous system, hormones, and autocrine/paracrine agents, and it can undergo spontaneous contractions.

Although there are significant differences in these three types of muscle, the force-generating mechanism is similar in all of them. Skeletal muscle will be described first, followed by a discussion of smooth muscle. Cardiac muscle, which combines some of the properties of both skeletal and smooth muscle, will be described in Chapter 12 in association with its role in the circulatory system.

SECTION A

Skeletal Muscle

STRUCTURE

A single skeletal muscle cell is known as a **muscle fiber.** Each muscle fiber is formed during development by the fusion of a number of undifferentiated, mononucleated cells, known as **myoblasts,** into a single cylindrical, multinucleated cell. Skeletal muscle differentiation is completed around the time of birth, and these differentiated fibers continue to increase in size during growth from infancy to adult stature, but no new fibers are formed from myoblasts. Adult skeletal muscle fibers have diameters between 10 and 100 μm and lengths that may extend up to 20 cm.

If skeletal muscle fibers are destroyed after birth as a result of injury, they cannot be replaced by the division of other existing muscle fibers. New fibers can be formed, however, from undifferentiated cells known as **satellite cells,** which are located adjacent to the muscle fibers and undergo differentiation similar to that followed by embryonic myoblasts. This capacity for forming new skeletal muscle fibers is considerable but will not restore a severely damaged muscle to full strength. Much of the compensation for a loss of muscle tissue occurs through an increase in the size of the remaining muscle fibers **(hypertrophy).**

The term **muscle** refers to a number of muscle fibers bound together by connective tissue (Figure 9–1). The relationship between a single muscle fiber and a muscle is analogous to that between a single neuron and a nerve, which is composed of the axons of many neurons. Muscles are usually linked to bones by bundles of collagen fibers known as **tendons.**

In some muscles the individual fibers extend the entire length of the muscle, but in most, the fibers are shorter, often oriented at an angle to the longitudinal axis of the muscle. The transmission of force from muscle to bone is like a number of people pulling on a rope, each person corresponding to a single muscle fiber and the rope corresponding to the connective tissue and tendons.

Some tendons are very long, with the site of tendon attachment to bone far removed from the end of the muscle. For example, some of the muscles that move the fingers are in the forearm (wiggle your fingers and feel the movement of the muscles in your lower arm). These muscles are connected to the fingers by long tendons.

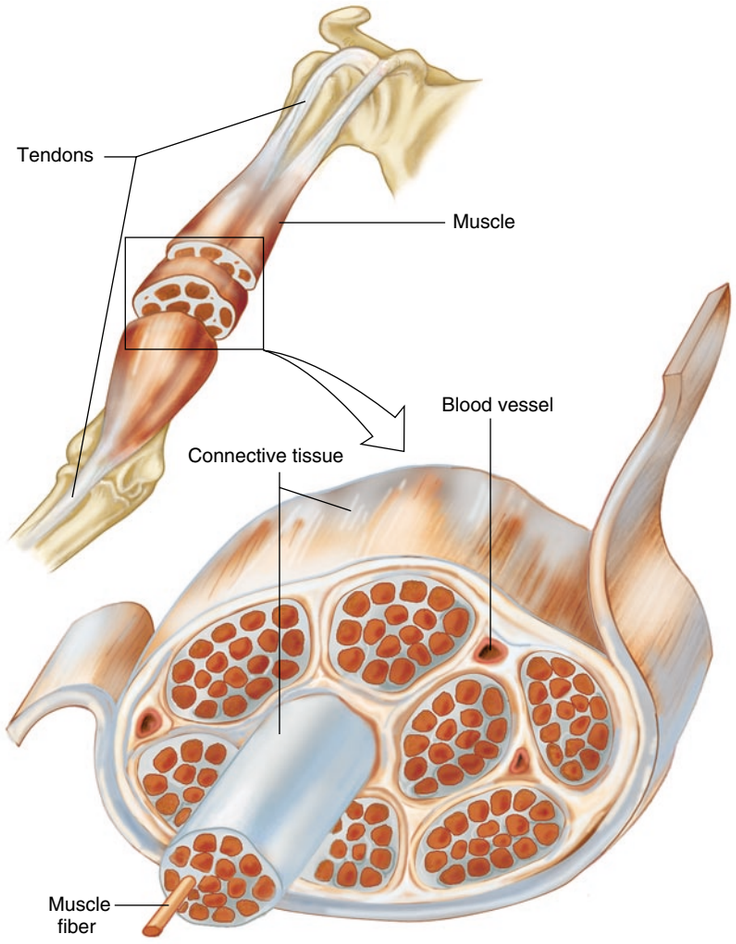

FIGURE 9–1
Organization of cylindrical skeletal muscle fibers in a muscle that is attached to bones by tendons.

The most striking feature seen when observing skeletal or cardiac muscle through a light microscope (Figure 9–2) is a series of light and dark bands perpendicular to the long axis. Because of this characteristic striped pattern, both types are known as **striated muscle** (Figure 9–3). Smooth muscle cells do not show a banding pattern. The striated pattern in skeletal and cardiac muscle results from the arrangement of numerous thick and thin filaments in the cytoplasm into approximately cylindrical bundles (1 to 2 μm in diameter) known as **myofibrils** (Figure 9–4). Most of the cytoplasm of a fiber is filled with myofibrils, each of which extends from one end of the fiber to the other and is linked to the tendons at the ends of the fiber.

The thick and thin filaments in each myofibril (Figures 9–4 and 9–5) are arranged in a repeating pattern along the length of the myofibril. One unit of this repeating pattern is known as a **sarcomere** (Greek, *sarco,* muscle; *mer,* part). The **thick filaments** are composed almost entirely of the contractile protein **myosin.** The **thin filaments** (which are about half the diameter of the thick filaments) contain the contractile protein **actin,** as well as two other proteins—troponin and tropomyosin—that play important roles in regulating contraction.

The thick filaments are located in the middle of each sarcomere, where their orderly parallel arrangement produces a wide, dark band known as the **A band** (Figure 9–4). Each sarcomere contains two sets of thin filaments, one at each end. One end of each thin filament is anchored to a network of interconnecting proteins known as the **Z line,** whereas the other end overlaps a portion of the thick filaments. Two successive Z lines define the limits of one sarcomere. Thus, thin filaments from two adjacent sarcomeres are anchored to the two sides of each Z line.

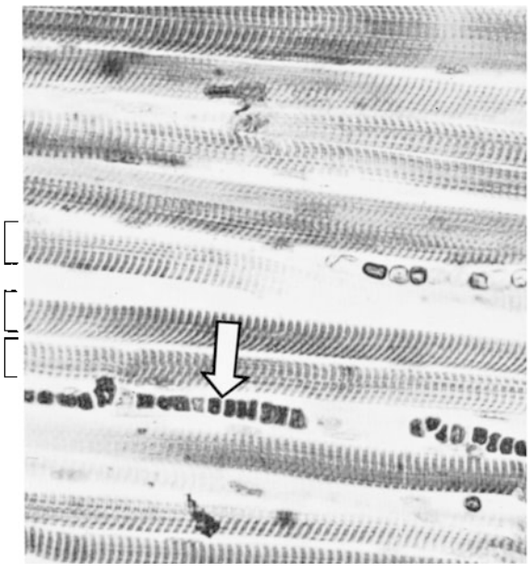

FIGURE 9–2

Skeletal muscle fibers viewed through a light microscope. Each bracket at the left indicates one muscle fiber. Arrow indicates a blood vessel containing red blood cells.

From Edward K. Keith and Michael H. Ross, "Atlas of Descriptive Histology," Harper & Row, New York, 1968.

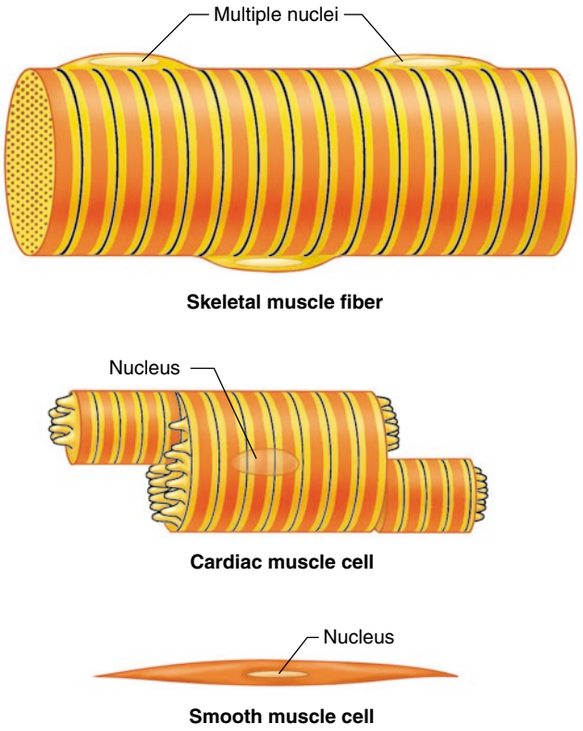

FIGURE 9–3

The three types of muscle fibers. Only a small portion of the skeletal muscle fiber is shown. (not drawn to scale)

A light band, known as the **I band** (Figure 9–4), lies between the ends of the A bands of two adjacent sarcomeres and contains those portions of the thin filaments that do not overlap the thick filaments. It is bisected by the Z line.

Two additional bands are present in the A-band region of each sarcomere (Figure 9–5). The **H zone** is a narrow, light band in the center of the A band. It corresponds to the space between the opposing ends of the two sets of thin filaments in each sarcomere. A narrow, dark band in the center of the H zone is known as the **M line** and corresponds to proteins that link together the central region of adjacent thick filaments. In addition, filaments composed of the elastic protein **titin** extend from the Z line to the M line and are linked to both the M-line proteins and the thick filaments. Both the M-line linkage between thick filaments and the titin filaments act to maintain the regular array of thick filaments in the middle of each sarcomere.

A cross section through the A bands (Figure 9–6), shows the regular arrangement of overlapping thick and thin filaments. Each thick filament is surrounded by a hexagonal array of six thin filaments, and each thin filament is surrounded by a triangular arrangement of three thick filaments. Altogether there are twice as many thin as thick filaments in the region of filament overlap.

The space between overlapping thick and thin filaments is bridged by projections known as **cross-bridges.** These are portions of myosin molecules that extend from the surface of the thick filaments toward the thin filaments (Figures 9–4 and 9–7). During muscle contraction, the cross-bridges make contact with the thin filaments and exert force on them.

MOLECULAR MECHANISMS OF CONTRACTION

The term **contraction,** as used in muscle physiology, does not necessarily mean "shortening". It simply refers to activation of the force-generating sites within muscle fibers—the cross-bridges. For example, holding a dumbbell at a constant position requires muscle contraction but not muscle shortening. Following contraction, the mechanisms that initiate force generation are turned off, and tension declines, allowing **relaxation** of the muscle fiber.

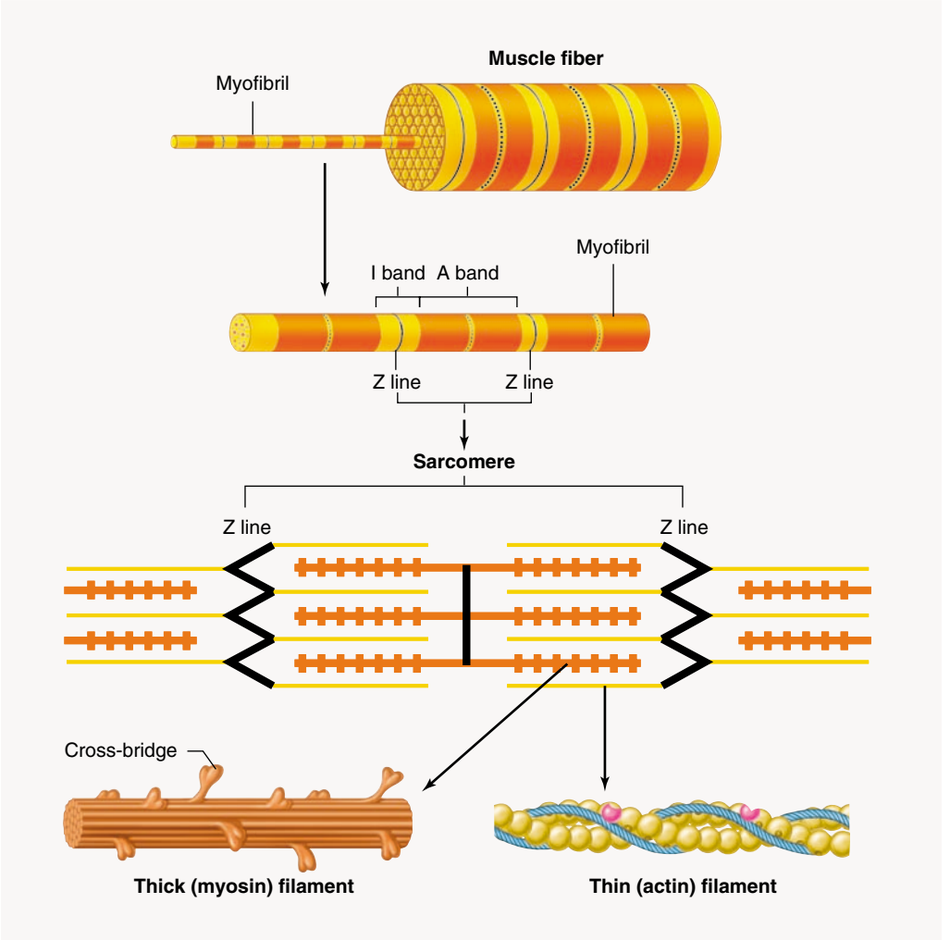

FIGURE 9–4
Arrangement of filaments in a skeletal muscle fiber that produces the striated banding pattern.

Sliding-Filament Mechanism

When force generation produces shortening of a skeletal muscle fiber, the overlapping thick and thin filaments in each sarcomere move past each other, propelled by movements of the cross-bridges. During this shortening of the sarcomeres, there is no change in the lengths of either the thick or thin filaments (Figure 9–8). This is known as the **sliding-filament mechanism** of muscle contraction.

During shortening, each myosin cross-bridge attached to a thin filament actin molecule moves in an arc much like an oar on a boat. This swiveling motion of many cross-bridges forces the thin filaments attached to successive Z lines toward the center of the sarcomere, thereby shortening the sarcomere (Figure 9–9). One stroke of a cross-bridge produces only a very small movement of a thin filament relative to a thick filament. As long as a muscle fiber remains activated, however, each cross-bridge repeats its swiveling motion many times, resulting in large displacements of the filaments. Thus, the ability of a muscle fiber to generate force and movement depends on the interaction of the contractile proteins actin and myosin.

An actin molecule is a globular protein composed of a single polypeptide that polymerizes with other actins to form two intertwined helical chains (Figure 9–10). These chains make up the core of a thin filament. Each actin molecule contains a binding site for myosin. The myosin molecule, on the other hand, is composed of two large polypeptide **heavy chains** and four smaller **light chains.** These polypeptides combine to form a molecule that consists of two globular heads (containing heavy and light chains) and a long

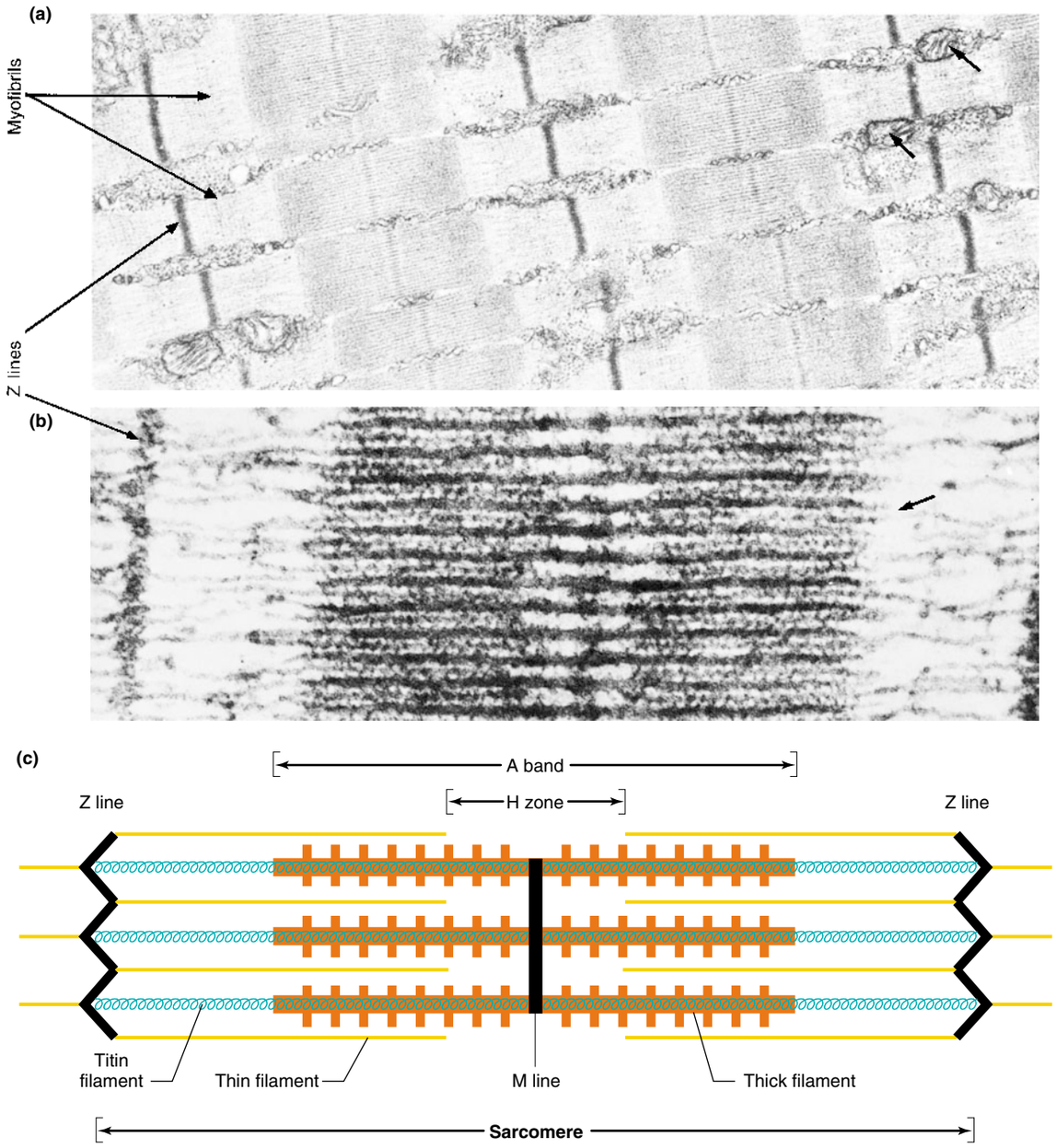

FIGURE 9–5

(a) Numerous myofibrils in a single skeletal muscle fiber (arrows in upper right corner indicate mitochondria between the myofibrils). (b) High magnification of a sarcomere within a myofibril (arrow at the right of A band indicates the end of a thick filament). (c) Arrangement of the thick and thin filaments in the sarcomere shown in b.

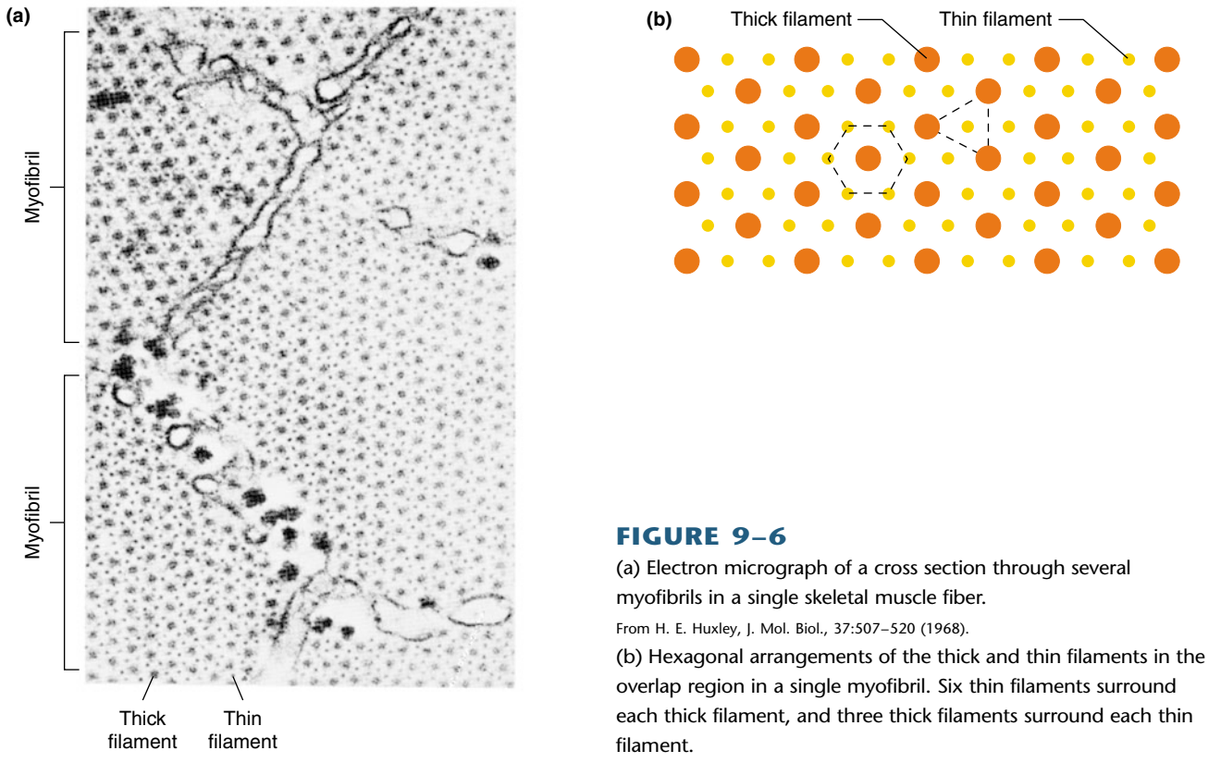

FIGURE 9–6

(a) Electron micrograph of a cross section through several myofibrils in a single skeletal muscle fiber.

From H. E. Huxley, J. Mol. Biol., 37:507–520 (1968).

(b) Hexagonal arrangements of the thick and thin filaments in the overlap region in a single myofibril. Six thin filaments surround each thick filament, and three thick filaments surround each thin filament.

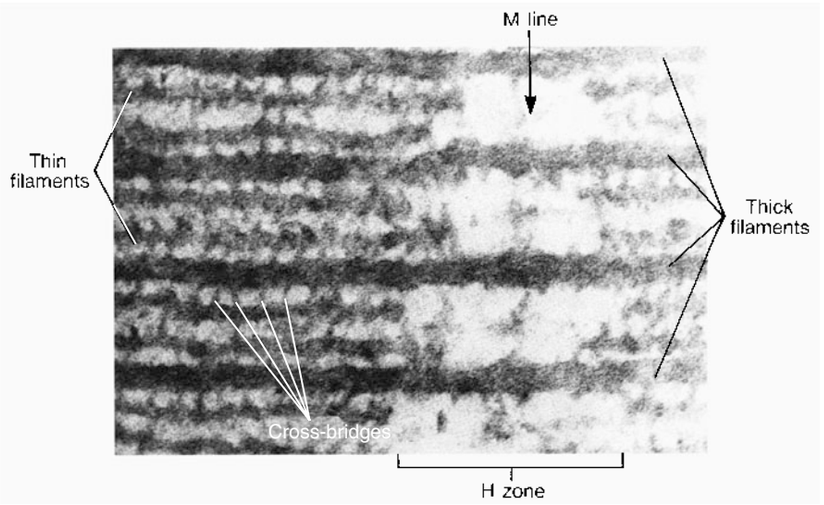

FIGURE 9–7

High-magnification electron micrograph in the filament overlap region near the middle of a sarcomere. Cross-bridges between the thick and thin filaments can be seen at regular intervals along the filaments.

From H. E. Huxley and J. Hanson, in G. H. Bourne (ed.), "The Structure and Function of Muscle," Vol. 1, Academic Press, New York, 1960.

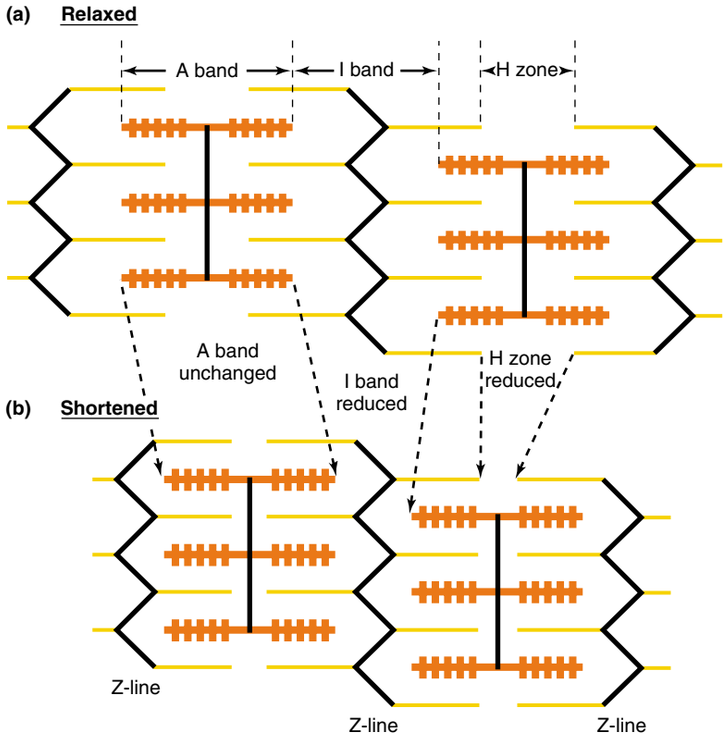

FIGURE 9–8
The sliding of thick filaments past overlapping thin filaments produces sarcomere shortening with no change in thick or thin filament length. The I band and H zone are reduced.

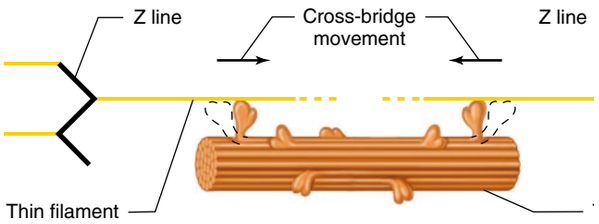

FIGURE 9–9
Cross-bridges in the thick filaments bind to actin in the thin filaments and undergo a conformational change that propels the thin filaments toward the center of a sarcomere. (Only two of the approximately 200 cross-bridges in each thick filament are shown.)

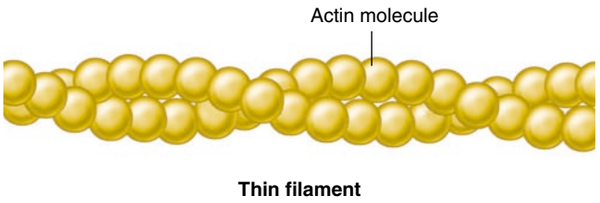

FIGURE 9–10
Two intertwined helical chains of actin molecules form the primary structure of the thin filaments.

tail formed by the two intertwined heavy chains (Figure 9–11b). The tail of each myosin molecule lies along the axis of the thick filament, and the two globular heads extend out to the sides, forming the cross-bridges. Each globular head contains two binding sites, one for actin and one for ATP. The ATP binding site also serves as an enzyme—an ATPase that hydrolyzes the bound ATP.

The myosin molecules in the two ends of each thick filament are oriented in opposite directions, such that their tail ends are directed toward the center of the filament (Figure 9–11a). Because of this arrangement, the power strokes of the cross-bridges move the attached thin filaments at the two ends of the sarcomere toward the center during shortening (see Figure 9–9).

The sequence of events that occurs between the time a cross-bridge binds to a thin filament, moves, and then is set to repeat the process is known as a **cross-bridge cycle.** Each cycle consists of four steps: (1) attachment of

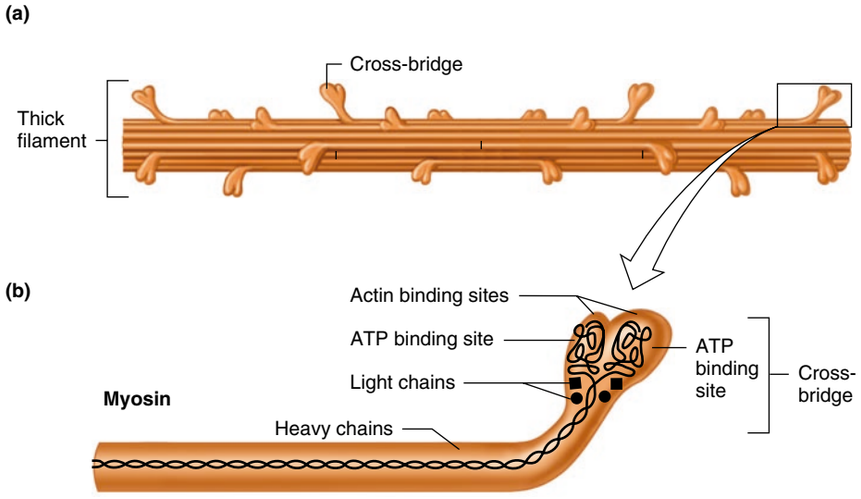

FIGURE 9–11

(a) The heavy chains of myosin molecules form the core of a thick filament. The myosin molecules are oriented in opposite directions in either half of a thick filament. (b) Structure of a myosin molecule. The two globular heads of each myosin molecule extend from the sides of a thick filament, forming a cross-bridge.

the cross-bridge to a thin filament, (2) movement of the cross-bridge, producing tension in the thin filament, (3) detachment of the cross-bridge from the thin filament, and (4) energizing the cross-bridge so that it can again attach to a thin filament and repeat the cycle. Each cross-bridge undergoes its own cycle of movement independently of the other cross-bridges. At any instant during contraction only a portion of the cross-bridges are attached to the thin filaments and producing tension, while others are in a detached portion of their cycle.

The chemical and physical events during the four steps of the cross-bridge cycle are illustrated in Figure 9–12. In a resting muscle fiber the cytoplasmic calcium concentration is low, and the myosin cross-bridges (M) cannot bind to actin (A). The cross-bridges, however, are in an energized state produced by the splitting of ATP, and the hydrolysis products (ADP and inorganic phosphate) are still bound to myosin. This storage of energy in myosin is analogous to the storage of potential energy in a stretched spring.

Cross-bridge cycling is initiated by calcium entry into the cytoplasm (by a mechanism that will be described shortly). The cycle begins with the binding of an energized myosin cross-bridge to a thin filament actin molecule (step 1):

$$\text{Step 1} \qquad \underset{\text{Actin binding}}{A + M{\cdot}ADP{\cdot}P_i \longrightarrow} \; A{\cdot}M{\cdot}ADP{\cdot}P_i$$

The binding of energized myosin to actin triggers the release of the strained conformation of the energized bridge, which produces the movement of the bound cross-bridge (sometimes called the **power stroke**) and the release of P_i and ADP (step2):

$$\text{Step 2} \qquad \underset{\text{Cross-bridge movement}}{A{\cdot}M{\cdot}ADP{\cdot}P_i \longrightarrow} \; A{\cdot}M + ADP + P_i$$

This sequence of energy storage and release by myosin is analogous to the operation of a mousetrap: Energy is stored in the trap by cocking the spring (ATP hydrolysis) and released after springing the trap (binding to actin).

During the cross-bridge movement, myosin is bound very firmly to actin, and this linkage must be broken in order to allow the cross-bridge to be re-energized and repeat the cycle. The binding of a new molecule of ATP to myosin breaks the link between actin and myosin (step 3):

$$\text{Step 3} \qquad \underset{\text{Cross-bridge dissociation from actin}}{A{\cdot}M + ATP \longrightarrow} \; A + M{\cdot}ATP$$

The dissociation of actin and myosin by ATP is an example of allosteric regulation of protein activity. The binding of ATP at one site on myosin decreases myosin's affinity for actin bound at another site. Note that ATP is not split in this step; that is, it is not acting as an energy source but only as an allosteric modulator of the myosin head that weakens the binding of myosin to actin.

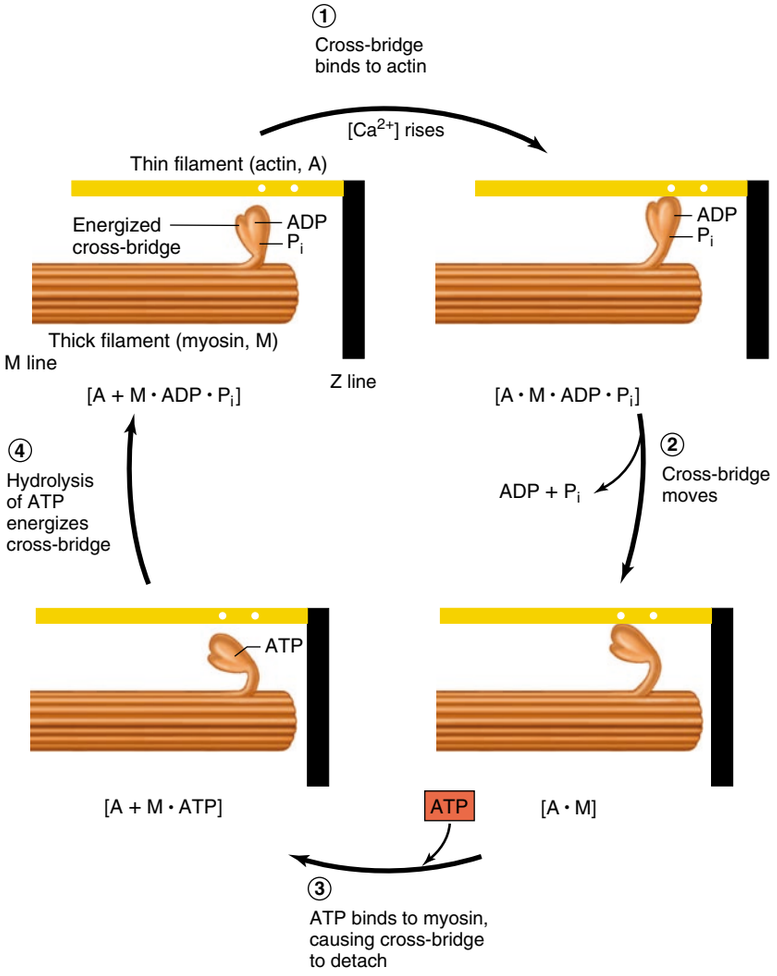

FIGURE 9–12

Chemical (shown in brackets) and mechanical representations of the four stages of a cross-bridge cycle. In a resting muscle fiber, contraction begins when calcium activates the thin filament.

Following the dissociation of actin and myosin, the ATP bound to myosin is split (step 4), thereby reforming the energized state of myosin.

Step 4 $\quad A + M{\cdot}ATP \longrightarrow A + M{\cdot}ADP{\cdot}P_i$

ATP hydrolysis

If calcium is still present at this time, the cross-bridge can reattach to a new actin molecule in the thin filament and the cross-bridge cycle repeats. Note that the hydrolysis of ATP (step 4) and the movement of the cross-bridge (step 2) are not simultaneous events.

To summarize, ATP performs two distinct roles in the cross-bridge cycle: (1) The energy released from ATP *hydrolysis* ultimately provides the energy for cross-bridge movement, and (2) ATP *binding* (not hydrolysis) to myosin breaks the link formed between actin and myosin during the cycle, allowing the cycle to be repeated.

The importance of ATP in dissociating actin and myosin during step 3 of a cross-bridge cycle is illustrated by **rigor mortis,** the stiffening of skeletal muscles that begins several hours after death and is complete after about 12 h. The ATP concentration in cells, including muscle cells, declines after death because the nutrients and oxygen required by the metabolic pathways to form ATP are no longer supplied by the circulation. In the absence of ATP, the breakage of the link between actin and myosin does not occur. The thick and thin filaments remain bound to each other by immobilized cross-bridges, producing a rigid condition in

which the thick and thin filaments cannot be pulled past each other. The stiffness of rigor mortis disappears about 48 to 60 h after death as a result of the disintegration of muscle tissue.

Roles of Troponin, Tropomyosin, and Calcium in Contraction

How does the presence of calcium in the cytoplasm regulate the cycling of cross-bridges? The answer requires a closer look at the thin filament proteins, **troponin** and **tropomyosin** (Figure 9–13).

Tropomyosin is a rod-shaped molecule composed of two intertwined polypeptides with a length approximately equal to that of seven actin molecules. Chains of tropomyosin molecules are arranged end to end along the actin thin filament. These tropomyosin molecules partially cover the myosin-binding site on each actin molecule, thereby preventing the cross-bridges from making contact with actin. Each tropomyosin molecule is held in this blocking position by troponin, a smaller, globular protein that is bound to both tropomyosin and actin. One molecule of troponin binds to each molecule of tropomyosin and regulates the access to myosin-binding sites on the seven actin molecules in contact with tropomyosin. This is the status of a resting muscle fiber; troponin and tropomyosin cooperatively block the interaction of cross-bridges with the thin filament.

What enables cross-bridges to bind to actin and begin cycling? For this to occur, tropomyosin molecules must be moved away from their blocking positions on actin. This happens when calcium binds to specific binding sites on troponin (not tropomyosin). The binding of calcium produces a change in the shape of troponin, which through troponin's linkage to tropomyosin, drags tropomyosin away from the myosin-binding site on each actin molecule. Conversely, removal of calcium from troponin reverses the process, turning off contractile activity.

Thus, cytosolic calcium-ion concentration determines the number of troponin sites occupied by calcium, which in turn determines the number of actin sites available for cross-bridge binding. Changes in cytosolic calcium concentration are controlled by electrical events in the muscle plasma membrane, which we now discuss.

Excitation-Contraction Coupling

Excitation-contraction coupling refers to the sequence of events by which an action potential in the plasma membrane of a muscle fiber leads to cross-bridge activity by the mechanisms just described. The skeletal muscle plasma membrane is an excitable membrane capable of generating and propagating action potentials by mechanisms similar to those described for nerve cells (Chapter 6). An action potential in a skeletal muscle fiber lasts 1 to 2 ms and is completed before any signs of mechanical activity begin (Figure 9–14). Once begun, the mechanical activity following an action potential may

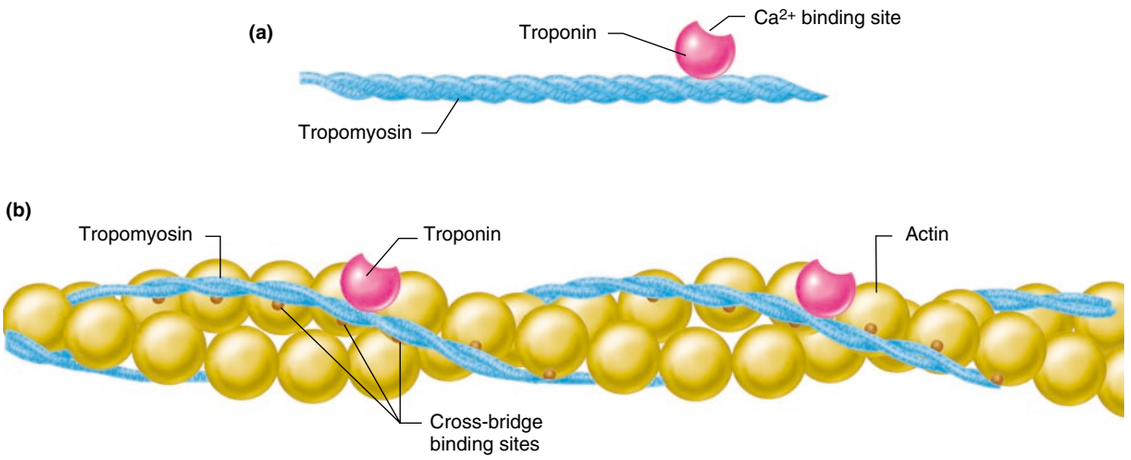

FIGURE 9–13

(a) Molecule of troponin bound to a molecule of tropomyosin. (b) Two chains of tropomyosin on a thin filament regulate access of cross-bridges to binding sites on actin.

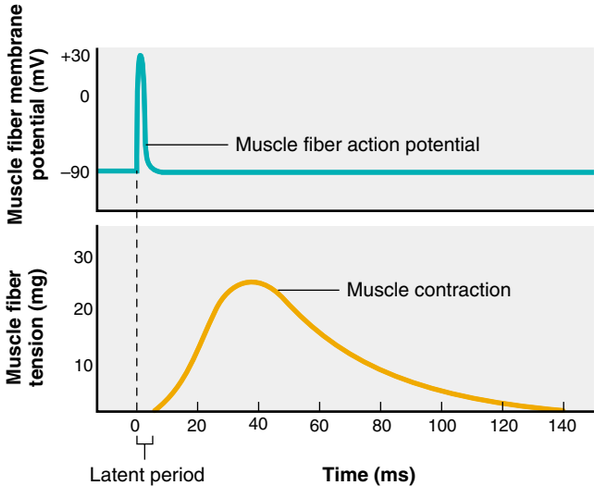

FIGURE 9–14

Time relations between a skeletal muscle fiber action potential and the resulting contraction and relaxation of the muscle fiber.

last 100 ms or more. The electrical activity in the plasma membrane does not *directly* act upon the contractile proteins but instead produces a state of increased cytosolic calcium concentration, which continues to activate the contractile apparatus long after the electrical activity in the membrane has ceased.

In a resting muscle fiber, the concentration of free, ionized calcium in the cytosol surrounding the thick and thin filaments is very low, about 10^{-7} mol/L. At this low calcium concentration, very few of the calcium-binding sites on troponin are occupied, and thus cross-bridge activity is blocked by tropomyosin. Following an action potential, there is a rapid increase in cytosolic calcium concentration, and calcium binds to troponin, removing the blocking effect of tropomyosin and allowing cross-bridge cycling. The source of the increased cytosolic calcium is the **sarcoplasmic reticulum** within the muscle fiber.

Sarcoplasmic Reticulum

The sarcoplasmic reticulum in muscle is homologous to the endoplasmic reticulum found in most cells and forms a series of sleevelike segments around each myofibril (Figure 9–15). At the end of each segment there are two enlarged regions, known as **lateral sacs,** that are connected to each other by a series of smaller tubular elements. The lateral sacs store the calcium that is released following membrane excitation.

A separate tubular structure, the **transverse tubule (T-tubule),** crosses the muscle fiber at the level of each A-I junction, passing between adjacent lateral sacs and eventually joining the plasma membrane. The lumen of the T-tubule is continuous with the extracellular fluid surrounding the muscle fiber. The membrane of the T-tubule, like the plasma membrane, is able to propagate action potentials. Once initiated in the plasma membrane, an action potential is rapidly conducted over the surface of the fiber and into its interior by way of the T-tubules.

A specialized mechanism couples T-tubule action potentials with calcium release from the sarcoplasmic reticulum (Figure 9-16, inset). The T-tubules are in intimate contact with the lateral sacs of the sarcoplasmic reticulum, connected by structures known as **junctional feet** or **"foot proteins."** This junction involves two integral membrane proteins, one in the T-tubule membrane, and the other in the membrane of the sarcoplasmic reticulum. The T-tubule protein is a modified voltage-sensitive calcium channel known as the **dihydropyridine (DHP) receptor** (so named because it binds the class of drugs called dihydropyridines). The main role of the DHP receptor, however, is not to conduct calcium, but rather to act as a voltage sensor. The protein embedded in the sarcoplasmic reticulum membrane is known as the **ryanodine receptor** (because it binds to the plant alkaloid ryanodine). This is a large molecule that not only constitutes the foot proteins but also forms a calcium channel. During a T-tubule action potential, charged amino acid residues within the DHP receptor protein induce a conformational change, which acts via the foot proteins to open the ryanodine receptor channel. Calcium is thus released from the lateral sacs of the sarcoplasmic reticulum into the cytosol, activating cross-bridge cycling. The rise in cytosolic calcium in response to a single action potential is normally enough to saturate all troponin binding sites on the thin filaments.

A contraction continues until calcium is removed from troponin, and this is achieved by lowering the calcium concentration in the cytosol back to its prerelease level. The membranes of the sarcoplasmic reticulum contain primary active-transport proteins—Ca^{2+}-ATPases—that pump calcium ions from the cytosol back into the lumen of the reticulum. As we just saw, calcium is released from the reticulum upon arrival of an action potential in the T-tubule, but the pumping of the released calcium back into the reticulum requires a much longer time. Therefore, the cytosolic calcium concentration remains elevated, and the contraction continues for some time after a single action potential.

To reiterate, just as contraction results from the release of calcium ions stored in the sarcoplasmic reticulum, so contraction ends and relaxation begins as

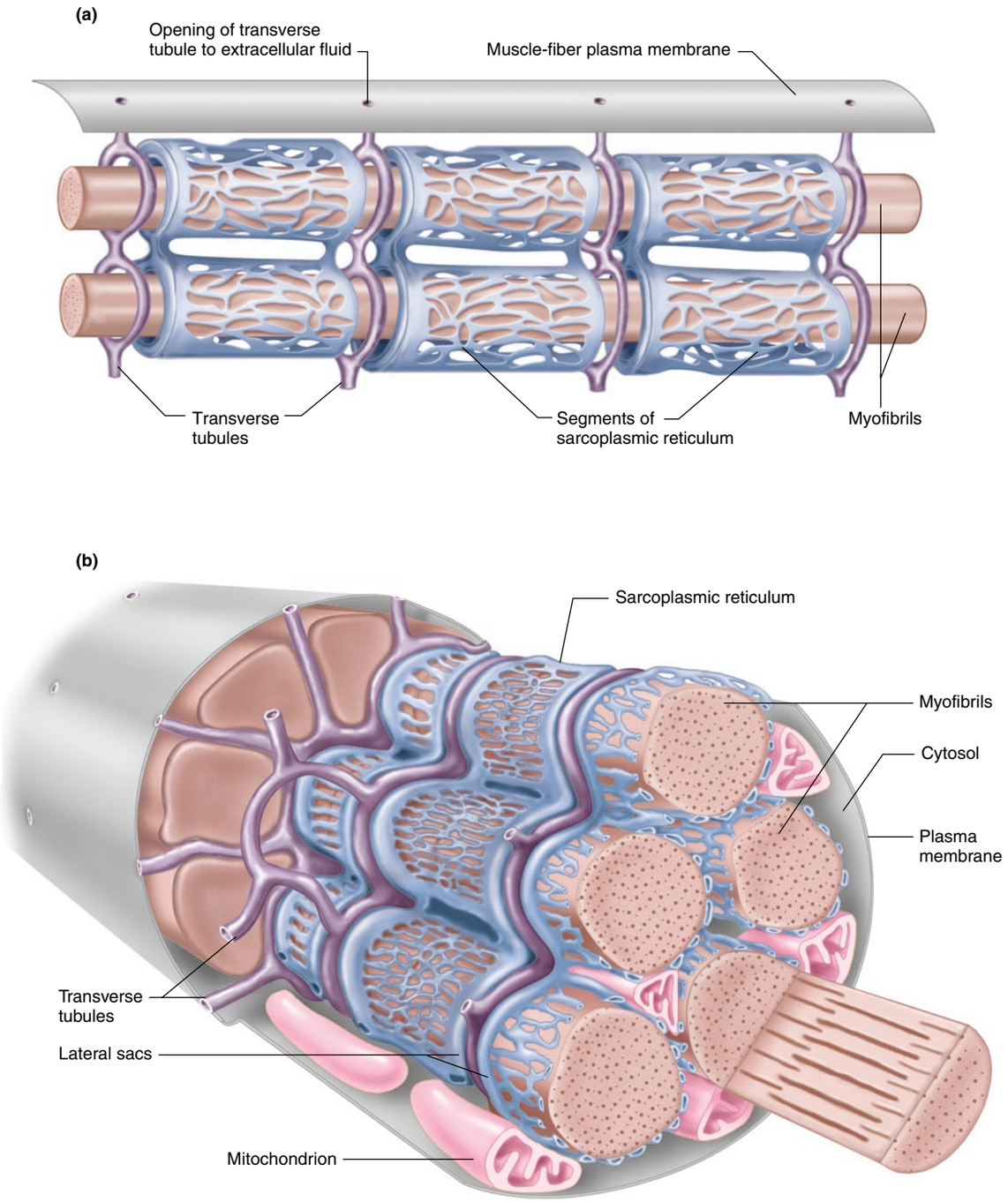

FIGURE 9–15

(a) Diagrammatic representation of the sarcoplasmic reticulum, the transverse tubules, and the myofibrils. (b) Anatomical structure of transverse tubules and sarcoplasmic reticulum in a single skeletal muscle fiber.

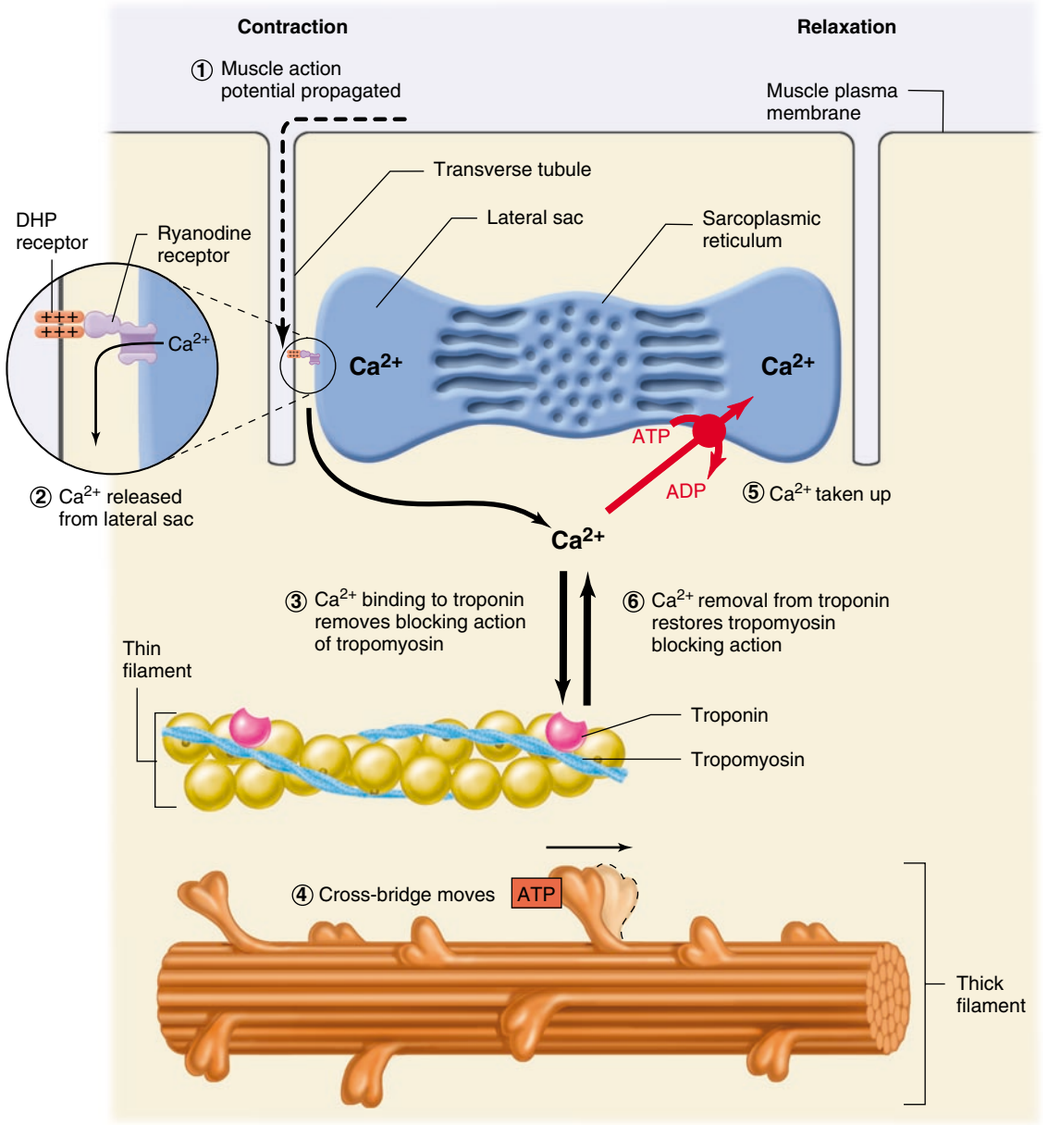

FIGURE 9–16
Release and uptake of calcium by the sarcoplasmic reticulum during contraction and relaxation of a skeletal muscle fiber.

calcium is pumped back into the reticulum (Figure 9–16). ATP is required to provide the energy for the calcium pump, and this is the third major role of ATP in muscle contraction (Table 9–1).

Membrane Excitation: The Neuromuscular Junction

We have just seen that an action potential in the plasma membrane of a skeletal muscle fiber is the signal that triggers contraction. We will now back up one step and ask the question: How are these action potentials initiated? Stimulation of the nerve fibers to a skeletal muscle is the only mechanism by which action potentials are initiated in this type of muscle. In subsequent sections you'll see that there are additional mechanisms for activating cardiac and smooth muscle contraction.

The nerve cells whose axons innervate skeletal muscle fibers are known as **motor neurons** (or somatic efferent neurons), and their cell bodies are located in either the brainstem or the spinal cord. The axons of motor neurons are myelinated and are the largest-diameter axons in the body. They are there-

TABLE 9–1 Functions of ATP in Skeletal Muscle Contraction

1. Hydrolysis of ATP by myosin energizes the cross-bridges, providing the energy for force generation.
2. Binding of ATP to myosin dissociates cross-bridges bound to actin, allowing the bridges to repeat their cycle of activity.
3. Hydrolysis of ATP by the Ca^{2+}-ATPase in the sarcoplasmic reticulum provides the energy for the active transport of calcium ions into the reticulum, lowering cytosolic calcium to prerelease levels, ending the contraction, and allowing the muscle fiber to relax.

fore able to propagate action potentials at high velocities, allowing signals from the central nervous system to be transmitted to skeletal muscle fibers with minimal delay.

Upon reaching a muscle, the axon of a motor neuron divides into many branches, each branch forming a single junction with a muscle fiber. A single motor neuron innervates many muscle fibers, but each muscle fiber is controlled by a branch from only one motor neuron. A motor neuron plus the muscle fibers it innervates is called a **motor unit** (Figure 9–17a). The muscle fibers in a single motor unit are located in one muscle, but they are scattered throughout the muscle and are not adjacent to each other (Figure 9–17b). When an action potential occurs in a motor neuron, all the muscle fibers in its motor unit are stimulated to contract.

The myelin sheath surrounding the axon of each motor neuron ends near the surface of a muscle fiber, and the axon divides into a number of short processes that lie embedded in grooves on the muscle fiber surface. The axon terminals of a motor neuron contain vesicles similar to the vesicles found at synaptic junctions between two neurons. The vesicles contain the neurotransmitter **acetylcholine (ACh).** The region of the muscle fiber plasma membrane that lies directly under the terminal portion of the axon is known as the **motor end plate.** The junction of an axon terminal with the motor end plate is known as a **neuromuscular junction** (Figure 9–18).

The events occurring at the neuromuscular junction are shown in Figure 9–19. When an action potential in a motor neuron arrives at the axon terminal, it depolarizes the plasma membrane, opening voltage-sensitive calcium channels and allowing calcium ions to diffuse into the axon terminal from

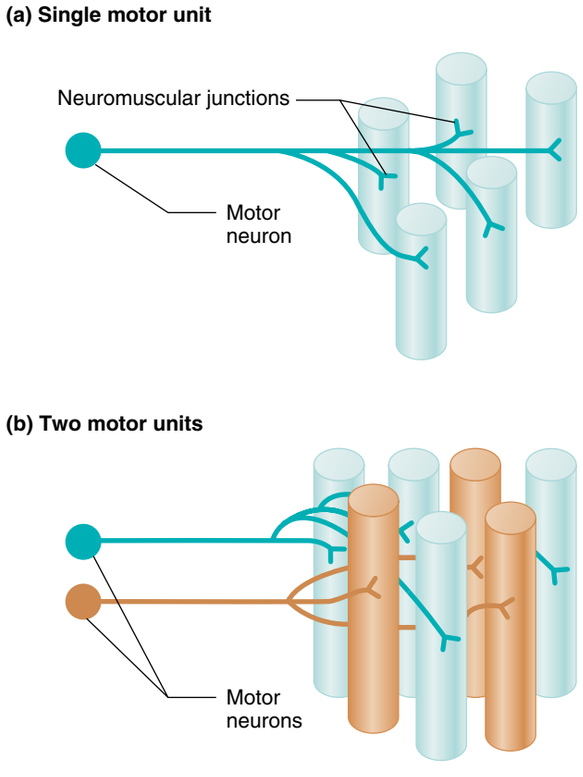

FIGURE 9–17
(a) Single motor unit consisting of one motor neuron and the muscle fibers it innervates. (b) Two motor units and their intermingled fibers in a muscle.

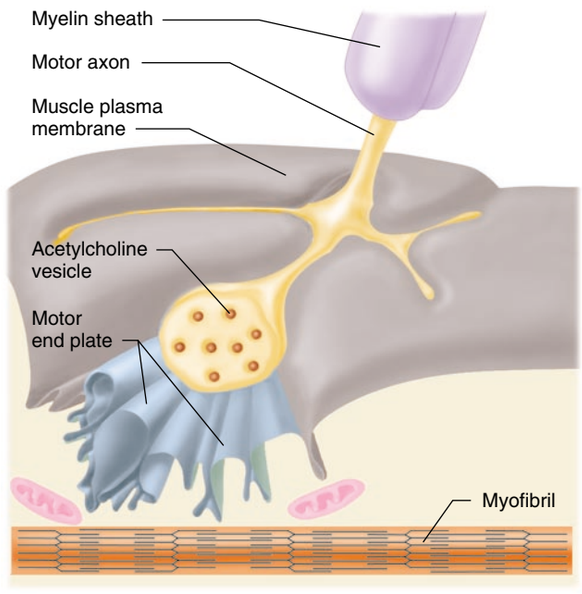

FIGURE 9–18
Neuromuscular junction. The motor axon terminals are embedded in grooves in the muscle fiber's surface.

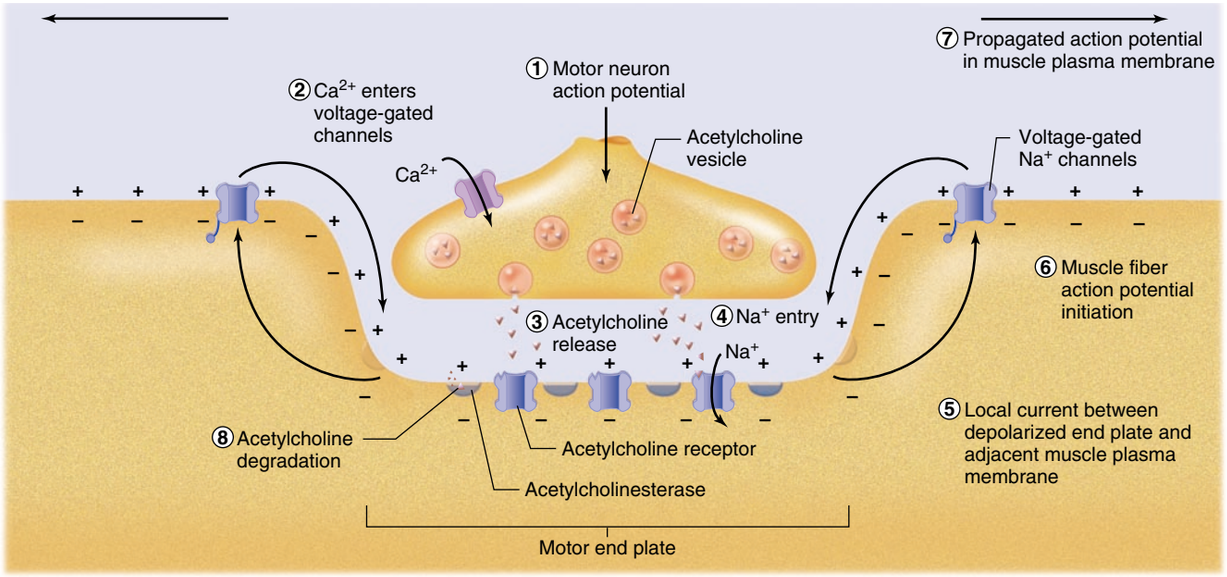

FIGURE 9–19

Events at the neuromuscular junction that lead to an action potential in the muscle fiber plasma membrane.

the extracellular fluid. This calcium binds to proteins that enable the membranes of acetylcholine-containing vesicles to fuse with the neuronal plasma membrane, thereby releasing acetylcho-line into the extracellular cleft separating the axon terminal and the motor end plate.

ACh diffuses from the axon terminal to the motor end plate where it binds to receptors [of the nicotinic type (Chapter 6)]. The binding of ACh opens an ion channel in each receptor protein. Both sodium and potassium ions can pass through these channels. Because of the differences in electrochemical gradients across the plasma membrane (Chapter 6), more sodium moves in than potassium out, producing a local depolarization of the motor end plate known as an **end-plate potential (EPP).** Thus, an EPP is analogous to an EPSP (excitatory postsynaptic potential) at a neuron–neuron synapse (Chapter 6).

The magnitude of a single EPP is, however, much larger than that of an EPSP because neurotransmitter is released over a larger surface area, binding to many more receptors and opening many more ion channels. For this reason, one EPP is normally more than sufficient to depolarize the muscle plasma membrane adjacent to the end-plate membrane to its threshold potential, initiating an action potential. This action potential is then propagated over the surface of the muscle fiber by the same mechanism described in Chapter 6 for the propagation of action potentials along axon membranes. Most neuromuscular junctions are located near the middle of a muscle fiber, and newly generated muscle action potentials propagate from this region in both directions toward the ends of the fiber and throughout the T-tubule network.

To repeat, every action potential in a motor neuron normally produces an action potential in each muscle fiber in its motor unit. This is quite different from synaptic junctions between neurons, where multiple EPSPs must occur in order for threshold to be reached and an action potential elicited in the postsynaptic membrane.

A second difference between interneuronal synapses and neuromuscular junctions should be noted. As we saw in Chapter 6, at some synaptic junctions, IPSPs (inhibitory postsynaptic potentials) are produced. They hyperpolarize or stabilize the postsynaptic membrane and decrease the probability of its firing an action potential. In contrast, inhibitory potentials do not occur in human skeletal muscle; *all neuromuscular junctions are excitatory.*

In addition to receptors for ACh, the surface of the motor end plate contains the enzyme **acetylcholinesterase,** which breaks down ACh, just like at ACh-mediated synapses in the nervous system. Choline is then transported back into the axon terminals where it is reused in the synthesis of new ACh. ACh bound to receptors is in equilibrium with free ACh in the cleft between the nerve and muscle membranes. As the concentration of free ACh falls because of its breakdown by acetylcholinesterase, less ACh is available to bind to the receptors. When the receptors no longer contain bound ACh, the ion channels in the end plate close. The de-

TABLE 9–2 Sequence of Events Between a Motor Neuron Action Potential and Skeletal Muscle Fiber Contraction

1. Action potential is initiated and propagates to motor neuron axon terminals.
2. Calcium enters axon terminals through voltage-gated calcium channels.
3. Calcium entry triggers release of ACh from axon terminals.
4. ACh diffuses from axon terminals to motor end plate in muscle fiber.
5. ACh binds to nicotinic receptors on motor end plate, increasing their permeability to Na^+ and K^+.
6. More Na^+ moves into the fiber at the motor end plate than K^+ moves out, depolarizing the membrane, producing the end plate potential (EPP).
7. Local currents depolarize the adjacent muscle cell plasma membrane to its threshold potential, generating an action potential that propagates over the muscle fiber surface and into the fiber along the T-tubules.
8. Action potential in T-tubules triggers release of Ca^{2+} from lateral sacs of sarcoplasmic reticulum.
9. Ca^{2+} binds to troponin on the thin filaments, causing tropomyosin to move away from its blocking position, thereby uncovering cross-bridge binding sites on actin.
10. Energized myosin cross-bridges on the thick filaments bind to actin:
$$A + M \cdot ADP \cdot P_i \longrightarrow A \cdot M \cdot ADP \cdot P_i$$
11. Cross-bridge binding triggers release of ATP hydrolysis products from myosin, producing an angular movement of each cross-bridge:
$$A \cdot M \cdot ADP \cdot P_i \longrightarrow A \cdot M + ADP + P_i$$
12. ATP binds to myosin, breaking linkage between actin and myosin and thereby allowing cross-bridges to dissociate from actin:
$$A \cdot M + ATP \longrightarrow A + M \cdot ATP$$
13. ATP bound to myosin is split, energizing the myosin cross-bridge:
$$M \cdot ATP \longrightarrow M \cdot ADP \cdot P_i$$
14. Cross-bridges repeat steps 10 to 13, producing movement (sliding) of thin filaments past thick filaments. Cycles of cross-bridge movement continue as long as Ca^{2+} remains bound to troponin.
15. Cytosolic Ca^{2+} concentration decreases as Ca^{2+} is actively transported into sarcoplasmic reticulum by Ca^{2+}-ATPase.
16. Removal of Ca^{2+} from troponin restores blocking action of tropomyosin, the cross-bridge cycle ceases, and the muscle fiber relaxes.

polarized end plate returns to its resting potential and can respond to the subsequent arrival of ACh released by another neuron action potential.

Table 9–2 summarizes the sequence of events that lead from an action potential in a motor neuron to the contraction and relaxation of a skeletal muscle fiber.

Disruption of Neuromuscular Signaling

There are many ways by which events at the neuromuscular junction can be modified by disease or drugs. For example, the deadly South American arrowhead poison ***curare*** binds strongly to nicotinic ACh receptors, but it does not open their ion channels and is not destroyed by acetylcholinesterase. When a receptor is occupied by curare, ACh cannot bind to the receptor. Therefore, although the motor nerves still conduct normal action potentials and release ACh, there is no resulting EPP in the motor end plate and no contraction. Since the skeletal muscles responsible for breathing, like all skeletal muscles, depend upon neuromuscular transmission to initiate their contraction, curare poisoning can lead to death by asphyxiation. Drugs similar to curare are used in small amounts to prevent muscular contractions during certain types of surgical procedures when it is necessary to immobilize the surgical field (***gallamine*** is one example). The use of such paralytic agents also reduces the required dose of general anesthetic, allowing patients to recover faster with fewer complications. Patients are artificially ventilated in order to maintain respiration until the drug has been removed from the system.

Neuromuscular transmission can also be blocked by inhibiting acetylcholinesterase. Some organophosphates, which are the main ingredients in certain pesticides and "nerve gases" (the latter developed for biological warfare), inhibit this enzyme. In the presence of such agents, ACh is released normally upon

the arrival of an action potential at the axon terminal and binds to the end-plate receptors. The ACh is not destroyed, however, because the acetylcholinesterase is inhibited. The ion channels in the end plate therefore remain open, producing a maintained depolarization of the end plate and the muscle plasma membrane adjacent to the end plate. A skeletal muscle membrane maintained in a depolarized state cannot generate action potentials because the voltage-gated sodium channels in the membrane have entered an inactive state, which requires repolarization to remove. Thus, the muscle does not contract in response to subsequent nerve stimulation, and the result is skeletal muscle paralysis and death from asphyxiation. Note that nerve gases also cause ACh to build up at muscarinic synapses, for example where parasympathetic neurons inhibit cardiac pacemaker cells (Chapter 12). Thus, the antidote for nerve gas exposure must include the muscarinic receptor antagonist ***atropine.***

A third group of substances, including the toxin produced by the bacterium *Clostridium botulinum*, blocks the release of acetylcholine from nerve terminals. Botulinum toxin is an enzyme that breaks down a protein required for the binding and fusion of ACh vesicles with the plasma membrane of the axon terminal. This toxin, which produces the food poisoning called ***botulism,*** is one of the most potent poisons known because of the very small amount necessary to produce an effect. Local application of botulinum toxin is increasingly being used for clinical and cosmetic procedures, including the inhibition of overactive extraocular muscles, prevention of excessive sweat gland activity, and reduction of aging-related skin wrinkles.

MECHANICS OF SINGLE-FIBER CONTRACTION

The force exerted on an object by a contracting muscle is known as muscle **tension,** and the force exerted on the muscle by an object (usually its weight) is the **load.** Muscle tension and load are opposing forces. Whether or not a fiber shortens depends on the relative magnitudes of the tension and the load. In order for muscle fibers to shorten, and thereby move a load, muscle tension must be greater than the opposing load.

When a muscle develops tension but does not shorten (or lengthen), the contraction is said to be **isometric** (constant length). Such contractions occur when the muscle supports a load in a constant position or attempts to move an otherwise supported load that is greater than the tension developed by the muscle. A contraction in which the muscle shortens, while the load on the muscle remains constant, is said to be **isotonic** (constant tension). Shortening contractions are also referred to as **concentric contractions.**

A third type of contraction is a **lengthening contraction (eccentric contraction).** This occurs when an unsupported load on a muscle is greater than the tension being generated by the cross-bridges. In this situation, the load pulls the muscle to a longer length in spite of the opposing force being produced by the cross-bridges. Such lengthening contractions occur when an object being supported by muscle contraction is lowered, like when the knee extensors in your thighs are used to lower you to a seat from a standing position. It must be emphasized that in these situations the lengthening of muscle fibers is not an active process produced by the contractile proteins, but a consequence of the external forces being applied to the muscle. In the absence of external lengthening forces, a fiber will only *shorten* when stimulated; it will never lengthen. All three types of contractions—isometric, isotonic, and lengthening—occur in the natural course of everyday activities.

During each type of contraction the cross-bridges repeatedly go through the four steps of the cross-bridge cycle illustrated in Figure 9–12. During step 2 of an isotonic contraction, the cross-bridges bound to actin move to their angled positions, causing shortening of the sarcomeres. In contrast, during an isometric contraction, the bound cross-bridges are unable to move the thin filaments because of the load on the muscle fiber, but they do exert a force on the thin filaments—isometric tension. If isometric contraction is prolonged, cycling cross-bridges repeatedly rebind to the same actin molecule. During a lengthening contraction, the cross-bridges in step 2 are pulled backward toward the Z lines by the load while still bound to actin and exerting force. The events of steps 1, 3, and 4 are the same in all three types of contractions. Thus, the chemical changes in the contractile proteins during each type of contraction are the same. The end result (shortening, no length change, or lengthening) is determined by the magnitude of the load on the muscle.

Contraction terminology applies to both single fibers and whole muscles. In this section, we describe the mechanics of single fiber contractions. Later we will discuss the factors controlling the mechanics of whole-muscle contraction.

Twitch Contractions

The mechanical response of a single muscle fiber to a single action potential is known as a **twitch.** Figure 9–20a shows the main features of an isometric twitch. Following the action potential, there is an interval of a

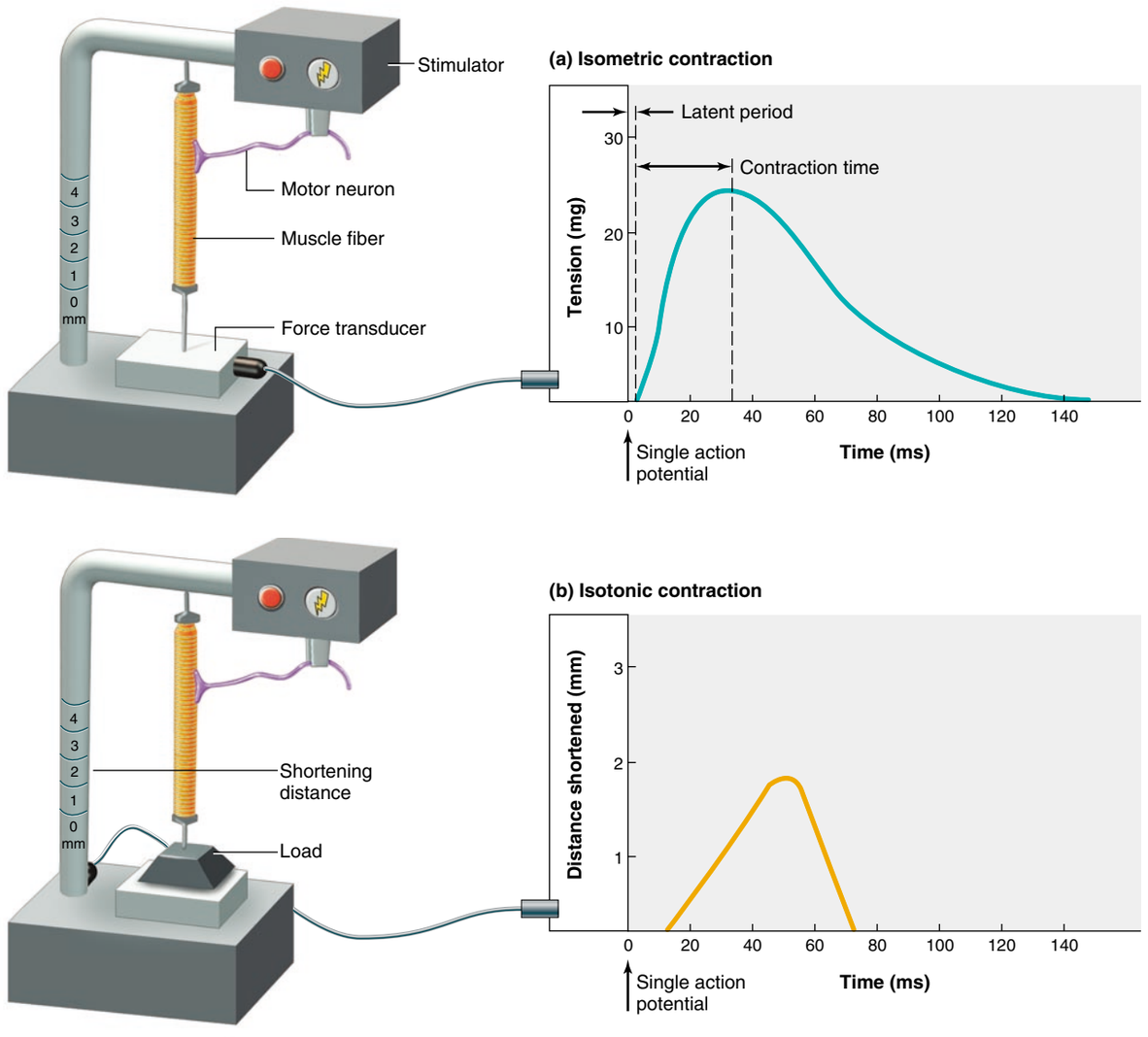

FIGURE 9–20

(a) Measurement of tension during a single isometric twitch of a skeletal muscle fiber. (b) Measurement of shortening during a single isotonic twitch of a skeletal muscle fiber.

few milliseconds, known as the **latent period,** before the tension in the muscle fiber begins to increase. During this latent period, the processes associated with excitation-contraction coupling are occurring. The time interval from the beginning of tension development at the end of the latent period to the peak tension is the **contraction time.** Not all skeletal muscle fibers have the same twitch contraction time. Some fast fibers have contraction times as short as 10 ms, whereas slower fibers may take 100 ms or longer. The duration of the contraction time depends in part on the time that cytosolic calcium remains elevated so that cross-bridges can continue to cycle. It is closely related to the Ca^{2+}-ATPase activity in the sarcoplasmic reticulum; activity is greater in fast-twitch fibers and less in slow-twitch fibers.

Comparing isotonic and isometric twitches in the same muscle fiber, one can see from Figure 9–20b that the latent period in an isotonic twitch is longer than that in an isometric contraction, while the duration of the mechanical event—shortening—is briefer in an isotonic twitch than the duration of force generation in an isometric twitch.

Moreover, the characteristics of an isotonic twitch depend upon the magnitude of the load being lifted (Figure 9–21): At heavier loads: (1) the latent period is longer, (2) the velocity of shortening (distance shortened per unit of time) is slower, (3) the duration

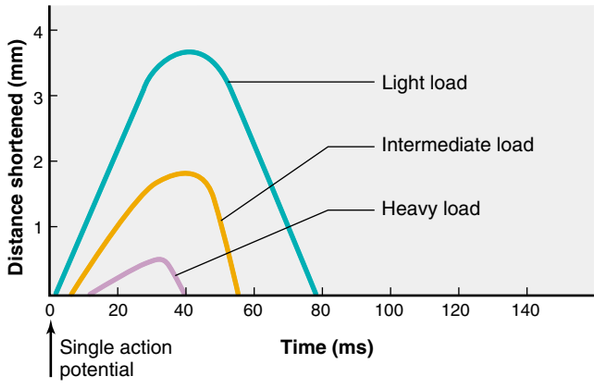

FIGURE 9–21

Isotonic twitches with different loads. The distance shortened, velocity of shortening, and duration of shortening all decrease with increased load, whereas the time from stimulation to the beginning of shortening increases with increasing load.

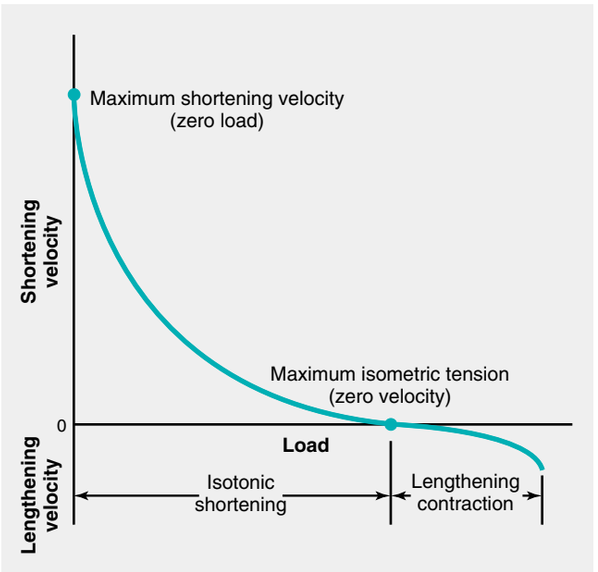

FIGURE 9–22

Velocity of skeletal muscle fiber shortening and lengthening as a function of load. Note that the force on the cross-bridges during a lengthening contraction is greater than the maximum isometric tension.

of the twitch is shorter, and (4) the distance shortened is less.

A closer look at the sequence of events in an isometric twitch explains this load-dependent behavior. Following excitation, the cross-bridges begin to develop force, but shortening does not begin until the muscle tension just exceeds the load on the fiber. Thus, before shortening, there is a period of *isometric* contraction during which the tension increases. The heavier the load, the longer it takes for the tension to increase to the value of the load, when shortening will begin. If the load on a fiber is increased, eventually a load is reached that the muscle is unable to lift, the velocity and distance of shortening will be zero, and the contraction will become completely isometric.

Load-Velocity Relation

It is a common experience that light objects can be moved faster than heavy objects. That is, the velocity at which a muscle fiber shortens decreases with increasing loads (Figure 9–22). The shortening velocity is maximal when there is no load and is zero when the load is equal to the maximal isometric tension. At loads greater than the maximal isometric tension, the fiber will *lengthen* at a velocity that increases with load.

The shortening velocity is determined by the rate at which individual cross-bridges undergo their cyclical activity. Because one ATP is split during each cross-bridge cycle, the rate of ATP splitting determines the shortening velocity. Increasing the load on a cross-bridge slows its forward movement during the power stroke. This reduces the overall rate of ATP hydrolysis, and thus the velocity of shortening.

Frequency-Tension Relation

Since a single action potential in a skeletal muscle fiber lasts 1 to 2 ms but the twitch may last for 100 ms, it is possible for a second action potential to be initiated during the period of mechanical activity. Figure 9–23 illustrates the tension generated during isometric contractions of a muscle fiber in response to three successive stimuli. In Figure 9–23a, the isometric twitch following the first stimulus S_1 lasts 150 ms. The second stimulus S_2, applied to the muscle fiber 200 ms after S_1 when the fiber has completely relaxed, causes a second identical twitch, and a third stimulus S_3, equally timed, produces a third identical twitch. In Figure 9–23b, the interval between S_1 and S_2 remains 200 ms, but a third stimulus is applied 60 ms after S_2, when the mechanical response resulting from S_2 is beginning to decrease but has not yet ended. Stimulus S_3 induces a contractile response whose peak tension is greater than that produced by S_2. In Figure 9–23c, the interval between S_2 and S_3 is further reduced to 10 ms, and the resulting peak tension is even greater. Indeed, the mechanical response to S_3 is a smooth continuation of the mechanical response already induced by S_2.

The increase in muscle tension from successive action potentials occurring during the phase of mechanical activity is known as **summation.** (Do not confuse

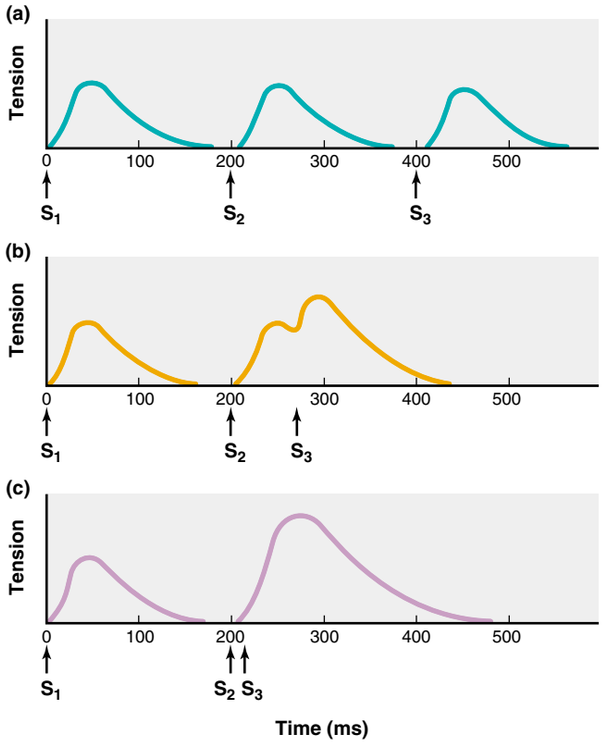

FIGURE 9–23

Summation of isometric contractions produced by shortening the time between stimuli S_2 and S_3.

this with the summation of neuronal postsynaptic potentials described in Chapter 6.) A maintained contraction in response to repetitive stimulation is known as a **tetanus** (tetanic contraction). At low stimulation frequencies, the tension may oscillate as the muscle fiber partially relaxes between stimuli, producing an **unfused tetanus.** A **fused tetanus,** with no oscillations, is produced at higher stimulation frequencies (Figure 9–24).

As the frequency of action potentials increases, the level of tension increases by summation until a maximal fused tetanic tension is reached, beyond which tension no longer increases with further increases in stimulation frequency. This maximal tetanic tension is about three to five times greater than the isometric twitch tension. Since different muscle fibers have different contraction times, the stimulus frequency that will produce a maximal tetanic tension differs from fiber to fiber.

Why is tetanic tension so much greater than twitch tension? Summation of tension can be explained in part by considering the relative timing of calcium availability and cross-bridge binding. The isometric tension produced by a muscle fiber at any instant depends mainly on the total number of cross-bridges bound to actin and undergoing step 2 of the cross-bridge cycle. Recall that even a single action potential in a skeletal muscle fiber releases enough calcium to saturate troponin, and all the myosin-binding sites on the thin filaments are therefore *initially* available. But the binding of energized cross-bridges to these sites (step 1 of the cross-bridge cycle) takes time, while the calcium released into the cytoplasm begins to be pumped back into the sarcoplasmic reticulum almost immediately. Thus, after a single action potential the calcium concentration begins to fall and the troponin/tropomyosin complex re-blocks many binding sites before cross-bridges have had time to attach to them.

In contrast, during a tetanic contraction, the successive action potentials each release calcium from the sarcoplasmic reticulum before all the calcium from the previous action potential has been pumped back into the reticulum. This results in a persistent elevation of cytosolic calcium concentration, which prevents a decline in the number of available binding sites on the thin filaments.

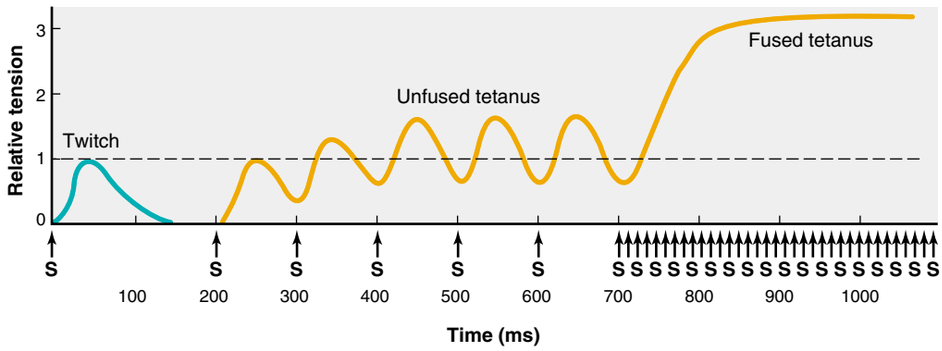

FIGURE 9–24

Isometric contractions produced by multiple stimuli(**S**) at 10 stimuli per second (unfused tetanus) and 100 stimuli per second (fused tetanus), as compared with a single twitch.

number of binding sites remains available, and many more cross-bridges are bound to the thin filaments at any instant.

Other causes of the lower tension seen in a single twitch are elastic structures, such as muscle tendons and the protein titin, which delay the transmission of cross-bridge force to the ends of a fiber. Because a single twitch is so brief, cross-bridge activity is already declining before force has been fully transmitted through these structures. This is less of a factor during tetanic stimulation because of the much longer duration of cross-bridge activity and force generation.

Length-Tension Relation

The springlike characteristics of the protein titin, which is attached to the Z line at one end and the thick filaments at the other, is responsible for most of the *passive* elastic properties of relaxed muscles. With increased stretch, the passive tension in a relaxed fiber increases, not from active cross-bridge movements but from elongation of the titin filaments. If the stretched fiber is released, its length will return to an equilibrium length, much like releasing a stretched rubber band. The critical point for this section is that the amount of *active* tension developed by a muscle fiber during contraction can also be altered by changing the length of the fiber. If you stretch a muscle fiber to various lengths and tetanically stimulate it at each length, the magnitude of the active tension will vary with length as shown in Figure 9–25.

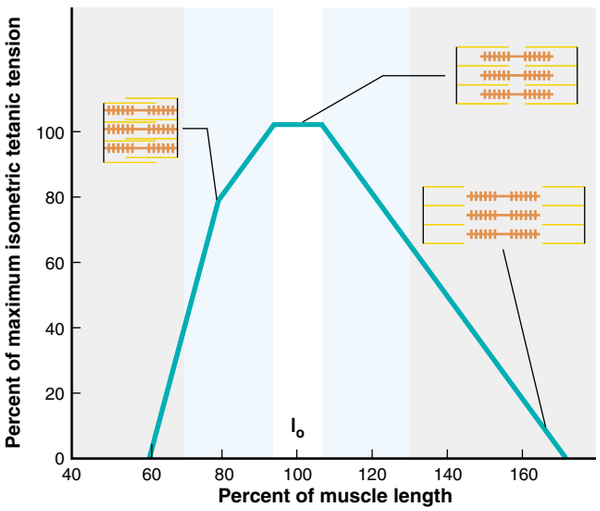

FIGURE 9–25

Variation in active isometric tetanic tension with muscle fiber length. The blue band represents the range of length changes that can normally occur in the body.

The length at which the fiber develops the greatest isometric active tension is termed the **optimal length, l_o.**

When a muscle fiber length is 60 percent of l_o, the fiber develops no tension when stimulated. As length is increased from this point, the isometric tension at each length is increased up to a maximum at l_o. Further lengthening leads to a *drop* in tension. At lengths of 175 percent l_o or beyond, the fiber develops no tension when stimulated.

When all the skeletal muscles in the body are relaxed, the lengths of most fibers are near l_o and thus near the optimal lengths for force generation. The length of a relaxed fiber can be altered by the load on the muscle or the contraction of other muscles that stretch the relaxed fibers, but the extent to which the relaxed length can be changed is limited by the muscle's attachments to bones. It rarely exceeds a 30 percent change from l_o and is often much less. Over this range of lengths, the ability to develop tension never falls below about half of the tension that can be developed at l_o (Figure 9–25).

The relationship between fiber length and the fiber's capacity to develop active tension during contraction can be partially explained in terms of the sliding-filament mechanism. Stretching a relaxed muscle fiber pulls the thin filaments past the thick filaments, changing the amount of overlap between them. Stretching a fiber to 1.75 l_o pulls the filaments apart to the point where there is no overlap. At this point there can be no cross-bridge binding to actin and no development of tension. Between 1.75 l_o and l_o, more and more filaments overlap, and the tension developed upon stimulation increases in proportion to the increased number of cross-bridges in the overlap region. Filament overlap is greatest at l_o, allowing the maximal number of cross-bridges to bind to the thin filaments, thereby producing maximal tension.

The tension decline at lengths less than l_o is the result of several factors. For example, (1) the overlapping sets of thin filaments from opposite ends of the sarcomere may interfere with the cross-bridges' ability to bind and exert force, and (2) at very short lengths the Z lines collide with the ends of the relatively rigid thick filaments, creating an internal resistance to sarcomere shortening.

SKELETAL MUSCLE ENERGY METABOLISM

As we have seen, ATP performs three functions directly related to muscle fiber contraction and relaxation (see Table 9–1). In no other cell type does the rate of ATP breakdown increase so much from one moment to the next as in a skeletal muscle fiber (20 to several hun-

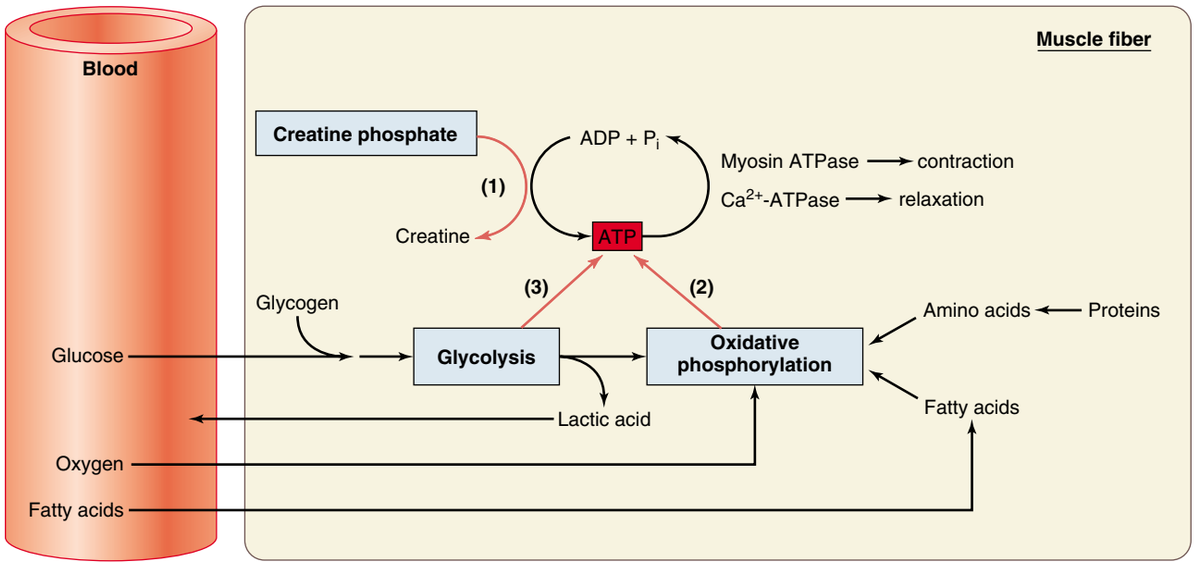

FIGURE 9–26

The three sources of ATP production during muscle contraction: (1) creatine phosphate, (2) oxidative phosphorylation, and (3) glycolysis.

dredfold depending on the type of muscle fiber) when it goes from rest to a state of contractile activity. The small supply of preformed ATP that exists at the start of contractile activity would only support a few twitches. If a fiber is to sustain contractile activity, molecules of ATP must be produced by metabolism as rapidly as they are broken down during the contractile process.

There are three ways a muscle fiber can form ATP (Figure 9–26): (1) phosphorylation of ADP by **creatine phosphate,** (2) oxidative phosphorylation of ADP in the mitochondria, and (3) phosphorylation of ADP by the glycolytic pathway in the cytosol.

Phosphorylation of ADP by creatine phosphate (CP) provides a very rapid means of forming ATP at the onset of contractile activity. When the chemical bond between creatine (C) and phosphate is broken, the amount of energy released is about the same as that released when the terminal phosphate bond in ATP is broken. This energy, along with the phosphate group, can be transferred to ADP to form ATP in a reversible reaction catalyzed by creatine kinase:

$$\text{CP} + \text{ADP} \overset{\text{Creatine kinase}}{\rightleftharpoons} \text{C} + \text{ATP}$$

Although creatine phosphate is a high-energy molecule, its energy cannot be released by myosin to drive cross-bridge activity. During periods of rest, muscle fibers build up a concentration of creatine phosphate approximately five times that of ATP. At the beginning of contraction, when the concentration of ATP begins to fall and that of ADP to rise owing to the increased rate of ATP breakdown by myosin, mass action favors the formation of ATP from creatine phosphate. This transfer of energy is so rapid that the concentration of ATP in a muscle fiber changes very little at the start of contraction, whereas the concentration of creatine phosphate falls rapidly.

Although the formation of ATP from creatine phosphate is very rapid, requiring only a single enzymatic reaction, the amount of ATP that can be formed by this process is limited by the initial concentration of creatine phosphate in the cell. If contractile activity is to be continued for more than a few seconds, the muscle must be able to form ATP from the other two sources listed previously. The use of creatine phosphate at the start of contractile activity provides the few seconds necessary for the slower, multienzyme pathways of oxidative phosphorylation and glycolysis to increase their rates of ATP formation to levels that match the rates of ATP breakdown.

At moderate levels of muscular activity, most of the ATP used for muscle contraction is formed by oxidative phosphorylation, and during the first 5 to 10 min of such exercise, breakdown of muscle glycogen to glucose provides the major fuel contributing to oxidative phosphorylation. For the next 30 min or so, blood-borne fuels become dominant, blood glucose and fatty acids

contributing approximately equally; beyond this period, fatty acids become progressively more important, and glucose utilization by muscle decreases.

If the intensity of exercise exceeds about 70 percent of the maximal rate of ATP breakdown, however, glycolysis contributes an increasingly significant fraction of the total ATP generated by the muscle. The glycolytic pathway, although producing only small quantities of ATP from each molecule of glucose metabolized, can produce large quantities of ATP when enough enzymes and substrate are available, and it can do so in the absence of oxygen (anaerobic). The glucose for glycolysis can be obtained from two sources: the blood or the stores of glycogen within the contracting muscle fibers. As the intensity of muscle activity increases, a greater fraction of the total ATP production is formed by anaerobic glycolysis. This is associated with a corresponding increase in the production of lactic acid.

At the end of muscle activity, creatine phosphate and glycogen levels in the muscle have decreased. To return a muscle fiber to its original state, therefore, these energy-storing compounds must be replaced. Both processes require energy, and so a muscle continues to consume increased amounts of oxygen for some time after it has ceased to contract. In addition, extra oxygen is required to metabolize accumulated lactic acid and return the blood and interstitial fluid oxygen concentrations to pre-exercise values. These processes are evidenced by the fact that you continue to breathe deeply and rapidly for a period of time immediately following intense exercise. This elevated consumption of oxygen following exercise repays what has been called the **oxygen debt**—that is, the increased production of ATP by oxidative phosphorylation following exercise that is used to restore the energy reserves in the form of creatine phosphate and glycogen.

Muscle Fatigue

When a skeletal muscle fiber is repeatedly stimulated, the tension developed by the fiber eventually decreases even though the stimulation continues (Figure 9–27). This decline in muscle tension as a result of previous contractile activity is known as **muscle fatigue.** Additional characteristics of fatigued muscle are a decreased shortening velocity and a slower rate of relaxation. The onset of fatigue and its rate of development depend on the type of skeletal muscle fiber that is active, the intensity and duration of contractile activity, and the degree of an individual's fitness.

If a muscle is allowed to rest after the onset of fatigue, it can recover its ability to contract upon restimulation (Figure 9–27). The rate of recovery depends upon the duration and intensity of the previous activity. Some muscle fibers fatigue rapidly if continuously stimulated but also recover rapidly after a brief rest. This is the type of fatigue (high-frequency fatigue) that accompanies high-intensity, short-duration exercise, such as weight lifting. In contrast, low-frequency fatigue develops more slowly with low-intensity, long-duration exercise, such as long-distance running, during which there are cyclical periods of contraction and relaxation. This type of fatigue requires much longer periods of rest, often up to 24 h, before the muscle achieves complete recovery.

It might seem logical that depletion of energy in the form of ATP would account for fatigue, but the ATP concentration in fatigued muscle is found to be only slightly lower than in a resting muscle, and not low enough to impair cross-bridge cycling. If contractile activity were to continue without fatigue, the ATP concentration could decrease to the point that the cross-bridges would become linked in a rigor configuration,

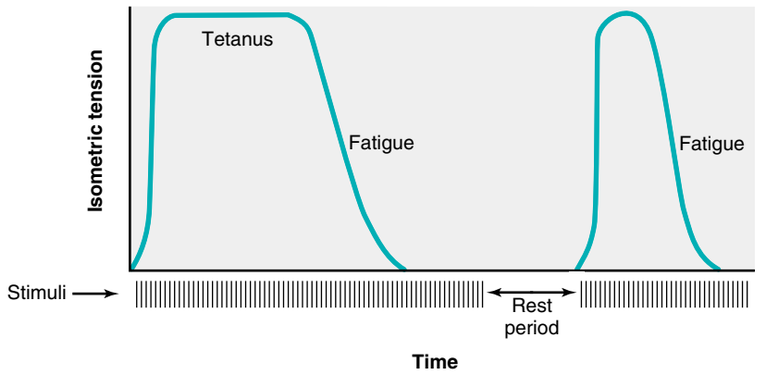

FIGURE 9–27
Muscle fatigue during a maintained isometric tetanus and recovery following a period of rest.

which is very damaging to muscle fibers. Thus, muscle fatigue may have evolved as a mechanism for preventing the onset of rigor.

Many factors can contribute to the fatigue of skeletal muscle. Fatigue from high-intensity, short duration exercise is thought to involve at least three different mechanisms:

1. **Conduction Failure.** The muscle action potential can fail to be conducted into the fiber along the T-tubules, which halts the release of calcium from the sarcoplasmic reticulum. The conduction failure results from the buildup of potassium ions in the small volume of the T-tubule during the repolarization of repetitive action potentials. Elevated external potassium concentration leads to a persistent depolarization of the membrane potential, and eventually a failure to produce action potentials in the T-tubular membrane (due to inactivation of sodium channels). Recovery is rapid with rest as the accumulated potassium diffuses out of the tubule, restoring excitability.
2. **Lactic Acid Buildup.** Elevated hydrogen ion concentration alters protein conformation and activity. Thus, the acidification of muscle by lactic acid alters a number of muscle proteins, including actin and myosin, as well as the proteins involved in calcium release. The function of the Ca^{2+}-ATPase pumps of the sarcoplasmic reticulum is also affected, which may in part explain the impaired relaxation of fatigued muscle.
3. **Inhibition of Cross-Bridge Cycling.** The buildup of ADP and P_i within muscle fibers during intense activity may directly inhibit cross-bridge cycling (in particular step 2) by mass action. Slowing the rate of this step delays cross-bridge detachment from actin, and thus slows the overall rate of cross-bridge cycling. These changes contribute to the reduced shortening velocity and impaired relaxation observed in muscle fatigue resulting from high-intensity exercise.

With low-intensity, long-duration exercise a number of processes have been implicated in fatigue, but no single process can completely account for it. The three factors just listed may play minor roles in this type of exercise as well, but it appears that depletion of fuel substrates may be more important. Although depletion of ATP is not a cause of fatigue, the decrease in muscle glycogen, which is supplying much of the fuel for contraction, correlates closely with fatigue onset. In addition, low blood glucose (hypoglycemia) and dehydration have been demonstrated to increase fatigue. Thus a certain level of carbohydrate metabolism appears necessary to prevent fatigue during low-intensity exercise, but the mechanism of this requirement is unknown.

Another type of fatigue quite different from muscle fatigue is due to failure of the appropriate regions of the cerebral cortex to send excitatory signals to the motor neurons. This is called **central command fatigue,** and it may cause a person to stop exercising even though the muscles are not fatigued. An athlete's performance depends not only on the physical state of the appropriate muscles but also upon the "will to win"—that is, the ability to initiate central commands to muscles during a period of increasingly distressful sensations.

TYPES OF SKELETAL MUSCLE FIBERS

Skeletal muscle fibers do not all have the same mechanical and metabolic characteristics. Different types of fibers can be identified on the basis of (1) their maximal velocities of shortening—fast or slow— and (2) the major pathway used to form ATP—oxidative or glycolytic.

Fast and slow fibers contain forms of myosin that differ in the maximal rates at which they split ATP. This, in turn, determines the maximal rate of cross-bridge cycling and thus the maximal shortening velocity. Fibers containing myosin with high ATPase activity are classified as **fast fibers,** and those containing myosin with lower ATPase activity are **slow fibers.** Although the rate of cross-bridge cycling is about four times faster in fast fibers than in slow fibers, the force produced by both types of cross-bridges is about the same.

The second means of classifying skeletal muscle fibers is according to the type of enzymatic machinery available for synthesizing ATP. Some fibers contain numerous mitochondria and thus have a high capacity for oxidative phosphorylation. These fibers are classified as **oxidative fibers.** Most of the ATP produced by such fibers is dependent upon blood flow to deliver oxygen and fuel molecules to the muscle. Not surprisingly, therefore, these fibers are surrounded by many small blood vessels. They also contain large amounts of an oxygen-binding protein known as **myoglobin,** which increases the rate of oxygen diffusion within the fiber and provides a small store of oxygen. The large amounts of myoglobin present in oxidative fibers give the fibers a dark-red color, and thus oxidative fibers are often referred to as **red muscle fibers.**

In contrast, **glycolytic fibers** have few mitochondria but possess a high concentration of glycolytic enzymes and a large store of glycogen. Corresponding to their limited use of oxygen, these fibers are surrounded by relatively few blood vessels and contain little myoglobin. The lack of myoglobin is responsible for the pale color of glycolytic fibers and their designation as **white muscle fibers.**

On the basis of these two characteristics, three types of skeletal muscle fibers can be distinguished:

1. **Slow-oxidative fibers** (type I) combine low myosin-ATPase activity with high oxidative capacity.
2. **Fast-oxidative fibers** (type IIa) combine high myosin-ATPase activity with high oxidative capacity.
3. **Fast-glycolytic fibers** (type IIb) combine high myosin-ATPase activity with high glycolytic capacity.

Note that the fourth theoretical possibility—slow-glycolytic fibers—is not found.

In addition to these biochemical differences, there are also size differences. Glycolytic fibers generally have much larger diameters than oxidative fibers (Figure 9–28). This fact has significance for tension development. The number of thick and thin filaments per unit of cross-sectional area is about the same in all types of skeletal muscle fibers. Therefore, the larger the diameter of a muscle fiber, the greater the total number of thick and thin filaments acting in parallel to produce force, and the greater the maximum tension it can develop (greater strength). Accordingly, the average glycolytic fiber, with its larger diameter, develops more tension when it contracts than does an average oxidative fiber.

These three types of fibers also differ in their capacity to resist fatigue. Fast-glycolytic fibers fatigue rapidly, whereas slow-oxidative fibers are very resistant to fatigue, which allows them to maintain contractile activity for long periods with little loss of tension. Fast-oxidative fibers have an intermediate capacity to resist fatigue (Figure 9–29).

The characteristics of the three types of skeletal muscle fibers are summarized in Table 9–3.

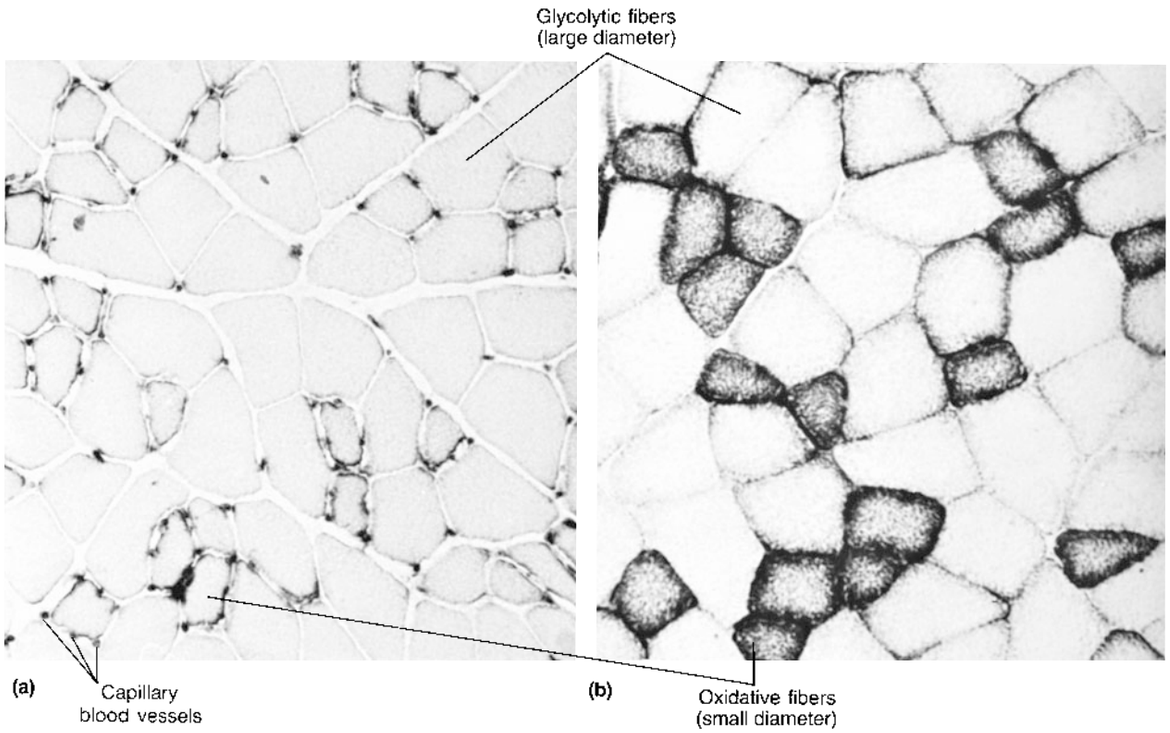

FIGURE 9–28

Cross sections of skeletal muscle. (a) The capillaries surrounding the muscle fibers have been stained. Note the large number of capillaries surrounding the small-diameter oxidative fibers. (b) The mitochondria have been stained, indicating the large numbers of mitochondria in the small-diameter oxidative fibers.

Courtesy of John A. Faulkner.

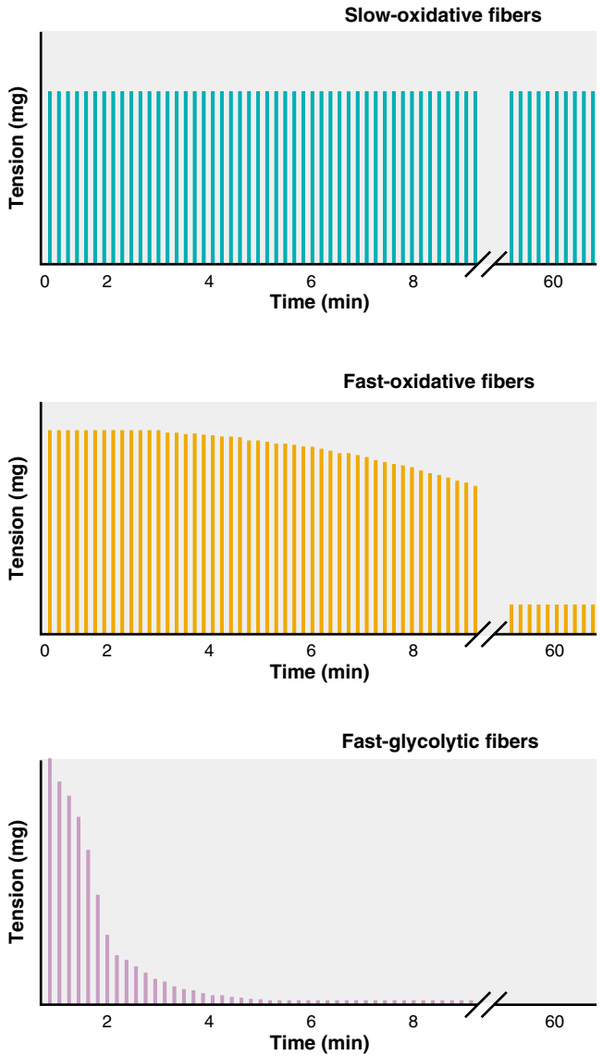

FIGURE 9–29

The rate of fatigue development in the three fiber types. Each vertical line is the contractile response to a brief tetanic stimulus and relaxation. The contractile responses occurring between about 9 min and 60 min are not shown on the figure.

WHOLE-MUSCLE CONTRACTION

As described earlier, whole muscles are made up of many muscle fibers organized into motor units. All the muscle fibers in a single motor unit are of the same fiber type. Thus, you can apply the fiber type designation to the motor unit and refer to slow-oxidative motor units, fast-oxidative motor units, and fast-glycolytic motor units.

Most muscles are composed of all three motor unit types interspersed with each other (Figure 9–30). No muscle has only a single fiber type. Depending on the proportions of the fiber types present, muscles can differ considerably in their maximal contraction speed, strength, and fatigability. For example, the muscles of the back, which must be able to maintain their activity for long periods of time without fatigue while supporting an upright posture, contain large numbers of slow-oxidative and fast-oxidative fibers. In contrast, the muscles in the arms may be called upon to produce large amounts of tension over a short time period, as when lifting a heavy object, and these muscles have a greater proportion of fast-glycolytic fibers.

We will now use the characteristics of single fibers to describe whole muscle contraction and its control.

Control of Muscle Tension

The total tension a muscle can develop depends upon two factors: (1) the amount of tension developed by each fiber, and (2) the number of fibers contracting at any time. By controlling these two factors, the nervous system controls whole-muscle tension, as well as shortening velocity. The conditions that determine the amount of tension developed in a single fiber have been discussed previously and are summarized in Table 9–4.

The number of fibers contracting at any time depends on: (1) the number of fibers in each motor unit (motor unit size), and (2) the number of active motor units.

Motor unit size varies considerably from one muscle to another. The muscles in the hand and eye, which produce very delicate movements, contain small motor units. For example, one motor neuron innervates only about 13 fibers in an eye muscle. In contrast, in the more coarsely controlled muscles of the legs, each motor unit is large, containing hundreds and in some cases several thousand fibers. When a muscle is composed of small motor units, the total tension produced by the muscle can be increased in small steps by activating additional motor units. If the motor units are large, large increases in tension will occur as each additional motor unit is activated. Thus, finer control of muscle tension is possible in muscles with small motor units.

The force produced by a single fiber, as we have seen earlier, depends in part on the fiber diameter—the greater the diameter, the greater the force. We have also noted that fast-glycolytic fibers have the largest diameters. Thus, a motor unit composed of 100 fast-glycolytic fibers produces more force than a motor unit composed of 100 slow-oxidative fibers. In addition, fast-glycolytic motor units tend to have more muscle fibers. For both of these reasons, activating a fast-glycolytic motor unit will produce more force than activating a slow-oxidative motor unit.

TABLE 9–3 Characteristics of the Three Types of Skeletal Muscle Fibers

	SLOW-OXIDATIVE FIBERS	FAST-OXIDATIVE FIBERS	FAST-GLYCOLYTIC FIBERS
Primary source of ATP production	Oxidative phosphorylation	Oxidative phosphorylation	Glycolysis
Mitochondria	Many	Many	Few
Capillaries	Many	Many	Few
Myoglobin content	High (red muscle)	High (red muscle)	Low (white muscle)
Glycolytic enzyme activity	Low	Intermediate	High
Glycogen content	Low	Intermediate	High
Rate of fatigue	Slow	Intermediate	Fast
Myosin-ATPase activity	Low	High	High
Contraction velocity	Slow	Fast	Fast
Fiber diameter	Small	Intermediate	Large
Motor unit size	Small	Intermediate	Large
Size of motor neuron innervating fiber	Small	Intermediate	Large

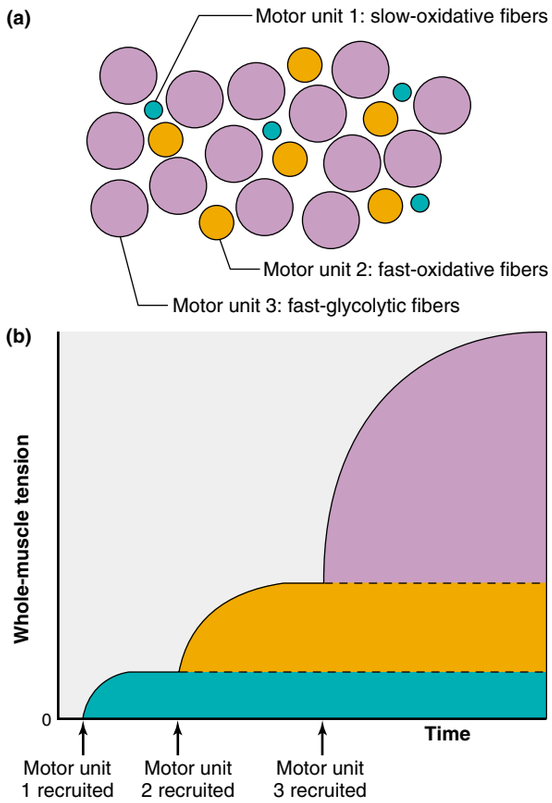

FIGURE 9–30

(a) Diagram of a cross section through a muscle composed of three types of motor units. (b) Tetanic muscle tension resulting from the successive recruitment of the three types of motor units. Note that motor unit 3, composed of fast-glycolytic fibers, produces the greatest rise in tension because it is composed of the largest-diameter fibers and contains the largest number of fibers per motor unit.

TABLE 9–4 Factors Determining Muscle Tension

I. Tension developed by each fiber
- a. Action potential frequency (frequency-tension relation)
- b. Fiber length (length-tension relation)
- c. Fiber diameter
- d. Fatigue

II. Number of active fibers
- a. Number of fibers per motor unit
- b. Number of active motor units

The process of increasing the number of motor units that are active in a muscle at any given time is called **recruitment.** It is achieved by activating excitatory synaptic inputs to more motor neurons. The greater the number of active motor neurons, the more motor units recruited, and the greater the muscle tension.

Motor neuron size plays an important role in the recruitment of motor units. The size of a motor neuron refers to the diameter of the nerve cell body, which is usually correlated with the diameter of its axon. Given the same number of sodium ions entering a cell at a single excitatory synapse in a large and in a small motor neuron, the small neuron will undergo a greater depolarization because these ions will be distributed over a smaller membrane surface area. Accordingly, given the same level of synaptic input, the smallest neurons will be recruited first—that is, will begin to generate action potentials first. The larger neurons will be recruited only as the level of synaptic input increases. Since the smallest motor neurons innervate the slow-oxidative motor units (see Table 9–3), these motor units are recruited first, followed by fast-oxidative motor units, and finally, during very strong contractions, by fast-glycolytic motor units (Figure 9–30).

Thus, during moderate-strength contractions, such as are used in most endurance types of exercise, relatively few fast-glycolytic motor units are recruited, and most of the activity occurs in oxidative fibers, which are more resistant to fatigue. The large fast-glycolytic motor units, which fatigue rapidly, begin to be recruited when the intensity of contraction exceeds about 40 percent of the maximal tension that can be produced by the muscle.

In conclusion, the neural control of whole-muscle tension involves (1) the frequency of action potentials in individual motor units (to vary the tension generated by the fibers in that unit) and (2) the recruitment of motor units (to vary the number of active fibers). Most motor neuron activity occurs in bursts of action potentials, which produce tetanic contractions of individual motor units rather than single twitches. Recall that the tension of a single fiber increases only three- to fivefold when going from a twitch to a maximal tetanic contraction. Therefore, varying the frequency of action potentials in the neurons supplying them provides a way to make only three- to fivefold adjustments in the tension of the recruited motor units. The force a whole muscle exerts can be varied over a much wider range than this, from very delicate movements to extremely powerful contractions, by the recruitment of motor units. Thus, recruitment provides the primary means of varying tension in a whole muscle. Recruitment is controlled by the central commands from the motor centers in the brain to the various motor neurons (Chapter 10).

Control of Shortening Velocity

As we saw earlier, the velocity at which a *single* muscle fiber shortens is determined by (1) the load on the fiber and (2) whether the fiber is a fast fiber or a slow fiber. Translated to a *whole* muscle, these characteristics become (1) the load on the whole muscle and (2) the types of motor units in the muscle. For the whole muscle, however, recruitment becomes a third very important factor, one that explains how the shortening velocity can be varied from very fast to very slow even though the load on the muscle remains constant. Consider, for the sake of illustration, a muscle composed of only two motor units of the same size and fiber type. One motor unit by itself will lift a 4-g load more slowly than a 2-g load because the shortening velocity decreases with increasing load. When both units are active and a 4-g load is lifted, each motor unit bears only half the load, and its fibers will shorten as if it were lifting only a 2-g load. In other words, the muscle will lift the 4-g load at a higher velocity when both motor units are active. Recruitment of motor units thus leads to an increase in both force and velocity.

Muscle Adaptation to Exercise

The regularity with which a muscle is used, as well as the duration and intensity of its activity, affects the properties of the muscle. If the neurons to a skeletal muscle are destroyed or the neuromuscular junctions become nonfunctional, the denervated muscle fibers will become progressively smaller in diameter, and the amount of contractile proteins they contain will decrease. This condition is known as ***denervation atrophy.*** A muscle can also atrophy with its nerve supply intact if the muscle is not used for a long period of time, as when a broken arm or leg is immobilized in a cast. This condition is known as ***disuse atrophy.***

In contrast to the decrease in muscle mass that results from a lack of neural stimulation, increased amounts of contractile activity—in other words, exercise—can produce an increase in the size (hypertrophy) of muscle fibers as well as changes in their capacity for ATP production.

Since the number of fibers in a muscle remains essentially constant throughout adult life, the changes in muscle size with atrophy and hypertrophy do not result from changes in the *number* of muscle fibers but in the metabolic capacity and size of each fiber.

Exercise that is of relatively low intensity but of long duration (popularly called "aerobic exercise"), such as running and swimming, produces increases in the number of mitochondria in the fibers that are recruited in this type of activity. In addition, there is an increase in the number of capillaries around these fibers. All these changes lead to an increase in the capacity for endurance activity with a minimum of fatigue. (Surprisingly, fiber diameter decreases slightly, and thus there is a small decrease in the maximal strength of muscles as a result of endurance exercise.) As we shall see in later chapters, endurance exercise produces changes not only in the skeletal muscles but also in the respiratory and circulatory systems, changes that improve the delivery of oxygen and fuel molecules to the muscle.

In contrast, short-duration, high-intensity exercise (popularly called "strength training"), such as weight lifting, affects primarily the fast-glycolytic fibers, which are recruited during strong contractions. These fibers undergo an increase in fiber diameter (hypertrophy) due to the increased synthesis of actin and myosin filaments, which form more myofibrils. In addition, the glycolytic activity is increased by increasing the synthesis of glycolytic enzymes. The result of such high-intensity exercise is an increase in the strength of the muscle and the bulging muscles of a conditioned weight lifter. Such muscles, although very powerful, have little capacity for endurance, and they fatigue rapidly.

Exercise produces limited change in the types of *myosin* enzymes formed by the fibers and thus little

change in the proportions of fast and slow fibers in a muscle. As described previously, however, exercise does change the rates at which *metabolic* enzymes are synthesized, leading to changes in the proportion of oxidative and glycolytic fibers within a muscle. With endurance training, there is a decrease in the number of fast-glycolytic fibers and an increase in the number of fast-oxidative fibers as the oxidative capacity of the fibers is increased. The reverse occurs with strength training as fast-oxidative fibers are converted to fast-glycolytic fibers.

The signals responsible for all these changes in muscle with different types of activity are unknown. They are related to the frequency and intensity of the contractile activity in the muscle fibers and thus to the pattern of action potentials produced in the muscle over an extended period of time.

Because different types of exercise produce quite different changes in the strength and endurance capacity of a muscle, an individual performing regular exercises to improve muscle performance must choose a type of exercise that is compatible with the type of activity he or she ultimately wishes to perform. Thus, lifting weights will not improve the endurance of a long-distance runner, and jogging will not produce the increased strength desired by a weight lifter. Most exercises, however, produce some effects on both strength and endurance.

These changes in muscle in response to repeated periods of exercise occur slowly over a period of weeks. If regular exercise is stopped, the changes in the muscle that occurred as a result of the exercise will slowly revert to their unexercised state.

The maximum force generated by a muscle decreases by 30 to 40 percent between the ages of 30 and 80. This decrease in tension-generating capacity is due primarily to a decrease in average fiber diameter. Some of the change is simply the result of diminishing physical activity with age and can be prevented by exercise programs. The ability of a muscle to adapt to exercise, however, decreases with age: The same intensity and duration of exercise in an older individual will not produce the same amount of change as in a younger person.

This effect of aging, however, is only partial, and there is no question that even in the elderly, exercise can produce significant adaptation. Aerobic training has received major attention because of its effect on the cardiovascular system (Chapter 12). Strength training of a modest degree, however, is also strongly recommended because it can partially prevent the loss of muscle tissue that occurs with aging. Moreover, it helps maintain stronger bones (Chapter 14).

Extensive exercise by an individual whose muscles have not been used in performing that particular type of exercise leads to muscle soreness the next day. This soreness is the result of a mild inflammation in the muscle, which occurs whenever tissues are damaged (Chapter 18). The most severe inflammation occurs following a period of lengthening contractions, indicating that the lengthening of a muscle fiber by an external force produces greater muscle damage than do either isotonic or isometric contractions. Thus, exercising by gradually lowering weights will produce greater muscle soreness than an equivalent amount of weight lifting.

The effects of anabolic steroids on skeletal muscle growth and strength are described in Chapter 17.

Lever Action of Muscles and Bones

A contracting muscle exerts a force on bones through its connecting tendons. When the force is great enough, the bone moves as the muscle shortens. A contracting muscle exerts only a pulling force, so that as the muscle shortens, the bones to which it is attached are pulled toward each other. **Flexion** refers to the *bending* of a limb at a joint, whereas **extension** is the *straightening* of a limb (Figure 9–31). These opposing motions require at least two muscles, one to cause flexion and the other extension. Groups of muscles that produce oppositely directed movements at a joint are known as **antagonists.** For example, from Figure 9–31 it can be seen that contraction of the biceps causes flexion of the arm at the elbow, whereas contraction of the antagonistic muscle, the triceps, causes the arm to extend. Both muscles exert only a pulling force upon the forearm when they contract.

Sets of antagonistic muscles are required not only for flexion-extension, but also for side-to-side movements or rotation of a limb. The contraction of some muscles leads to two types of limb movement, depending on the contractile state of other muscles acting on the same limb. For example, contraction of the gastrocnemius muscle in the leg causes a flexion of the leg at the knee, as in walking (Figure 9–32). However, contraction of the gastrocnemius muscle with the simultaneous contraction of the quadriceps femoris (which causes extension of the lower leg) prevents the knee joint from bending, leaving only the ankle joint capable of moving. The foot is extended, and the body rises on tiptoe.

The muscles, bones, and joints in the body are arranged in lever systems. The basic principle of a lever is illustrated by the flexion of the arm by the biceps muscle (Figure 9–33), which exerts an upward pulling force on the forearm about 5 cm away from the elbow joint. In this example, a 10-kg weight held in the hand exerts a downward force of 10 kg about 35 cm from the elbow. A law of physics tells us that the forearm is in mechan-

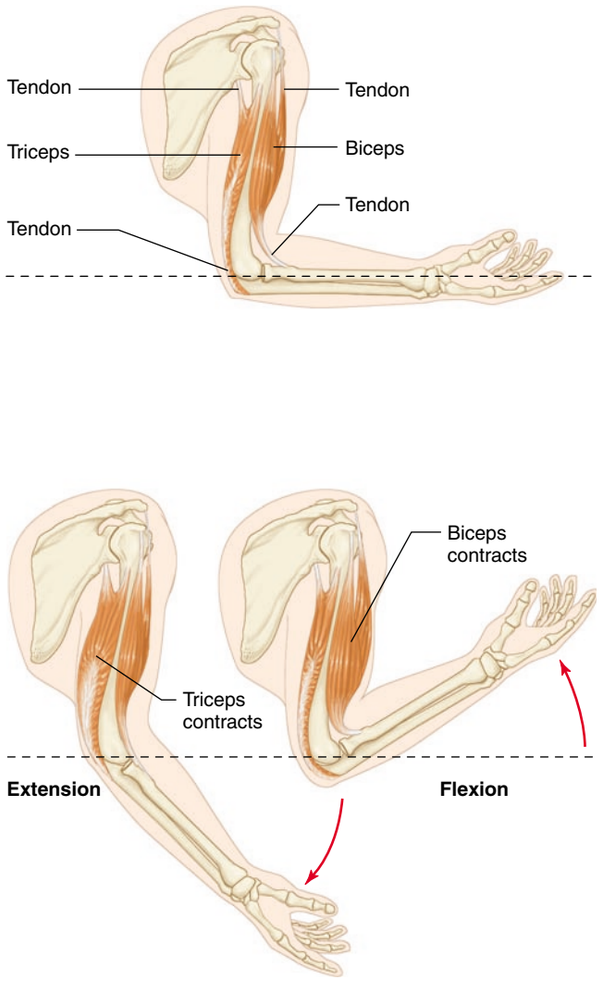

FIGURE 9–31
Antagonistic muscles for flexion and extension of the forearm.

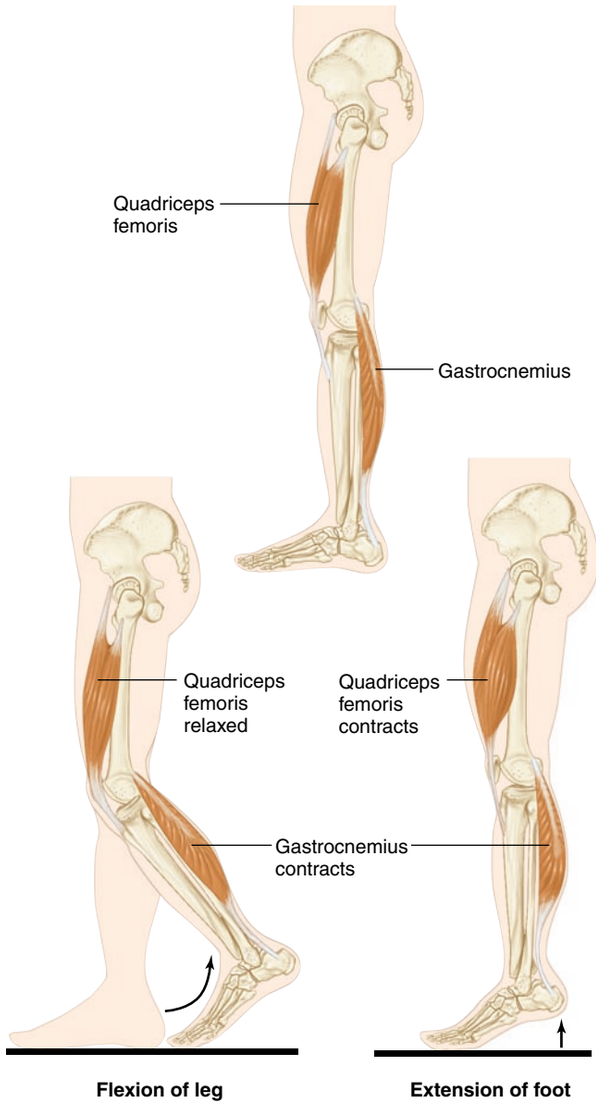

FIGURE 9–32
Contraction of the gastrocnemius muscle in the calf can lead either to flexion of the leg, if the quadriceps femoris muscle is relaxed, or to extension of the foot, if the quadriceps is contracting, preventing bending of the knee joint.

ical equilibrium (no net forces acting on the system) when the product of the downward force (10 kg) and its distance from the elbow (35 cm) is equal to the product of the isometric tension exerted by the muscle (X), and its distance from the elbow (5 cm); that is, $10 \times 35 = 5 \times X$. Thus $X = 70$ kg. The important point is that this system is working at a mechanical disadvantage since the force exerted by the muscle (70 kg) is considerably greater than the load (10 kg) it is supporting.

However, the mechanical disadvantage under which most muscle lever systems operate is offset by increased maneuverability. In Figure 9–34, when the biceps shortens 1 cm, the hand moves through a distance of 7 cm. Since the muscle shortens 1 cm in the same amount of time that the hand moves 7 cm, the velocity at which the hand moves is seven times greater than the rate of muscle shortening. The lever system amplifies the velocity of muscle shortening so that short, relatively slow movements of the muscle produce faster movements of the hand. Thus, a pitcher can throw a baseball at 90 to 100 mi/h even though his muscles shorten at only a small fraction of this velocity.

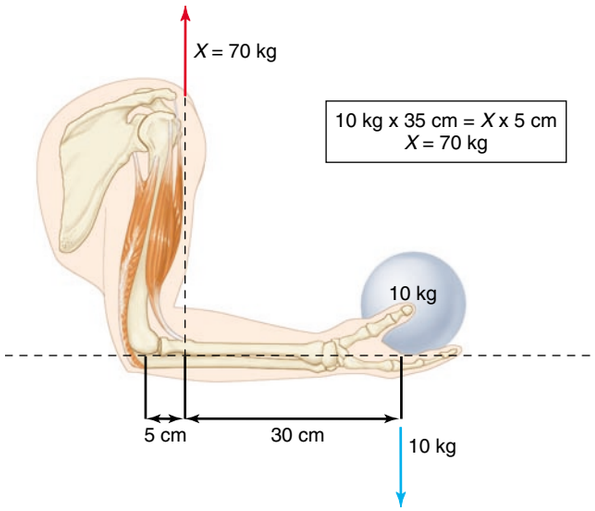

FIGURE 9–33
Mechanical equilibrium of forces acting on the forearm while supporting a 10-kg load.

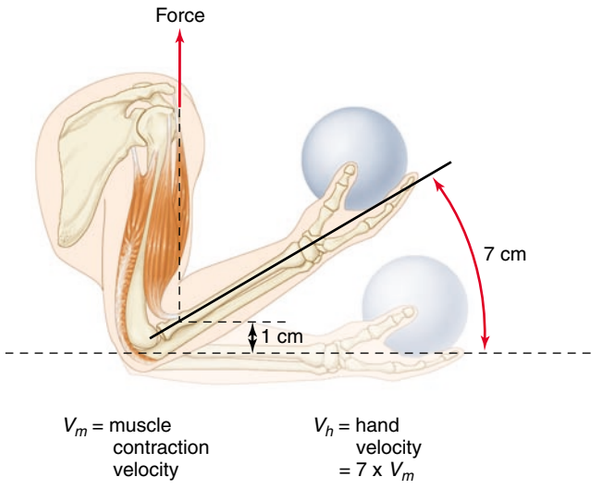

FIGURE 9–34
Velocity of the biceps muscle is amplified by the lever system of the arm, producing a greater velocity of the hand. The range of movement is also amplified (1 cm of shortening by the muscle produces 7 cm of movement by the hand).

ADDITIONAL CLINICAL EXAMPLES

A number of diseases can affect the contraction of skeletal muscle. Many of them are due to defects in the parts of the nervous system that control contraction of the muscle fibers rather than to defects in the muscle fibers themselves. For example, ***poliomyelitis*** is a viral disease that destroys motor neurons, leading to the paralysis of skeletal muscle, and may result in death due to respiratory failure.

MUSCLE CRAMPS

Involuntary tetanic contraction of skeletal muscles produces ***muscle cramps.*** During cramping, nerve action potentials fire at abnormally high rates, a much greater rate than occurs during maximal voluntary contraction. The specific cause of this high activity is uncertain but is probably related to electrolyte imbalances in the extracellular fluid surrounding both the muscle and nerve fibers. These imbalances may arise from overexercise or persistent dehydration, and they can directly induce action potentials in motor neurons and muscle fibers. Another theory is that sensory receptors in the muscle are stimulated by chemical imbalances within the muscle, and the motor neurons to the area are reflexly activated when those signals reach the spinal cord.

HYPOCALCEMIC TETANY

Similar in symptoms to muscular cramping is ***hypocalcemic tetany,*** the involuntary tetanic contraction of skeletal muscles that occurs when the extracellular calcium concentration falls to about 40 percent of its normal value. This may seem surprising, since we have seen that calcium is required for excitation-contraction coupling. However, recall that this calcium is sarcoplasmic reticulum calcium, not extracellular calcium. The effect of changes in extracellular calcium is exerted not on the sarcoplasmic reticulum calcium, but directly on the plasma membrane. Low extracellular calcium (**hypocalcemia**) increases the opening of sodium channels in excitable membranes, leading to membrane depolarization and the spontaneous firing of action potentials. It is this that causes the increased muscle contractions. The mechanisms controlling the extracellular concentration of calcium ions are discussed in Chapter 14.

MUSCULAR DYSTROPHY

This disease is one of the most frequently encountered genetic diseases, affecting one in every 3500 males (but much less commonly in females) born in America. ***Muscular dystrophy***

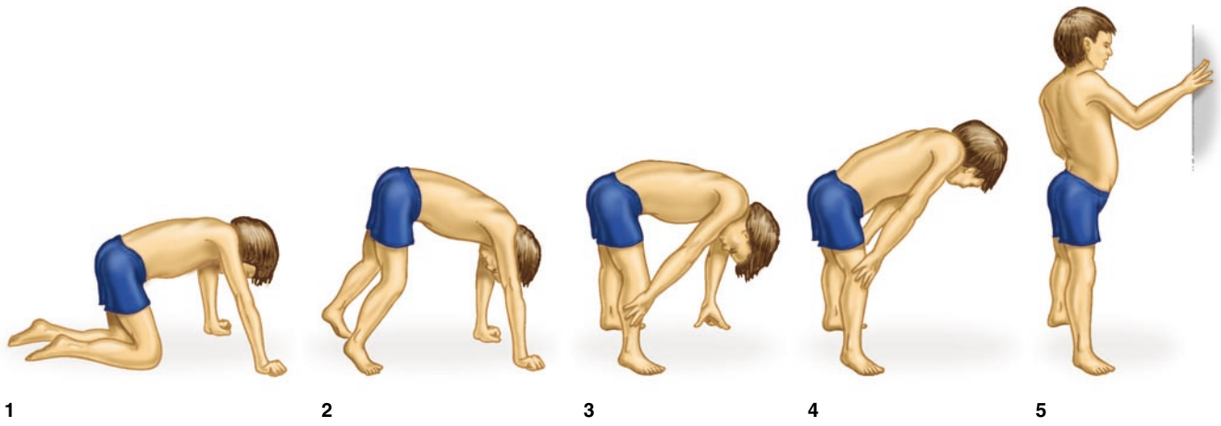

FIGURE 9–35

Boy with Duchenne muscular dystrophy. Muscles of the hip girdle and trunk are the first to weaken, requiring patients to use their arms to climb up the legs in attempting to go from lying to standing.

is associated with the progressive degeneration of skeletal and cardiac muscle fibers, weakening the muscles and leading ultimately to death from respiratory or cardiac failure (Figure 9 – 35). The symptoms become evident at about 2 to 6 years of age, and most affected individuals do not survive much beyond the age of 20.

The recessive gene responsible for a major form of muscular dystrophy (***Duchenne muscular dystrophy***) has been identified on the X chromosome, and muscular dystrophy is a sex-linked recessive disease. (As described in Chapter 17, girls have two X chromosomes and boys only one. Accordingly, a girl with one abnormal X chromosome and one normal one will not generally develop the disease. This is why the disease is so much more common in boys.) This gene codes for a protein known as dystrophin, which is either absent or present in a nonfunctional form in patients with the disease. Dystrophin is a large protein that links cytoskeletal proteins to membrane glycoproteins. It resembles other known cytoskeletal proteins and may be involved in maintaining the structural integrity of the plasma membrane or of elements within the membrane, such as ion channels, in fibers subjected to repeated structural deformation during contraction. Preliminary attempts are being made to treat the disease by inserting the normal gene into dystrophic muscle cells.

Myasthenia Gravis

Myasthenia gravis is a collection of neuromuscular disorders characterized by muscle fatigue and weakness that progressively worsens as the muscle is used. It affects about 12,000 Americans. One type of the disease results from a decrease in the number of ACh receptors on the motor end plate. The release of ACh from the nerve terminals is normal, but the magnitude of the end-plate potential is markedly reduced because of the decreased number of receptors. Even in normal muscle, the amount of ACh released with each action potential decreases with repetitive activity, and thus the magnitude of the resulting EPP falls. In normal muscle, however, the EPP remains well above the threshold necessary to initiate a muscle action potential. In contrast, after a few motor nerve impulses in a myasthenia gravis patient, the magnitude of the EPP falls below the threshold for initiating a muscle action potential. As described in Chapter 18, the destruction of the ACh receptors is brought about by the body's own defense mechanisms gone awry, specifically because of the formation of antibodies to the nicotinic ACh-receptor proteins.

A number of approaches are currently used to treat the disease. One is to administer acetylcholinesterase inhibitors (e.g., ***neostygmine***). This can partially compensate for the reduction in ACh receptor numbers by prolonging the time that acetylcholine is available at the synapse. Other therapies aim at blunting the immune response. Removal of the thymus gland **(*thymectomy*)** reduces the production of antibodies and reverses symptoms in about 50 percent of patients. ***Plasmapheresis*** is a treatment that involves removing the liquid fraction of blood (plasma), which contains the offending antibodies. A combination of these treatments has greatly reduced the mortality rate for myasthenia gravis.

SECTION A SUMMARY

I. There are three types of muscle—skeletal, smooth, and cardiac. Skeletal muscle is attached to bones and moves and supports the skeleton. Smooth muscle surrounds hollow cavities and tubes. Cardiac muscle is the muscle of the heart.

Structure

I. Skeletal muscles, composed of cylindrical muscle fibers (cells), are linked to bones by tendons at each end of the muscle.
II. Skeletal muscle fibers have a repeating, striated pattern of light and dark bands due to the arrangement of the thick and thin filaments within the myofibrils.
III. Actin-containing thin filaments are anchored to the Z lines at each end of a sarcomere, while their free ends partially overlap the myosin-containing thick filaments in the A band at the center of the sarcomere.

Molecular Mechanisms of Contraction

I. When a skeletal muscle fiber actively shortens, the thin filaments are propelled toward the center of their sarcomere by movements of the myosin cross-bridges that bind to actin.
   a. The two globular heads of each cross-bridge contain a binding site for actin and an enzymatic site that splits ATP.
   b. The four steps occurring during each cross-bridge cycle are summarized in Figure 9–12. The cross-bridges undergo repeated cycles during a contraction, each cycle producing only a small increment of movement.
   c. The three functions of ATP in muscle contraction are summarized in Table 9–1.
II. In a resting muscle, attachment of cross-bridges to actin is blocked by tropomyosin molecules that are in contact with the actin subunits of the thin filaments.
III. Contraction is initiated by an increase in cytosolic calcium concentration. The calcium ions bind to troponin, producing a change in its shape that is transmitted via tropomyosin to uncover the binding sites on actin, allowing the cross-bridges to bind to the thin filaments.
   a. The rise in cytosolic calcium concentration is triggered by an action potential in the plasma membrane. The action potential is propagated into the interior of the fiber along the transverse tubules to the region of the sarcoplasmic reticulum, where it produces a release of calcium ions from the reticulum.
   b. Relaxation of a contracting muscle fiber occurs as a result of the active transport of cytosolic calcium ions back into the sarcoplasmic reticulum.
IV. Branches of a motor neuron axon form neuromuscular junctions with the muscle fibers in its motor unit. Each muscle fiber is innervated by a branch from only one motor neuron.
   a. Acetylcholine released by an action potential in a motor neuron binds to receptors on the motor end plate of the muscle membrane, opening ion channels that allow the passage of sodium and potassium ions, which depolarize the end-plate membrane.
   b. A single action potential in a motor neuron is sufficient to produce an action potential in a skeletal muscle fiber.
   c. Figure 9–19 summarizes events at the neuromuscular junction.
V. Table 9–2 summarizes the events leading to the contraction of a skeletal muscle fiber.

Mechanics of Single-Fiber Contraction

I. Contraction refers to the turning on of the cross-bridge cycle. Whether there is an accompanying change in muscle length depends upon the external forces acting on the muscle.
II. Three types of contractions can occur following activation of a muscle fiber: (1) an isometric contraction in which the muscle generates tension but does not change length; (2) an isotonic contraction in which the muscle shortens, moving a load; and (3) a lengthening contraction in which the external load on the muscle causes the muscle to lengthen during the period of contractile activity.
III. Increasing the frequency of action potentials in a muscle fiber increases the mechanical response (tension or shortening), up to the level of maximal tetanic tension.
IV. Maximum isometric tetanic tension is produced at the optimal sarcomere length l_o. Stretching a fiber beyond its optimal length or decreasing the fiber length below l_o decreases the tension generated.
V. The velocity of muscle fiber shortening decreases with increases in load. Maximum velocity occurs at zero load.

Skeletal Muscle Energy Metabolism

I. Muscle fibers form ATP by the transfer of phosphate from creatine phosphate to ADP, by oxidative phosphorylation of ADP in mitochondria, and by substrate-level phosphorylation of ADP in the glycolytic pathway.
II. At the beginning of exercise, muscle glycogen is the major fuel consumed. As the exercise proceeds, glucose and fatty acids from the blood provide most of the fuel, fatty acids becoming progressively more important during prolonged exercise. When the intensity of exercise exceeds about 70 percent of maximum, glycolysis begins to contribute an increasing fraction of the total ATP generated.
III. Muscle fatigue is caused by a variety of factors, including internal changes in acidity, cross-bridge inhibition, glycogen depletion, and excitation-contraction coupling failure, but not by a lack of ATP.

Types of Skeletal Muscle Fibers

I. Three types of skeletal muscle fibers can be distinguished by their maximal shortening velocities and the predominate pathway used to form ATP: slow-oxidative, fast-oxidative, and fast-glycolytic fibers.
   a. Differences in maximal shortening velocities are due to different myosin enzymes with high or low ATPase activities, giving rise to fast and slow fibers.
   b. Fast-glycolytic fibers have a larger average diameter than oxidative fibers and therefore produce greater tension, but they also fatigue more rapidly.

II. All the muscle fibers in a single motor unit belong to the same fiber type, and most muscles contain all three types.

III. Table 9–3 summarizes the characteristics of the three types of skeletal muscle fibers.

Whole-Muscle Contraction

I. The tension produced by whole-muscle contraction depends on the amount of tension developed by each fiber and the number of active fibers in the muscle (Table 9–4).

II. Muscles that produce delicate movements have a small number of fibers per motor unit, whereas large postural muscles have much larger motor units.

III. Fast-glycolytic motor units not only have large-diameter fibers but also tend to have large numbers of fibers per motor unit.

IV. Increases in muscle tension are controlled primarily by increasing the number of active motor units in a muscle, a process known as recruitment. Slow-oxidative motor units are recruited first during weak contractions, then fast-oxidative motor units, and finally fast-glycolytic motor units during very strong contractions.

V. Increasing motor-unit recruitment increases the velocity at which a muscle will move a given load.

VI. The strength and susceptibility to fatigue of a muscle can be altered by exercise.
   a. Long-duration, low-intensity exercise increases a fiber's capacity for oxidative ATP production by increasing the number of mitochondria and blood vessels in the muscle, resulting in increased endurance.
   b. Short-duration, high-intensity exercise increases fiber diameter as a result of increased synthesis of actin and myosin, resulting in increased strength.

VII. Movement around a joint requires two antagonistic groups of muscles: one flexes the limb at the joint, and the other extends the limb.

VIII. The lever system of muscles and bones requires muscle tensions far greater than the load in order to sustain a load in an isometric contraction, but the lever system produces a shortening velocity at the end of the lever arm that is greater than the muscle-shortening velocity.

SECTION A KEY TERMS

A band 270
acetylcholine (ACh) 280
acetylcholinesterase 282
actin 269
antagonist 295
cardiac muscle 268
central command fatigue 290
concentric contraction 283
contraction 270
contraction time 284
creatine phosphate 288
cross-bridge 270
cross-bridge cycle 272
dihydropyridine (DHP) receptor 279
eccentric contraction 283
end-plate potential (EPP) 281
excitation-contraction coupling 277
extension 295
fast fiber 290
fast-glycolytic fiber 291
fast-oxidative fiber 291
flexion 295
foot proteins 278
fused tetanus 285
glycolytic fiber 291
H zone 270
heavy chains 271
hypertrophy 268
hypocalcemia 297
I band 270
isometric contraction 283
isotonic contraction 283
junctional feet 278
latent period 284
lateral sac 277
lengthening contraction 283
light chains 271
load 283
M line 270
motor end plate 281
motor neuron 280
motor unit 280
muscle 268
muscle fatigue 289
muscle fiber 268
myoblast 268
myofibril 269
myoglobin 291
myosin 269
neuromuscular junction 281
optimal length (l_o) 287
oxidative fiber 291
oxygen debt 289
power stroke 274
recruitment 293
red muscle fiber 291
relaxation 270
rigor mortis 276
ryanodine receptor 279
sarcomere 269
sarcoplasmic reticulum 277
satellite cell 268
skeletal muscle 268
sliding-filament mechanism 270
slow fiber 290
slow-oxidative fiber 291
smooth muscle 268
striated muscle 269
summation 285
tendon 268
tension 283
tetanus 285
thick filament 269
thin filament 269
titin 270
transverse tubule (T-tubule) 277
tropomyosin 276
troponin 276
twitch 284
unfused tetanus 285
white muscle fiber 291
Z line 270

SECTION A CLINICAL TERMS

atropine 283
botulism 283
curare 283
denervation atrophy 294
disuse atrophy 294
duchenne muscular dystrophy 298
gallamine 283
hypocalcemic tetany 297
muscle cramps 297
muscular dystrophy 298
myasthenia gravis 298
neostigmine 298
plasmapheresis 298
poliomyelitis 297
thymectomy 298

SECTION A REVIEW QUESTIONS

1. List the three types of muscle cells and their locations.
2. Diagram the arrangement of thick and thin filaments in a striated muscle sarcomere, and label the major bands that give rise to the striated pattern.
3. Describe the organization of myosin and actin molecules in the thick and thin filaments.
4. Describe the four steps of one cross-bridge cycle.
5. Describe the physical state of a muscle fiber in rigor mortis and the conditions that produce this state.
6. What three events in skeletal muscle contraction and relaxation are dependent on ATP?
7. What prevents cross-bridges from attaching to sites on the thin filaments in a resting skeletal muscle?
8. Describe the role and source of calcium ions in initiating contraction in skeletal muscle.
9. Describe the location, structure, and function of the sarcoplasmic reticulum in skeletal muscle fibers.
10. Describe the structure and function of the transverse tubules.
11. Describe the events that result in the relaxation of skeletal muscle fibers.
12. Define a motor unit and describe its structure.
13. Describe the sequence of events by which an action potential in a motor neuron produces an action potential in the plasma membrane of a skeletal muscle fiber.
14. What is an end-plate potential, and what ions produce it?
15. Compare and contrast the transmission of electrical activity at a neuromuscular junction with that at a synapse.
16. Describe isometric, isotonic, and lengthening contractions.
17. What factors determine the duration of an isotonic twitch in skeletal muscle? An isometric twitch?
18. What effect does increasing the frequency of action potentials in a skeletal muscle fiber have upon the force of contraction? Explain the mechanism responsible for this effect.
19. Describe the length-tension relationship in striated muscle fibers.
20. Describe the effect of increasing the load on a skeletal muscle fiber on the velocity of shortening.
21. What is the function of creatine phosphate in skeletal muscle contraction?
22. What fuel molecules are metabolized to produce ATP during skeletal muscle activity?
23. List the factors responsible for skeletal muscle fatigue.
24. What component of skeletal muscle fibers accounts for the differences in the fibers' maximal shortening velocities?
25. Summarize the characteristics of the three types of skeletal muscle fibers.
26. Upon what two factors does the amount of tension developed by a whole skeletal muscle depend?
27. Describe the process of motor-unit recruitment in controlling (a) whole-muscle tension and (b) velocity of whole-muscle shortening.
28. During increases in the force of skeletal muscle contraction, what is the order of recruitment of the different types of motor units?
29. What happens to skeletal muscle fibers when the motor neuron to the muscle is destroyed?
30. Describe the changes that occur in skeletal muscles following a period of (a) long-duration, low-intensity exercise training; and (b) short-duration, high-intensity exercise training.
31. How are skeletal muscles arranged around joints so that a limb can push or pull?
32. What are the advantages and disadvantages of the muscle-bone-joint lever system?

SECTION B

Smooth Muscle

We now examine the second of the three types of muscle found in the body—smooth muscle. Two characteristics are common to all smooth muscles: they lack the cross-striated banding pattern found in skeletal and cardiac fibers (which makes them "smooth"), and the nerves to them are derived from the autonomic division of the nervous system rather than the somatic division. Thus, smooth muscle is not normally under direct voluntary control.

Smooth muscle, like skeletal muscle, uses cross-bridge movements between actin and myosin filaments to generate force, and calcium ions to control cross-bridge activity. However, the organization of the contractile filaments and the process of excitation-contraction coupling are quite different in these two types of muscle. Furthermore, there is considerable diversity among smooth muscles with respect to the mechanism of excitation-contraction coupling.

STRUCTURE OF SMOOTH MUSCLE

Each smooth muscle fiber is a spindle-shaped cell with a diameter ranging from 2 to 10 μm, as compared to a range of 10 to 100 μm for skeletal muscle fibers (see

Figure 9–3). While skeletal muscle fibers are multinucleate cells that are unable to divide once they have differentiated, smooth muscle fibers have a single nucleus and have the capacity to divide throughout the life of an individual. Smooth muscle cells can be stimulated to divide by a variety of paracrine agents, often in response to tissue injury.

Two types of filaments are present in the cytoplasm of smooth muscle fibers (Figure 9–36): thick myosin-containing filaments and thin actin-containing filaments. The thin filaments are anchored either to the plasma membrane or to cytoplasmic structures known as **dense bodies,** which are functionally similar to the Z lines in skeletal muscle fibers. Note in Figure 9–36 that the filaments are oriented slightly diagonally to the long axis of the cell. When the fiber shortens, the regions of the plasma membrane between the points where actin is attached to the membrane balloon out. The thick and thin filaments are not organized into myofibrils, as in striated muscles, and there is no regular alignment of these filaments into sarcomeres, which accounts for the absence of a banding pattern (Figure 9–37). Nevertheless, smooth muscle contraction occurs by a sliding-filament mechanism.

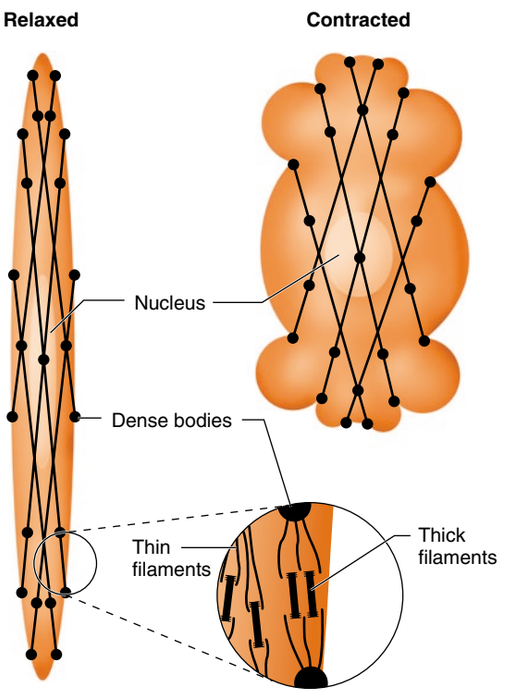

FIGURE 9–36
Thick and thin filaments in smooth muscle are arranged in slightly diagonal chains that are anchored to the plasma membrane or to dense bodies within the cytoplasm. When activated, the thick and thin filaments slide past each other, causing the smooth muscle fiber to shorten and thicken.

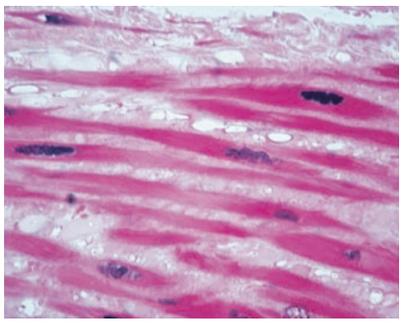

FIGURE 9–37
Photomicrograph of a sheet of smooth muscle cells. Note the spindle shape, single nucleus, and lack of striations.

The concentration of myosin in smooth muscle is only about one-third of that in striated muscle, whereas the actin content can be twice as great. In spite of these differences, the maximal tension per unit of cross-sectional area developed by smooth muscles is similar to that developed by skeletal muscle.

The isometric tension produced by smooth muscle fibers varies with fiber length in a manner qualitatively similar to that observed in skeletal muscle. There is an optimal length at which tension development is maximal, and less tension is generated at lengths shorter or longer than this optimal length. The range of muscle lengths over which smooth muscle is able to develop tension is greater, however, than it is in skeletal muscle. This property is highly adaptive since most smooth muscles surround hollow organs that undergo changes in volume with accompanying changes in the lengths of the smooth muscle fibers in their walls. Even with relatively large increases in volume, as during the accumulation of large amounts of urine in the bladder, the smooth muscle fibers in the wall retain some ability to develop tension, whereas such distortion might stretch skeletal muscle fibers beyond the point of thick- and thin-filament overlap.

SMOOTH MUSCLE CONTRACTION AND ITS CONTROL

Changes in cytosolic calcium concentration control the contractile activity in smooth muscle fibers, as in striated muscle. However, there are significant differences between the two types of muscle in the way in which

calcium activates cross-bridge cycling and in the mechanisms by which stimulation leads to alterations in calcium concentration.

Cross-Bridge Activation

The thin filaments in smooth muscle do not have the calcium-binding protein troponin that mediates calcium-triggered cross-bridge activity in both skeletal and cardiac muscle. *Instead, cross-bridge cycling in smooth muscle is controlled by a calcium-regulated enzyme that phosphorylates myosin.* Only the phosphorylated form of smooth muscle myosin can bind to actin and undergo cross-bridge cycling.

The following sequence of events occurs after a rise in cytosolic calcium in a smooth muscle fiber (Figure 9–38): (1) Calcium binds to calmodulin, a calcium-binding protein that is present in the cytoplasm of most cells (Chapter 5) and whose structure is related to that of troponin. (2) The calcium-calmodulin complex binds to another cytosolic protein, **myosin light-chain kinase,** thereby activating the enzyme. (3) Active myosin light-chain kinase then uses ATP to phosphorylate myosin light chains in the globular head of myosin. (4) The phosphorylated cross-bridge binds to actin. A key difference here is that cross-bridge activity in smooth muscle is turned on by calcium-mediated changes in the thick filaments, whereas in striated muscle, calcium mediates changes in the thin filaments.

The smooth muscle form of myosin has a very low maximal rate of ATPase activity, on the order of 10 to 100 times less than that of skeletal muscle myosin. Since the rate of ATP splitting determines the rate of cross-bridge cycling and thus shortening velocity,

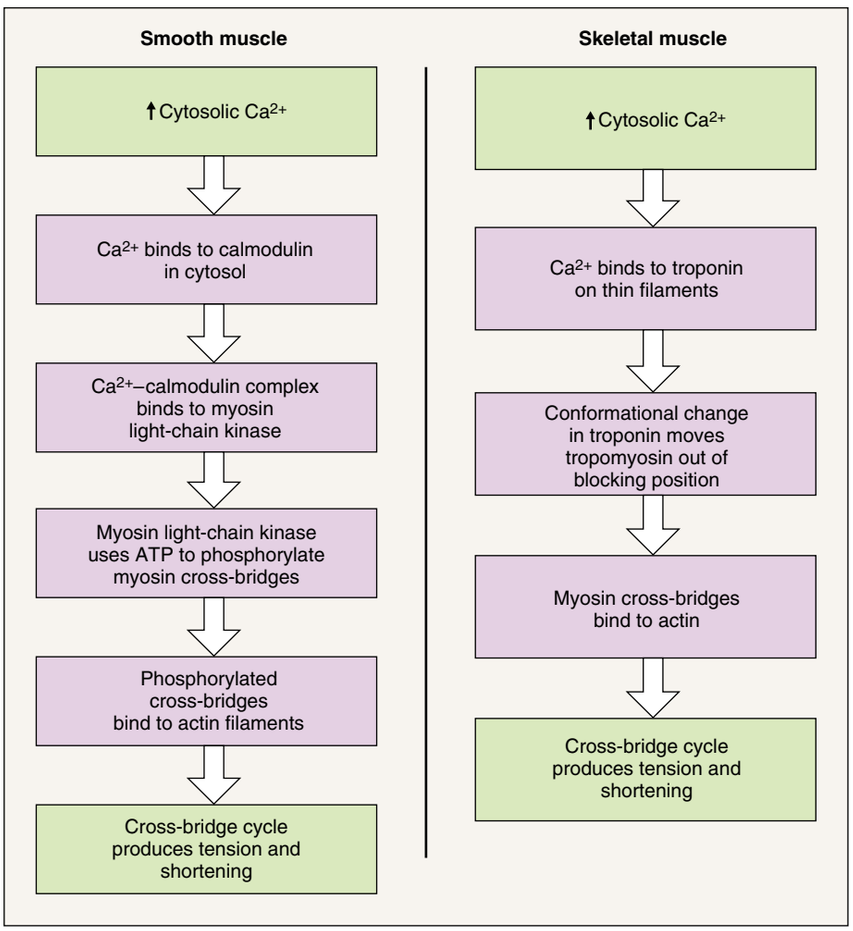

FIGURE 9–38

Pathways leading from increased cytosolic calcium to cross-bridge cycling in smooth and skeletal muscle fibers.

smooth muscle shortening is much slower than that of skeletal muscle. Due to this slow rate of energy usage, smooth muscle does not undergo fatigue during prolonged periods of activity.

To relax a contracted smooth muscle, myosin must be dephosphorylated because dephosphorylated myosin is unable to bind to actin. This dephosphorylation is mediated by the enzyme **myosin light-chain phosphatase,** which is continuously active in smooth muscle during periods of rest and contraction. When cytosolic calcium rises, the rate of myosin phosphorylation by the activated kinase exceeds the rate of dephosphorylation by the phosphatase, and the amount of phosphorylated myosin in the cell increases, producing a rise in tension. When the cytosolic calcium concentration decreases, the rate of dephosphorylation exceeds the rate of phosphorylation, and theamount of phosphorylated myosin decreases, producing relaxation.

In some smooth muscles, when stimulation is persistent and cytosolic calcium concentration remains elevated, the rate of ATP splitting by the cross-bridges declines even though isometric tension is maintained. This condition is known as the **latch state** and occurs when a phosphorylated cross-bridge becomes dephosphorylated *while still attached* to actin. In this circumstance it can maintain tension in a rigorlike state without movement. Dissociation of these dephosphorylated cross-bridges from actin by the binding of ATP occurs at a much slower rate than dissociation of phosphorylated bridges. The net result is the ability to maintain tension for long periods of time with a very low rate of ATP consumption. A good example of the usefulness of this mechanism is seen in blood vessel walls, where smooth muscle must maintain diameter for prolonged periods against persistent pressure.

Sources of Cytosolic Calcium

Two sources of calcium contribute to the rise in cytosolic calcium that initiates smooth muscle contraction: (1) the sarcoplasmic reticulum and (2) extracellular calcium entering the cell through plasma-membrane calcium channels. The amount of calcium contributed by these two sources differs among various smooth muscles, some being more dependent on extracellular calcium than the stores in the sarcoplasmic reticulum, and vice versa.

First we'll examine the role of the sarcoplasmic reticulum. The total quantity of this organelle in smooth muscle is smaller than in skeletal muscle, and it is not arranged in any specific pattern in relation to the thick and thin filaments. Moreover, there are no T-tubules connected to the plasma membrane in smooth muscle. The small fiber diameter and the slow rate of contraction do not require such a rapid mechanism for getting an excitatory signal into the muscle fiber. Portions of the sarcoplasmic reticulum are located near the plasma membrane, however, forming associations similar to the relationship between T tubules and the lateral sacs in skeletal muscle. Action potentials in the plasma membrane can be coupled to the release of sarcoplasmic reticulum calcium at these sites. In addition, second messengers released from the plasma membrane or generated in the cytosol in response to the binding of extracellular chemical messengers to plasma-membrane receptors, can trigger the release of calcium from the more centrally located sarcoplasmic reticulum.

What about extracellular calcium in excitation-contraction coupling? There are voltage-sensitive calcium channels in the plasma membranes of smooth muscle cells, as well as calcium channels controlled by extracellular chemical messengers. Since the concentration of calcium in the extracellular fluid is 10,000 times greater than in the cytosol, the opening of calcium channels in the plasma membrane results in an increased flow of calcium into the cell. Because of the small cell size, the entering calcium does not have far to diffuse to reach binding sites within the cell.

Removal of calcium from the cytosol to bring about relaxation is achieved by the active transport of calcium back into the sarcoplasmic reticulum as well as out of the cell across the plasma membrane. The rate of calcium removal in smooth muscle is much slower than in skeletal muscle, with the result that a single twitch lasts several seconds in smooth muscle but lasts only a fraction of a second in skeletal muscle.

Moreover, whereas in skeletal muscle a single action potential releases sufficient calcium to saturate all troponin sites on the thin filaments, only a portion of the cross-bridges are activated in a smooth muscle fiber in response to most stimuli. Therefore, the tension generated by a smooth muscle fiber can be *graded* by varying cytosolic calcium concentration. The greater the increase in calcium concentration, the greater the number of cross-bridges activated, and the greater the tension.

In some smooth muscles, the cytosolic calcium concentration is sufficient to maintain a low level of basal cross-bridge activity in the absence of external stimuli. This activity is known as **smooth muscle tone.** Its intensity can be varied by factors that alter the cytosolic calcium concentration.

As in our description of skeletal muscle, we have approached the question of excitation-contraction

TABLE 9–5 Inputs Influencing Smooth Muscle Contractile Activity

1. Spontaneous electrical activity in the plasma membrane of the muscle fiber
2. Neurotransmitters released by autonomic neurons
3. Hormones
4. Locally induced changes in the chemical composition (paracrine agents, acidity, oxygen, osmolarity, and ion concentrations) of the extracellular fluid surrounding the fiber
5. Stretch

coupling in smooth muscle by first describing the coupling (the changes in cytosolic calcium). Now we must back up a step and ask what constitutes the excitation that elicits these changes in calcium concentration.

Membrane Activation

In contrast to skeletal muscle, in which membrane activation is dependent on a single input—the somatic neurons to the muscle—many inputs to a smooth muscle plasma membrane can alter the contractile activity of the muscle (Table 9–5). Some of these increase contraction while others inhibit it. Moreover, at any one time, multiple inputs may be occurring, with the contractile state of the muscle dependent on the relative intensity of the various inhibitory and excitatory stimuli. All these inputs influence contractile activity by altering cytosolic calcium concentration as described in the previous section.

Some smooth muscles contract in response to membrane depolarization, whereas others can contract in the absence of any membrane potential change. Interestingly, in smooth muscles in which action potentials occur, calcium ions, rather than sodium ions, carry positive charge into the cell during the rising phase of the action potential—that is, depolarization of the membrane opens voltage-gated calcium channels, producing calcium-mediated action potentials rather than sodium-mediated ones.

Another very important point needs to be made about electrical activity and cytosolic calcium concentration in smooth muscle. Unlike the situation in skeletal muscle, in smooth muscle cytosolic calcium concentration can be increased (or decreased) by *graded* depolarizations (or hyperpolarizations) in membrane potential, which increase or decrease the number of open calcium channels.

Spontaneous Electrical Activity

Some types of smooth muscle fibers generate action potentials spontaneously in the absence of any neural or hormonal input. The plasma membranes of such fibers do not maintain a constant resting potential. Instead, they gradually depolarize until they reach the threshold potential and produce an action potential. Following repolarization, the membrane again begins to depolarize (Figure 9–39), so that a sequence of action potentials occurs, producing a tonic state of contractile activity. The membrane potential change occurring during the spontaneous depolarization to threshold is known as a **pacemaker potential.** Pacemaker cells are found throughout the gastrointestinal tract, and thus gut smooth muscle tends to contract rhythmically even in the absence of neural input. As described in other chapters, some cardiac muscle fibers and a few neurons in the central nervous system also have pacemaker potentials and can spontaneously generate action potentials in the absence of external stimuli.

Nerves and Hormones

The contractile activity of smooth muscles is influenced by neurotransmitters released by autonomic nerve endings. Unlike skeletal muscle fibers, smooth muscle fibers do not have a specialized motor endplate region. As the axon of a postganglionic autonomic neuron enters the region of smooth muscle fibers, it divides into many branches, each branch containing a series of swollen regions known as **varicosities.** Each varicosity contains many vesicles filled with neurotransmitter, some of which are released when

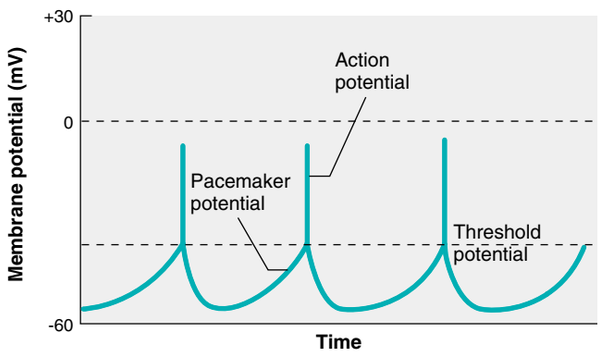

FIGURE 9–39
Generation of action potentials in a smooth muscle fiber resulting from spontaneous depolarizations of the membrane (pacemaker potentials).

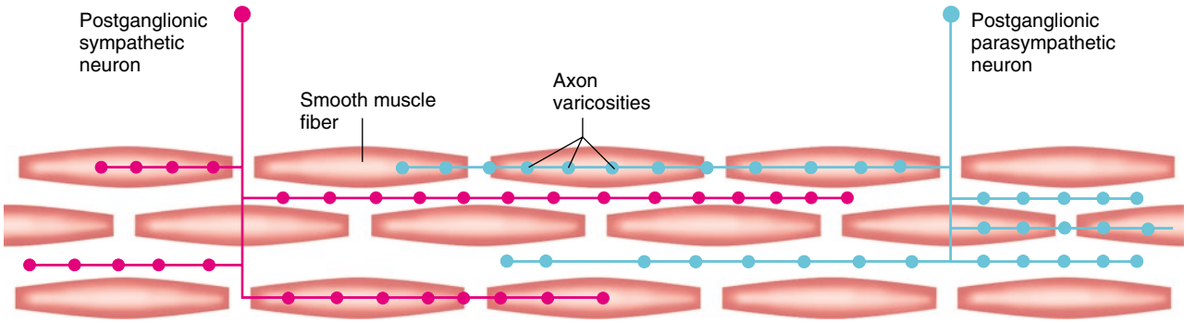

FIGURE 9–40

Innervation of smooth muscle by postganglionic autonomic neurons. Neurotransmitter is released from the varicosities along the branched axons and diffuses to receptors on muscle fiber plasma membranes.

an action potential passes the varicosity. Varicosities from a single axon may be located along several muscle fibers, and a single muscle fiber may be located near varicosities belonging to postganglionic fibers of both sympathetic and parasympathetic neurons (Figure 9–40). Therefore, a number of smooth muscle fibers are influenced by the neurotransmitters released by a single nerve fiber, and a single smooth muscle fiber may be influenced by neurotransmitters from more than one neuron.

Whereas some neurotransmitters enhance contractile activity, others produce a *lessening* of contractile activity. Thus, in contrast to skeletal muscle, which receives only excitatory input from its motor neurons, smooth muscle tension can be either increased or decreased by neural activity.

Moreover, a given neurotransmitter may produce opposite effects in different smooth muscle tissues. For example, norepinephrine, the neurotransmitter released from most postganglionic sympathetic neurons, enhances contraction of most vascular smooth muscle by acting on alpha-adrenergic receptors. By contrast, the same neurotransmitter produces relaxation of airway (bronchiolar) smooth muscle by acting on beta-2 adrenergic receptors. Thus, the type of response (excitatory or inhibitory) depends not on the chemical messenger per se, but on the receptors to which the chemical messenger binds in the membrane and the intracellular signaling mechanisms activated by those receptors.

In addition to receptors for neurotransmitters, smooth muscle plasma membranes contain receptors for a variety of hormones. Binding of a hormone to its receptor may lead to either increased or decreased contractile activity.

Although most changes in smooth muscle contractile activity induced by chemical messengers are accompanied by a change in membrane potential, this is not always the case. Second messengers, for example, inositol trisphosphate, can cause the release of calcium from the sarcoplasmic reticulum, producing a contraction without a change in membrane potential.

Local Factors

Local factors, including paracrine agents, acidity, oxygen concentration, osmolarity, and the ion composition of the extracellular fluid, can also alter smooth muscle tension. Responses to local factors provide a means for altering smooth muscle contraction in response to changes in the muscle's immediate internal environment, which can lead to regulation that is independent of long-distance signals from nerves and hormones.

Many of these local factors induce smooth muscle relaxation. Nitric oxide (NO) is one of the most commonly encountered paracrine agents that produces smooth muscle relaxation. NO is released from some nerve terminals as well as a variety of epithelial and endothelial cells. Because of the short life span of this reactive molecule, it acts as a paracrine agent, influencing only those cells that are very near its release site.

Some smooth muscles can also respond by contracting when they are stretched. Stretching opens mechanosensitive ion channels, leading to membrane depolarization. The resulting contraction opposes the forces acting to stretch the muscle.

It is well to remember that seldom is a single agent acting on a smooth muscle, but rather the state of contractile activity at any moment depends on the simultaneous magnitude of the signals promoting contraction versus those promoting relaxation.

Types of Smooth Muscle

The great diversity of the factors that can influence the contractile activity of smooth muscles from various organs has made it difficult to classify smooth muscle fibers. Many smooth muscles can be placed, however,

into one of two groups, based on the electrical characteristics of their plasma membrane: **single-unit smooth muscles** and **multiunit smooth muscles.**

Single-Unit Smooth Muscle

The muscle fibers in a single-unit smooth muscle undergo synchronous activity, both electrical and mechanical; that is, the whole muscle responds to stimulation as a single unit. This occurs because each muscle fiber is linked to adjacent fibers by gap junctions, through which action potentials occurring in one cell are propagated to other cells by local currents. Therefore, electrical activity occurring anywhere within a group of single-unit smooth muscle fibers can be conducted to all the other connected cells (Figure 9–41).

Some of the fibers in a single-unit muscle are pacemaker cells that spontaneously generate action potentials. These action potentials are conducted by way of gap junctions to the rest of the fibers, most of which are not capable of pacemaker activity.

The contractile activity of single-unit smooth muscles can be altered by nerves, hormones, and local factors, using the variety of mechanisms described previously for smooth muscles in general. The extent to which these muscles are innervated varies considerably in different organs. The nerve terminals are often restricted to the regions of the muscle that contain pacemaker cells. The activity of the entire muscle can be controlled by regulating the frequency of the pacemaker cells' action potentials.

One additional characteristic of single-unit smooth muscles is that a contractile response can often be induced by stretching the muscle. In several hollow organs—the stomach, for example—stretching the smooth muscles in the walls of the organ as a result of increases in the volume of material in the lumen initiates a contractile response.

The smooth muscles of the intestinal tract, uterus, and small-diameter blood vessels are examples of single-unit smooth muscles.

Multiunit Smooth Muscle

Multiunit smooth muscles have no or few gap junctions. Each fiber responds independently of its neighbors, and the muscle behaves as multiple units. Multiunit smooth muscles are richly innervated by branches of the autonomic nervous system. The contractile response of the whole muscle depends on the number of muscle fibers that are activated and on the frequency of nerve stimulation. Although stimulation of the nerve fibers to the muscle leads to some degree of depolarization and a contractile response, action potentials do not occur in most multiunit smooth muscles. Circulating hormones can increase or decrease contractile activity in multiunit smooth muscle, but stretching does not induce contraction in this type of muscle. The smooth muscle in the large airways to the lungs, in large arteries, and attached to the hairs in the skin are examples of multiunit smooth muscles.

It must be emphasized that most smooth muscles do not show all the characteristics of either single-unit or multiunit smooth muscles. These two prototypes represent the two extremes in smooth muscle characteristics, with many smooth muscles having characteristics that overlap the two groups.

Table 9–6 compares the properties of the different types of muscle. Cardiac muscle has been included for completeness although its properties are discussed in Chapter 12.

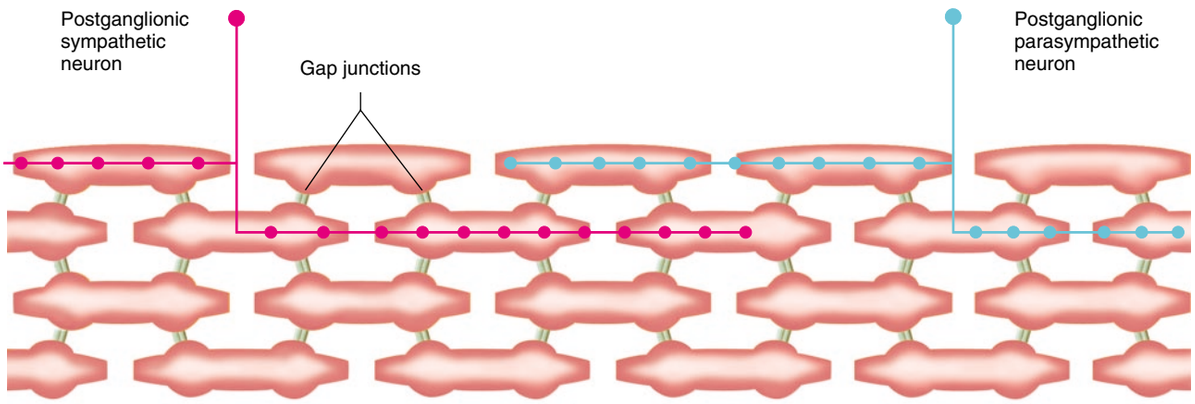

FIGURE 9–41

Innervation of a single-unit smooth muscle is often restricted to only a few fibers in the muscle. Electrical activity is conducted from fiber to fiber throughout the muscle by way of the gap junctions between the fibers.

TABLE 9–6 Characteristics of Muscle Fibers

		Smooth Muscle		
CHARACTERISTIC	SKELETAL MUSCLE	SINGLE UNIT	MULTIUNIT	CARDIAC MUSCLE
Thick and thin filaments	Yes	Yes	Yes	Yes
Sarcomeres—banding pattern	Yes	No	No	Yes
Transverse tubules	Yes	No	No	Yes
Sarcoplasmic reticulum (SR)*	++++	+	+	++
Gap junctions between fibers	No	Yes	Few	Yes
Source of activating calcium	SR	SR and extracellular	SR and extracellular	SR and extracellular
Site of calcium regulation	Troponin	Myosin	Myosin	Troponin
Speed of contraction	Fast-slow	Very slow	Very slow	Slow
Spontaneous production of action potentials by pacemakers	No	Yes	No	Yes in certain fibers, but most not spontaneously active
Tone (low levels of maintained tension in the absence of external stimuli)	No	Yes	No	No
Effect of nerve stimulation	Excitation	Excitation or inhibition	Excitation or inhibition	Excitation or inhibition
Physiological effects of hormones on excitability and contraction	No	Yes	Yes	Yes
Stretch of fiber produces contraction	No	Yes	No	No

*Number of plus signs (+) indicates the relative amount of sarcoplasmic reticulum present in a given muscle type.

SECTION B SUMMARY

Structure

I. Smooth muscle fibers are spindle-shaped cells that lack striations, have a single nucleus, and are capable of cell division. They contain actin and myosin filaments and contract by a sliding-filament mechanism.

Contraction and Its Control

I. An increase in cytosolic calcium leads to the binding of calcium by calmodulin. The calcium-calmodulin complex then binds to myosin light-chain kinase, activating the enzyme, which uses ATP to phosphorylate smooth muscle myosin. Only phosphorylated myosin can bind to actin and undergo cross-bridge cycling.

II. Smooth muscle myosin has a low rate of ATP splitting, resulting in a much slower shortening velocity than is found in striated muscle. However, the tension produced per unit cross-sectional area is equivalent to that of skeletal muscle.

III. Two sources of the cytosolic calcium ions that initiate smooth muscle contraction are the sarcoplasmic reticulum and extracellular calcium. The opening of calcium channels in the smooth muscle plasma membrane and sarcoplasmic reticulum, mediated by a variety of factors, allows calcium ions to enter the cytosol.

IV. The increase in cytosolic calcium resulting from most stimuli does not activate all the cross-bridges. Therefore smooth muscle tension can be increased by agents that increase the concentration of cytosolic calcium ions.

V. Table 9–5 summarizes the types of stimuli that can initiate smooth muscle contraction by opening or closing calcium channels in the plasma membrane or sarcoplasmic reticulum.

VI. Most, but not all, smooth muscle cells can generate action potentials in their plasma membrane upon membrane depolarization. The rising phase of the

smooth muscle action potential is due to the influx of calcium ions into the cell through voltage-gated calcium channels.

VII. Some smooth muscles generate action potentials spontaneously, in the absence of any external input, because of pacemaker potentials in the plasma membrane that repeatedly depolarize the membrane to threshold.

VIII. Smooth muscle cells do not have a specialized end-plate region. A number of smooth muscle fibers may be influenced by neurotransmitters released from the varicosities on a single nerve ending, and a single smooth muscle fiber may be influenced by neurotransmitters from more than one neuron. Neurotransmitters may have either excitatory or inhibitory effects on smooth muscle contraction.

IX. Smooth muscles can be classified broadly as single-unit or multiunit smooth muscle (Table 9–6).

SECTION B KEY TERMS

dense body 00
latch state 00
multiunit smooth muscle 00
myosin light-chain kinase 00
myosin light-chain phosphatase 00
pacemaker potential 00
single-unit smooth muscle 00
smooth muscle tone 00
varicosity 00

SECTION B REVIEW QUESTIONS

1. How does the organization of thick and thin filaments in smooth muscle fibers differ from that in striated muscle fibers?
2. Compare the mechanisms by which a rise in cytosolic calcium concentration initiates contractile activity in skeletal and smooth muscle fibers.
3. What are the two sources of calcium that lead to the increase in cytosolic calcium that triggers contraction in smooth muscle?
4. What types of stimuli can trigger a rise in cytosolic calcium in smooth muscle fibers?
5. What effect does a pacemaker potential have on a smooth muscle cell?
6. In what ways does the neural control of smooth muscle activity differ from that of skeletal muscle?
7. Describe how a stimulus may lead to the contraction of a smooth muscle cell without a change in the plasma membrane potential.
8. Describe the differences between single-unit and multiunit smooth muscles.

CHAPTER 9 THOUGHT QUESTIONS

(Answers are given in appendix A.)

1. Which of the following corresponds to the state of myosin (M) under resting conditions and in rigor mortis? (a) M · ATP, (b) M · ADP · P_i, (c) A · M · ADP · P_i, (d) A · M.
2. If the transverse tubules of a skeletal muscle are disconnected from the plasma membrane, will action potentials trigger a contraction? Give reasons.
3. When a small load is attached to a skeletal muscle that is then tetanically stimulated, the muscle lifts the load in an isotonic contraction over a certain distance, but then stops shortening and enters a state of isometric contraction. With a heavier load, the distance shortened before entering an isometric contraction is shorter. Explain these shortening limits in terms of the length-tension relation of muscle.
4. What conditions will produce the maximum tension in a skeletal muscle fiber?
5. A skeletal muscle can often maintain a moderate level of active tension for long periods of time, even though many of its fibers become fatigued. Explain.
6. If the blood flow to a skeletal muscle were markedly decreased, which types of motor units would most rapidly have their ability to produce ATP for muscle contraction severely reduced? Why?
7. As a result of an automobile accident, 50 percent of the muscle fibers in the biceps muscle of a patient were destroyed. Ten months later, the biceps muscle was able to generate 80 percent of its original force. Describe the changes that took place in the damaged muscle that enabled it to recover.
8. In the laboratory, if an isolated skeletal muscle is placed in a solution that contains no calcium ions, will the muscle contract when it is stimulated (1) directly by depolarizing its membrane, or (2) by stimulating the nerve to the muscle? What would happen if it were a smooth muscle?
9. The following experiments were performed on a single-unit smooth muscle in the gastrointestinal tract.
   a. Stimulating the parasympathetic nerves to the muscle produced a contraction.
   b. Applying a drug that blocks the voltage-sensitive sodium channels in most plasma membranes led to a failure to contract upon stimulating the parasympathetic nerves.
   c. Applying a drug that binds to muscarinic receptors (Chapter 6), and hence blocks the action of ACh at these receptors, did not prevent the muscle from contracting when the parasympathetic nerve was stimulated.

   From these observations, what might one conclude about the mechanism by which parasympathetic nerve stimulation produces a contraction of the smooth muscle?