Musculoskeletal System 5

CONTENTS

STRUCTURE OF SKELETAL MUSCLE

SKELETAL MUSCLE TYPES
- Neuromuscular Transmission
- Excitation-Contraction Coupling
- Skeletal Muscle Mechanics

SMOOTH MUSCLE
- Contraction
- Excitation

CARDIAC MUSCLE

SKELETON
- Movement
- Heat Production

TOP 5 TAKE-HOME POINTS

There are three general types of muscle in the body: skeletal, cardiac, and smooth. The muscle types are distinguished based on the presence of striations, source of innervation, and mechanism of contraction (Table 5-1).

The musculoskeletal system consists of skeletal muscle attached to the bony skeleton. Physiologically, the musculoskeletal system enables changes in movement and position. The rigid bony skeleton provides support, protection, and a movable frame. The connective tissue of joints and ligaments allows adjacent bones to articulate smoothly as they move. Skeletal muscle attaches to the bones of the skeleton. Skeletal muscle contraction shortens the length of the muscle and generates movement of this frame.

Skeletal muscle is the effector organ for movement (Fig. 5-1). Movement is initiated in the upper motor neurons of the central nervous system (CNS) motor cortex. Efferent motor cortex axons synapse on the spinal cord and generate an action potential in the α-motor neuron. The action potential travels to the axon terminal, releasing acetylcholine into the synaptic cleft. Acetylcholine binds a receptor on the skeletal muscle cell and generates an action potential, increasing Ca^{++} release from the sarcoplasmic reticulum. Ca^{++} initiates contraction, resulting in shortening of the muscle cell and, consequently, movement.

The musculoskeletal system contributes to electrolyte and metabolic balance. The skeleton is a storage pool for Ca^{++} and other ions. Skeletal muscle cells, which account for 40% to 50% of body weight, are a major storage pool for body K^{+}. Skeletal muscle also plays a major role in metabolism and in temperature regulation.

Cardiac and smooth muscle support the activities of the cardiovascular, respiratory, GI, and renal systems. Cardiac muscle generates the pressure that propels blood through the body (see Chapter 7). Smooth muscle also regulates movement of numerous substances, including blood, within the body. GI smooth muscle controls gastric motility (see Chapter 12). Respiratory airway smooth muscle determines airway resistance to airflow (see Chapter 10). Vascular smooth muscle controls resistance to blood flow (see Chapters 8 and 9). This chapter describes the normal function of skeletal and smooth muscle as a tissue.

STRUCTURE OF SKELETAL MUSCLE

Skeletal muscle is attached to the bones of the skeleton by very thin extensions of fascia or by tendons. *Tendons* (fibrous cords) make strong connections to bone. The contraction of skeletal muscle exerts force on bones or skin and moves them. Most skeletal muscles are under voluntary control of the nervous system.

Skeletal muscle is composed of successively smaller structures: the muscle fascicle, muscle fiber, and finally myofibrils. Skeletal muscle has a regular arrangement of actin (I band) and myosin (A band) filaments, giving it a striated appearance. Myofibrils are attached to each other within the I band at the Z disk. *Actin* filaments are composed of actin, tropomyosin, and troponin proteins. *Myosin* filaments are composed of myosin proteins. *Titin* is a structural protein that provides an elastic connection between the opposing ends of the actin and myosin filaments (Fig. 5-2).

Muscle cells can be functionally classified into smaller segments called sarcomeres, delineated by Z bands. The *sarcomere* is the structure in the muscle where the actual contraction occurs. Two primary myofilaments are present in the sarcomere: thick myosin filaments and thin actin filaments. The filaments are proteins that briefly attach and

TABLE 5-1. Comparison of the Three Muscle Types

Characteristic	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Histologic appearance	Striated	Striated	Smooth
Contraction speed	Fastest	Intermediate	Slowest
Fiber proteins	Actin, myosin, troponin, and tropomyosin	Actin, myosin, troponin, and tropomyosin	Actin, myosin, and tropomyosin
Control	Voluntary Ca^{++} and troponin Fibers are independent	Involuntary Ca^{++} and troponin Gap junctions join fibers	Involuntary Ca^{++} and calmodulin Gap junctions join fibers
Nervous control	α-Motor neuron	Autonomic neurons	Autonomic neurons
Morphology	Multinucleate; large, cylindrical fibers	Uninucleate; shorter branching fibers	Uninucleate; small spindle-shaped fibers
Key internal structures	T tubule and SR	T tubule and SR	No T tubules; SR reduced or absent
Activation	Troponin	Troponin	Calmodulin MLCK
Calcium source	Intracellular (SR)	Extracellular and SR	Extracellular and SR
Calcium mobilization	T-tubule depolarization DHPR/RyR coupling	ΔE_M/DHPR trigger Ca^{++}	IP_3 ΔE_M-gated channels Ligand-gated channels
Regulation of force	Recruitment	Δ Contractility	MLC20 latch

DHPR, dihydropyridine receptor; MLC20, myosin light chain of 20 kDa; MLCK, myosin light-chain kinase; RyR, ryanodine receptor; SR, sarcoplasmic reticulum.

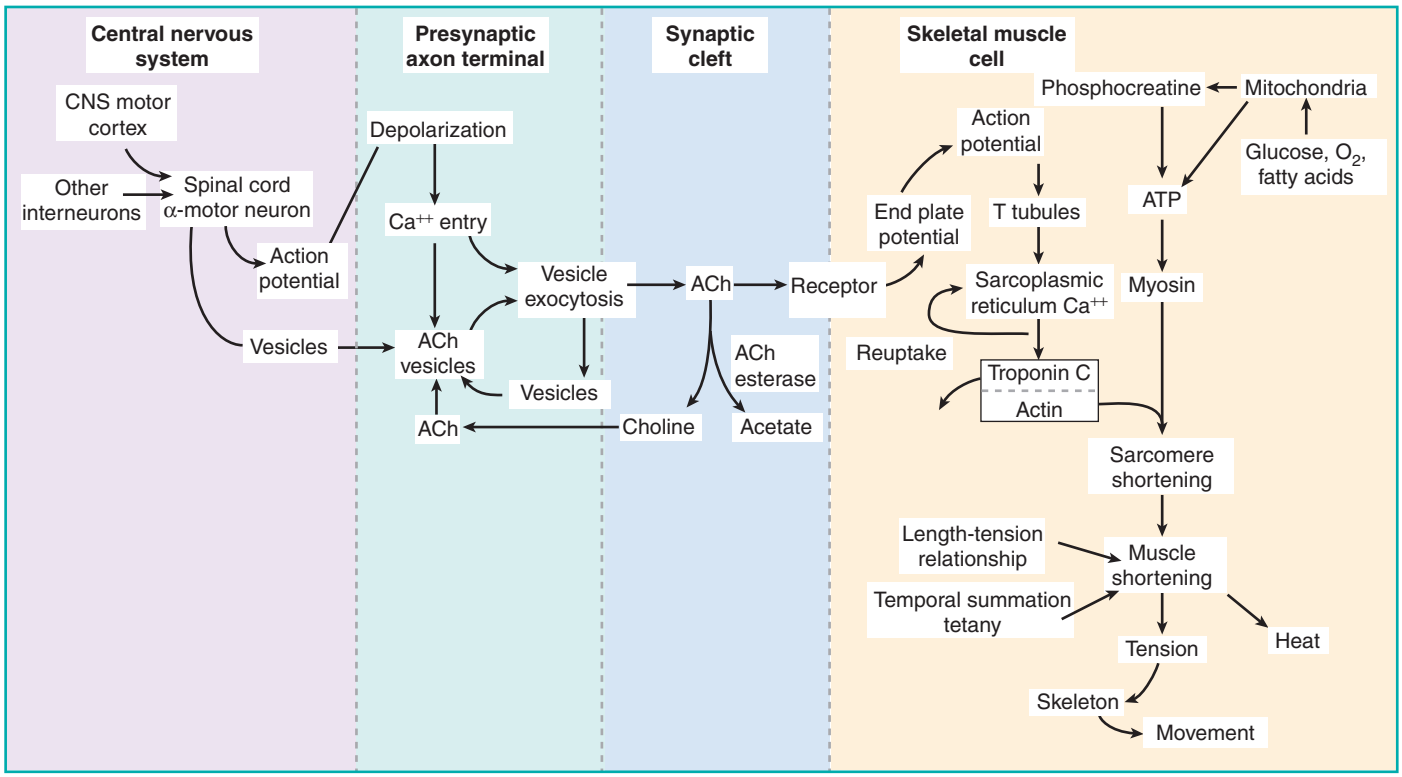

Figure 5-1. Skeletal muscle physiologic processes can be grouped according to the region in which they occur. The neural signal for voluntary movement originates in the CNS and passes along the motor neurons to the neuromuscular junction. Acetylcholine, released from the presynaptic neuron, depolarizes the muscle cell and initiates muscle contraction.

ANATOMY

Skeletal Muscle

Skeletal muscles are named according to the following properties: (1) action (e.g., flexor, extensor), (2) shape (e.g., quadrilateral, pennate), (3) origin (i.e., stationary attachment of muscle to skeleton), (4) insertion (i.e., movable attachment of the muscle), (5) number of divisions, (6) location, or (7) direction of fibers (i.e., transverse).

ratchet or slide across one another causing the muscle to generate force or movement.

SKELETAL MUSCLE TYPES

Skeletal muscle consists of two different types of fibers. *Fast twitch fibers* have a myosin ATPase that rapidly hydrolyzes ATP. Consequently, fast twitch fibers have a relatively rapid rate of tension development. Fast twitch fibers generally are large and depend on glycolysis for energy. Fast fibers are white in appearance because of the relatively low amount of myoglobin and the low number of mitochondria. These muscles respond and fatigue rapidly and consequently are adapted for short bursts of activity.

Slow twitch fibers have a myosin ATPase that more slowly hydrolyzes ATP. Slow twitch fibers generally are smaller than fast twitch fibers and depend on oxidative phosphorylation for energy. Slow fibers respond more slowly than fast fibers but are resistant to fatigue. The high concentration of the oxygen-binding protein myoglobin gives the slow twitch muscles a red appearance. These muscles are adapted for maintained activity, such as standing.

Human muscles are mixtures of fast and slow twitch fibers. The relative proportion of fast versus slow twitch is characteristic of individual muscles. Extensive aerobic training can cause some fibers in fast twitch muscles to perform in a more oxidative fashion, functionally mimicking slow twitch fibers (Table 5-2).

Neuromuscular Transmission

Neuromuscular transmission represents a prototype for synaptic transmission. At the neuromuscular junction, an action potential carried along the axon of an α-motor neuron releases acetylcholine (ACh) into the synaptic cleft. ACh diffuses across the synaptic cleft and binds to nicotinic receptors on the end plate region of the skeletal muscle cell. An action potential is initiated in the skeletal muscle cell, which is transduced to an intracellular Ca^{++} signal that triggers muscle contraction.

α-Motor neurons are large, myelinated fibers that originate in the anterior horns of the spinal cord. An axon can branch at its terminal and innervate multiple muscle cells. A muscle cell, however, receives only one synapse. This means that a muscle cell is dependent on a single motor neuron for activation, providing great specificity for muscle control. In contrast, a given motor neuron can innervate multiple muscle cells, allowing a coordinated response of larger muscles. The motor unit consists of the motor neuron and all the muscles that it innervates.

The number of muscle fibers making up each motor unit determines the degree of control of contraction that is possible. Small motor units allow fine control, such as the muscles of the hand involved in writing. Large motor units coordinate the response of large muscles, such as the muscles of the leg used for lifting.

The neuromuscular junction, or motor end plate, consists of a nerve terminal that rests in a trough on the muscle cell surface called the synaptic trough. The membranes of the two cells are separated by a 20 to 30 nm space called the synaptic cleft. The neuron is considered to be the presynaptic cell, and the muscle cell is the postsynaptic cell (Fig. 5-3).

The presynaptic nerve terminal contains approximately 300,000 synaptic vesicles that contain the neurotransmitter acetylcholine. The sides of the presynaptic membrane contain voltage-activated Ca^{++} channels. The synaptic region of the presynaptic membrane is called the active zone because it is the site where ACh is released.

The synaptic gap spans the distance between the presynaptic and postsynaptic membranes. Acetylcholinesterase, which degrades ACh into acetate and choline, is found in the synaptic cleft. The postsynaptic membrane is part of the muscle cell end plate region and contains numerous ACh receptors.

Figure 5-3 illustrates the steps in synaptic transmission:

1. Vesicles arrive at the axon terminal and are loaded with acetylcholine.
2. An action potential in the presynaptic neuron depolarizes the nerve terminal.
3. Depolarization activates voltage-sensitive Ca^{++} channels in the active zone, and Ca^{++} enters the axon terminal.
4. The influx of Ca^{++} activates calcium/calmodulin–dependent kinase and leads to translocation of vesicles to the presynaptic membrane, where they dock.
5. After docking, fusion proteins bind Ca^{++} and prime the vesicles, and the vesicle contents are released by exocytosis.
6. The ACh diffuses across the cleft and binds to ACh receptors on the muscle membrane. The ACh receptor channels open, and ion movement creates a depolarizing end plate potential.
7. ACh dissociates from the receptor, and the channel closes. ACh is broken down to choline and acetate in the cleft. Choline is transported into the terminal in an Na^{+}-dependent secondary active transport process.
8. Membrane that was added to the terminal membrane during exocytosis is taken up and reused to form new vesicles.

Approximately 200 vesicles fuse with the membrane at the active zone and release ACh into the cleft during excitation of the motor neuron. Each vesicle contains approximately 10,000 ACh molecules. These numbers become important in describing the both the efficiency of neuromuscular transmission and also the characteristics of neuromuscular diseases.

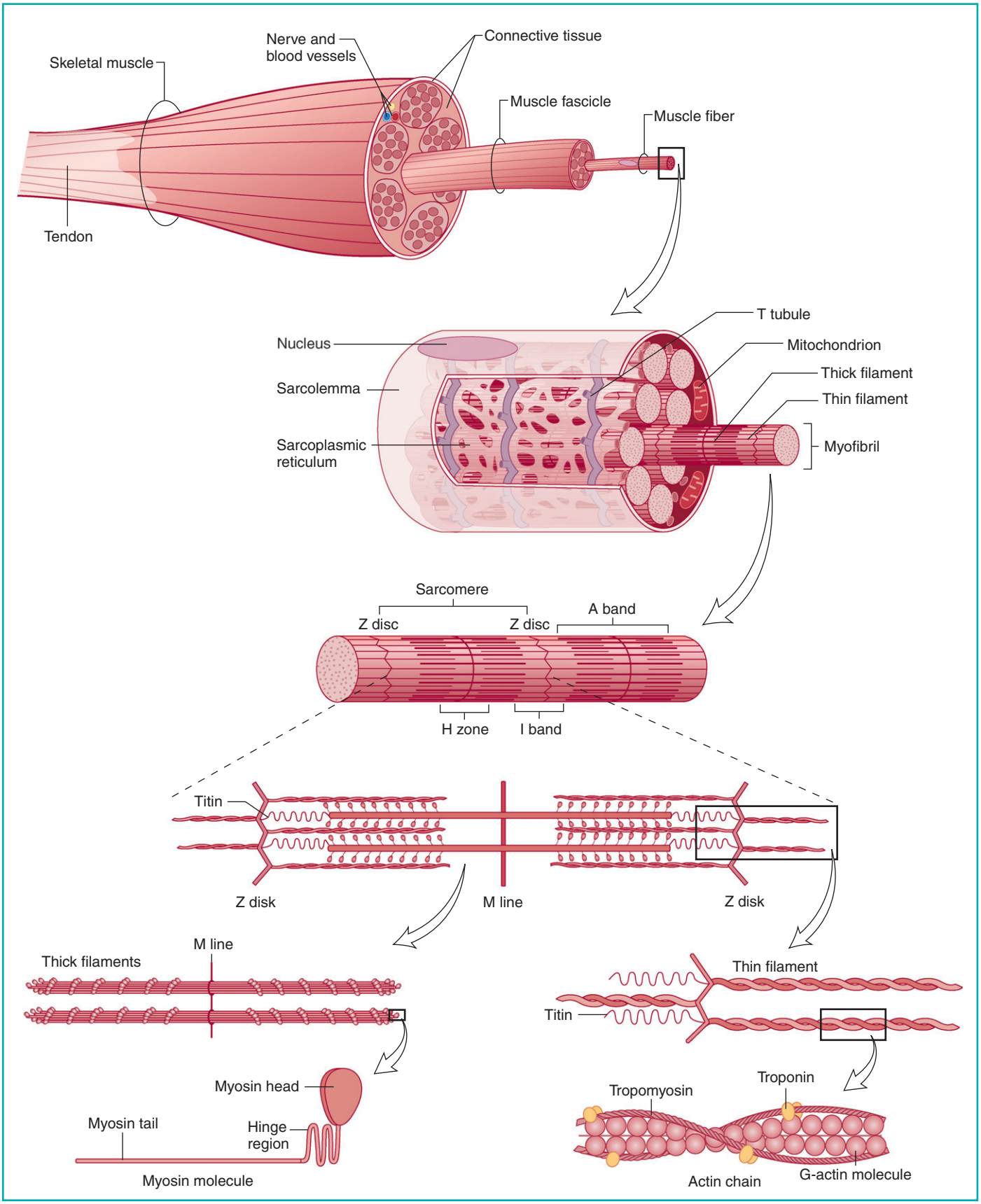

Figure 5-2. Skeletal muscle can be broken down into progressively smaller units, ending with the functional unit of the sarcomere. The histology of the sarcomere is based on the regular arrangement of thin and thick filaments, containing actin and myosin, respectively. Sarcomeres are the structural elements of the muscle fibers, and the muscle fascicle is a bundle of muscle fibers.

TABLE 5-2. Classification of Fiber Types in Skeletal Muscle

Characteristic	Slow Twitch Fiber	Fast Twitch Fiber
Other names	Type I Oxidative Red	Type II Glycolytic White
Myosin isoenzyme ATPase rate	Slow	Fast
Calcium-pumping capacity of sarcoplasmic reticulum	Moderate	High
Diameter	Moderate	Large
Glycolytic capacity	Moderate	High
Oxidative capacity (correlates with content of mitochondria, capillary density, myoglobin content)	High	Low

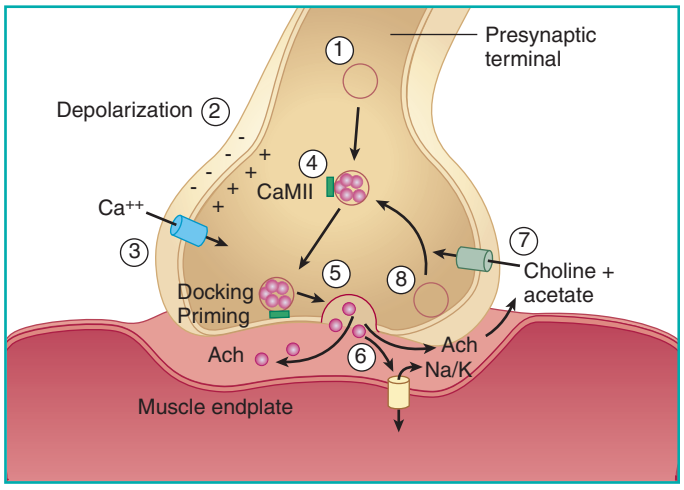

Figure 5-3. Acetylcholine is released into the neuromuscular cleft following depolarization of the α-motor neuron nerve terminal. Depolarization causes the entry of extracellular Ca^{++}, which causes translocation and binding of vesicles to the presynaptic membrane and stimulates exocytosis. CaMII, calmodulin-dependent kinase.

Presynaptic Event Details

Neurotransmitter vesicles are assembled in the cell body of the neuron and transported by kinesins along the axon microtubule system to the axon terminal. In the terminal, the vesicle is acidified by an H^+-ATPase. Acetylcholine is then transported into the vesicle in exchange for H^+. Drugs that disrupt microtubules, such as paclitaxel, can cause temporary paralysis owing to a reduction in the number of synaptic vesicles.

ACh vesicles in the axon terminal can be at the active zone, ready for exocytosis, or away from the active zone in the cytosol. Cytosolic vesicles must be translocated to the active zone, dock with the membrane, and be prepared for fusion (primed) when needed. The SNAP-SNARE mechanism mediates vesicle exocytosis. Synapsin 1, synaptobrevin, SNAP-25, syntaxin, synaptotagmin, and synaptophysin are proteins involved in vesicle translocation and exocytosis. Intracellular Ca^{++} enters during depolarization, and following repolarization Ca^{++} exits the cell. Repetitive depolarization causes an increase in intracellular Ca^{++} in the terminal, and thus facilitates vesicle release in response to subsequent excitation.

Prior to activation by depolarization, numerous vesicles are docked and primed, allowing for maximal release upon the arrival of an action potential. The quantity of ACh released is greater than what is required to generate an action potential in the skeletal muscle cell, thereby creating a "safety factor." The excess release of ACh normally ensures that nerve activation leads to muscle activation. The amount of ACh released with each action potential decreases as more action potentials invade the nerve terminal. The decrease is due to the time required for new vesicles to be positioned at the active zone and fully primed. Consequently, the safety factor decreases with high-frequency stimulation, but in normal individuals no loss of function is observed.

Postsynaptic Event Details

The skeletal muscle end plate region has a high density of nicotinic ACh receptors. This ACh receptor is an integral membrane protein consisting of five subunits that form a cation-selective ion channel. Simultaneous binding of 2 ACh molecules to the receptor protein opens the channel, allowing Na^+ and K^+ to diffuse across the membrane. The same protein functions both as the ACh receptor and the channel—no signal transduction is required.

The ACh receptor channel conducts Na^+ and K^+ with equal ease. Normally, a channel that conducts only one ion shifts the membrane potential toward the Nernst potential for that ion. Opening a K^+ channel shifts the membrane potential toward −90 mV, and opening an Na^+ channel shifts the membrane potential toward +60 mV (Fig. 5-4). The skeletal muscle ACh receptor conducts both ions equally, and opening

PHARMACOLOGY

Botulinum

Botulinum toxin produced by *Clostridium botulinum* bacteria depresses end plate potential amplitude. The toxin is extremely potent, with a lethal dose of 2 to 3 mg. The mechanism involves cleavage of proteins involved in vesicle priming (synaptobrevin, syntaxin, and SNAP-25) and subsequent inhibition of Ca^{++}-induced vesicle release from presynaptic terminals and degeneration of the terminals. Very dilute preparations of botulinum toxin can be used to treat disorders involving hyperactivity of neuromuscular junctions, such as would be seen in cases of prolonged muscle spasm, and to reduce facial muscle contractions that cause wrinkles.

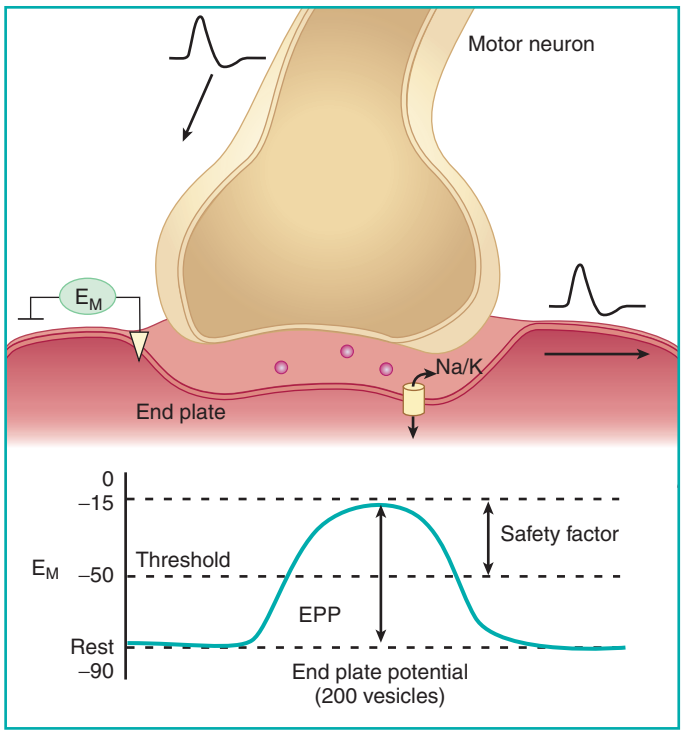

Figure 5-4. Release of acetylcholine causes depolarization of the end plate region of the postsynaptic membrane on the skeletal muscle cell. The 200 vesicles of acetylcholine released during neuromuscular transmission is sufficient to depolarize the end plate to –15 mV (end plate potential), well past the threshold required to initiate an action potential in the skeletal muscle cell. This excess depolarizing ability creates a safety factor, ensuring that neuromuscular transmission causes the depolarization and contraction of the muscle cell.

the channel shifts membrane potential at the end plate region of the skeletal muscle toward the arithmetic average of the Na^+ and K^+ Nernst values, about –15 mV.

The binding of ACh to the muscle cell ACh receptors causes depolarization. The amplitude of the depolarization is dependent on the number of functional receptors and the percentage of the functional receptors bound by ACh. ACh is released from the axon terminal in packets of 10,000 molecules, the amount in one vesicle. Release of one vesicle causes a 0.4 mV depolarization of the skeletal muscle end plate region, called a miniature end plate potential (MEPP). MEPPs occur spontaneously at neuromuscular junctions and are thought to be due to unstimulated exocytosis of single ACh vesicles.

Normal neuromuscular transmission causes the release of up to 200 vesicles, and that amount of ACh causes a 75 mV depolarization, from the resting membrane potential of –90 mV to –15 mV. This depolarization is an end plate potential (EPP). Depolarization of the muscle end plate to –50 mV is sufficient to activate voltage-sensitive Na^+ channels in the muscle cell membrane and induce an action potential, so the normal 75 mV depolarization provides a safety factor ensuring that each neuromuscular transmission causes depolarization and contraction of the target skeletal muscle.

PATHOLOGY

Myasthenia Gravis

Myasthenia gravis is a type of muscle fatigability due to reduction in the number of functional ACh receptors. It is thought to be an autoimmune disease in which antibodies are produced against the nicotinic ACh receptors resulting in increased turnover of the protein. It is characterized by depression of the end plate potential with sequential stimulation due to a decrease in safety factor. In these patients, however, a small change in safety factor is sufficient to alter muscle function owing to the decreased number of ACh receptors at the end plate. The disease is treated with inhibitors of acetylcholinesterase that increase the concentration of ACh in the synaptic cleft (e.g., neostigmine) or by thymectomy, which reduces antibody production.

ACh is rapidly cleared from the synaptic cleft by acetylcholinesterase. This process ensures that continuing ACh receptor stimulation depends on continuing release of ACh from the motor neuron. Sustained contraction, or tetany, depends on sustained activity of the motor neuron. EPP amplitude is not constant but is dependent on the amount of ACh in the cleft and number of functional nicotinic receptors in the postsynaptic membrane. Action potentials that are close together in time increase EPP amplitude through a process known as facilitation. *Facilitation* is enhanced ACh release due to increased priming of vesicles by Ca^{++} in the presynaptic terminal. Increased ACh concentration in the cleft leads to a larger than normal EPP. Facilitation plays a role in normal activation of muscle but is most noticeable in patients with decreased numbers of functional nicotinic ACh receptors. In these patients, initial attempts to activate a muscle lead to weak contractions. Continued use facilitates the release of ACh, which partially compensates for the decreased numbers of receptors, and contraction strength improves.

The size of the EPP increases as motor neuron action potential frequency increases. A high-frequency stimulation that yields a maximal EPP is called a tetanic stimulation. During a normal contraction, muscle cells are stimulated by the innervating motor neuron at a tetanic frequency.

The extended series of motor neuron action potentials leads to posttetanic potentiation. Following high-frequency stimulation, a subsequent action potential in the motor neuron evokes an EPP that is larger than normal owing to enhanced release of ACh.

At the other extreme, high-frequency stimulation for prolonged periods can lead to transient depletion of primed ACh vesicles near the membrane and depression of neuromuscular transmission, or synaptic fatigue. Depression is rarely observed in normal individuals under voluntary control. However, it is routinely observed in some diseases of the neuromuscular junction, such as myasthenia gravis.

A number of toxins and drugs affect the ACh receptors at the neuromuscular junction and induce flaccid paralysis.

Curare, d-tubocurarine, and gallamine block the nicotinic channels from opening and induce flaccid paralysis. These agents are used for relaxing skeletal muscle during surgical procedures. Succinylcholine is an agonist of the nicotinic ACh receptor, but it is not degraded by AChE. Therefore, it causes prolonged depolarization of the muscle end plate and inactivation of the fast Na^+ channels, leading to elevation of threshold in the muscle cell and relaxation. Elapid snake venoms (krait and cobra) contain α-bungarotoxin, a curare-like drug with high affinity for the ACh receptor.

The skeletal muscle action potential is similar to the motor neuron action potential except that it is longer in duration and does not exhibit a hyperpolarizing afterpotential. The long duration of the muscle action potential allows time for mobilization of Ca^{++} and activation of actomyosin ATPase.

Excitation-Contraction Coupling

The action potential generated at the motor end plate region spreads along the membrane of skeletal muscle cell and into the T tubules. The T tubules contain dihydropyridine receptors that connect to the Ca^{++} channels of sarcoplasmic reticulum. Depolarization of T tubules opens the sarcoplasmic reticulum Ca^{++} channels. Calcium exits the sarcoplasmic reticulum and diffuses through the cytoplasm (Fig. 5-5).

Contraction results from the interaction of the actin and myosin filaments, a process described as the sliding filament mechanism. The sequence of the interaction of the actin and myosin proteins is shown in Figure 5-6. The troponin C component of the actin filament binds Ca^{++} and exposes the active sites of the actin protein. Actin now binds strongly to myosin (1), and the myosin filament heads pivot (2), using previously hydrolyzed ATP as an energy source. This pivoting generates a "power stroke," sliding the actin filaments along the myosin filaments toward the center of the sarcomere and causing the sarcomere to shorten. Pivoting also releases P_i and ADP (3, 4) and allows new ATP to bind the head of the myosin (5). The binding of new ATP detaches the myosin from the actin (6). The myosin hydrolyzes ATP, and the myosin head stores the energy until bound again by actin. The process

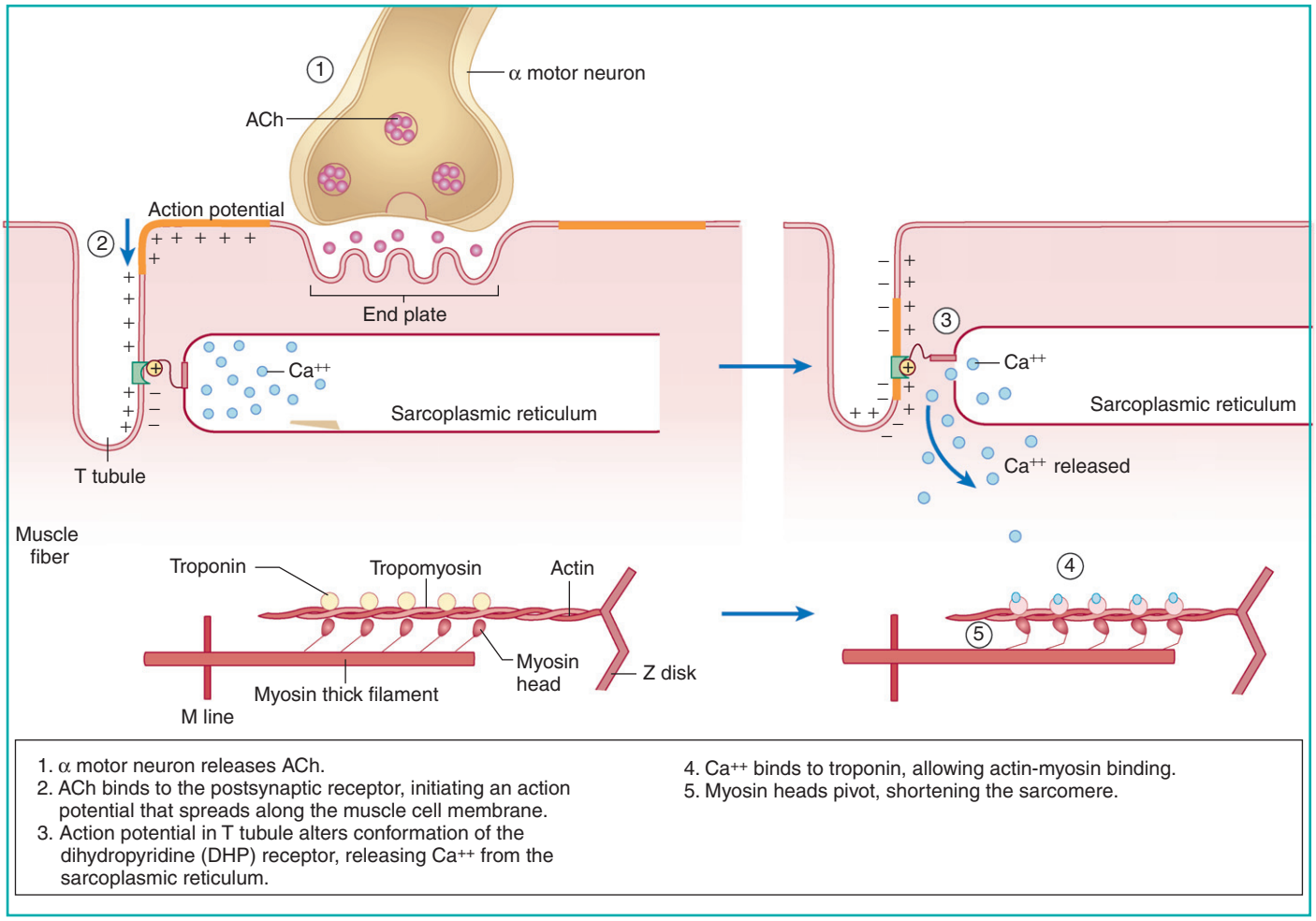

Figure 5-5. Excitation-contraction transduces the depolarization of the skeletal muscle cell membrane to movement of the actin and myosin filaments. An action potential generated at the neuromuscular junction (*2*) spreads through the cell membrane and T tubule system of the skeletal muscle cell. Dihydropyridine receptors on the T tubule (*3*) stimulate the release of Ca^{++} from the sarcoplasmic reticulum. Ca^{++} exposes the binding surface of the actin protein (*4*), allowing it to bind to myosin and initiate the contraction process (*5*).

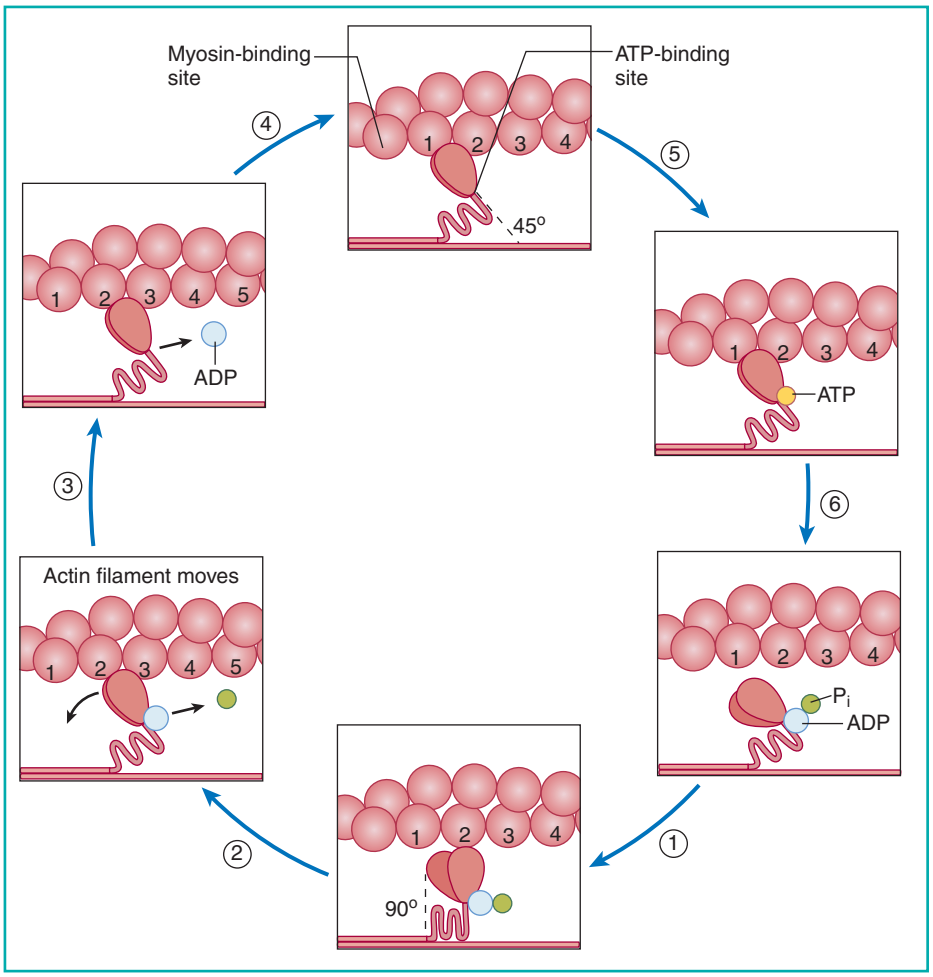

Figure 5-6. Muscle movement is due to conformational of changes in the myosin motor protein. Ca^{++} entry exposes the actin-binding sites. The contraction process is initiated (1) by the binding of the myosin head to actin. Release of inorganic phosphate (P_i) (2) initiates the power stroke, moving the myosin heads to a 45-degree angle, and shortening the sarcomere. (3) Following the power stroke and dissociation of ADP, (4) myosin is tightly bound to actin at a 45-degree angle in a rigor complex. (5) Binding of ATP to myosin breaks the actin-myosin bond. Hydrolysis of ATP moves the myosin head to a 90-degree angle, where it can again bind to actin, returning to (1). Following the power stroke, the process repeats provided that there are sufficient stores of ATP and that Ca^{++} keeps the actin-binding sites exposed.

repeats until Ca^{++} is resequestered or ATP stores are depleted.

ATP used for muscle contraction and active transport of ions comes from phosphocreatinine, glycolysis, and oxidative phosphorylation. Phosphocreatinine is the first energy store accessed and provides up to 10 seconds of energy. The high-energy phosphate on the creatinine is hydrolyzed during the resynthesis of ATP from ADP and P_i. Skeletal muscle stores of glycogen provide the next pool of energy, as anaerobic glycogenolysis allows the replenishment of ATP. The final—and most abundant—energy source is the mitochondrial oxidative phosphorylation. This process depends on the number of mitochondria and the availability of O_2.

The excitation contraction process stops when Ca^{++} is resequestered in the sarcoplasmic reticulum. The SERCA (*s*arcoplasmic and *e*ndoplasmic *r*eticulum *c*alcium *A*TPase) moves Ca^{++} from the cytosol back into the sarcoplasmic reticulum against a significant concentration gradient, thus requiring ATP for function. Free [Ca^{++}] within the sarcoplasmic reticulum is buffered by Ca^{++} binding to the proteins calsequestrin and calreticulin.

BIOCHEMISTRY

Oxidative Phosphorylation

Oxidative phosphorylation is the process by which ATP is formed by the mitochondrial transfer of electrons from the electron donors NADH and $FADH_2$ to O_2. Complete oxidation of a molecule of glucose to CO_2 and H_2O consumes up to 2 ATP and generates up to 38 ATP. This includes 26 ATP generated from NADH, 4 from FADH, and 6 from substrate-level phosphorylation. The net maximum energy production is 36 molecules of ATP from each molecule of glucose.

Skeletal Muscle Mechanics

A skeletal muscle is composed of numerous muscle fibers and motor units. Contraction of the intact muscle is the result of the contraction of a portion of the muscle fibers in the muscle.

Tension developed by the muscle contraction is increased by temporal summation and by recruitment. Temporal

summation results from an increase in the rate of individual motor unit activity. This produces tetanization, or sustained contraction of skeletal muscle. Recruitment increases the number of motor units activated, increasing the tension developed by the contracting muscle. Tension developed in the contracting muscle is transmitted to the skeleton by tendons.

The mechanics of contraction are best modeled at the sarcomere level. The muscle striations are due to the regular arrangement of the thin actin and thick myosin filaments. Sarcomere contraction results from the sliding of the overlapping actin and myosin filaments, rather than from shortening of the actual proteins themselves. Consequently, the A-band length does not change, but the adjacent Z lines are brought closer together (Fig. 5-7).

The sarcomere model also illustrates the length-tension relationship. The tension developed by a contracting muscle depends on the number of points of attachment between actin and myosin during the myosin power stroke. The maximum amount of tension developed by the sarcomere is at the middle of the length-tension curve, where every myosin head is across from an actin molecule. At lengths longer than the optimal, some myosin heads are not across from an actin. These heads cannot participate in the power stroke, and consequently the tension developed by the contracting sarcomere is diminished. At sarcomere lengths shorter than optimal, the myosin filaments are already approaching the point of attachment for the actin filaments, and consequently shortening is impeded (Fig. 5-8).

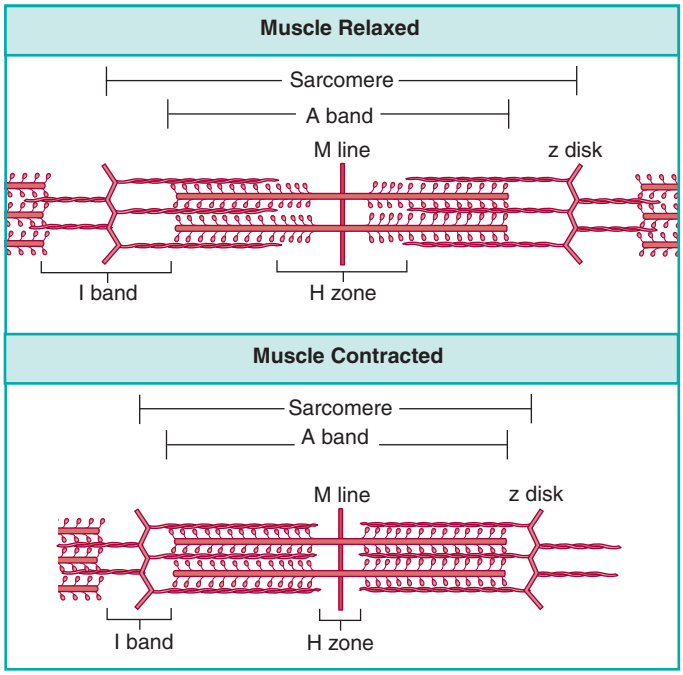

Figure 5-7. Contraction of the sarcomere involves the sliding of thick and thin filaments past each other. During contraction, the adjacent Z lines move toward each other, and the length of the A band does not change.

This effect carries over to the intact muscle, since both overstretch and understretch of resting muscle diminishes developed tension. The resting length of the muscle (before contraction is initiated) helps determine the maximal amount of tension that can be developed during contraction. For skeletal muscle, the optimal length is close to the normal resting length of the muscle. For cardiac muscle, the amount of stretch on the muscle before a contraction has special significance and is called preload.

Normal muscle activity is a combination of isometric and isotonic contractions. An isometric contraction involves the development of tension without any change in length. An isotonic contraction involves a change in length without any change in tension. The apparatus in Figure 5-9 illustrates the tension and length changes developed by a contracting muscle.

The bar on the right side can be adjusted to set the resting length. The muscle is attached to a tension gauge and an immovable plate at the top. The muscle is attached to a spring and finally to a weight at the bottom. Stimulation of the muscle by an electrode induces contraction.

Stage 1 shows the length and tension of the muscle at rest. Any tension is the result of stretch of the muscle connective tissue, caused by altering the resting length. Following stimulation, there is an increase in tension as the sarcomeres shorten and develop force during the isometric phase of contraction (stage 2). The weight remains on the platform because the tension developed in the muscle is not sufficient to lift the weight. The sarcomere shortening only stretches the elastic tissue within the muscle. Stage 3 occurs when the tension developed by the muscle equals 10 kg, the same as the weight. At this point, there is no further increase in tension, and contraction of the sarcomere now results in shortening of the muscle. This is the isotonic portion of the contraction. When the stimulus is removed, the muscle ceases its contraction, passing through stage 4, an isotonic period in which the muscle is lengthening, and as the weight returns to the platform, stage 5, in which the tension in the muscle is diminished and the elastic tissue returns to the starting condition.

The load to be lifted determines both the maximum tension that is developed and the velocity of shortening. In the contracting muscle, tension develops until it is sufficient to lift the load, at which point the muscle shortens. The tension does not change further; consequently, the load sets the maximum tension. In contrast, velocity of shortening is decreased as the load increases. At zero load, the muscle contracts with a maximal velocity of shortening. A heavy load that cannot be lifted does not allow shortening of the muscle, producing an isometric (same length) contraction.

Strength of muscle contraction is also increased by previous activity, called a staircase, or treppe, effect. This effect is probably due to enhanced intracellular Ca^{++} levels in

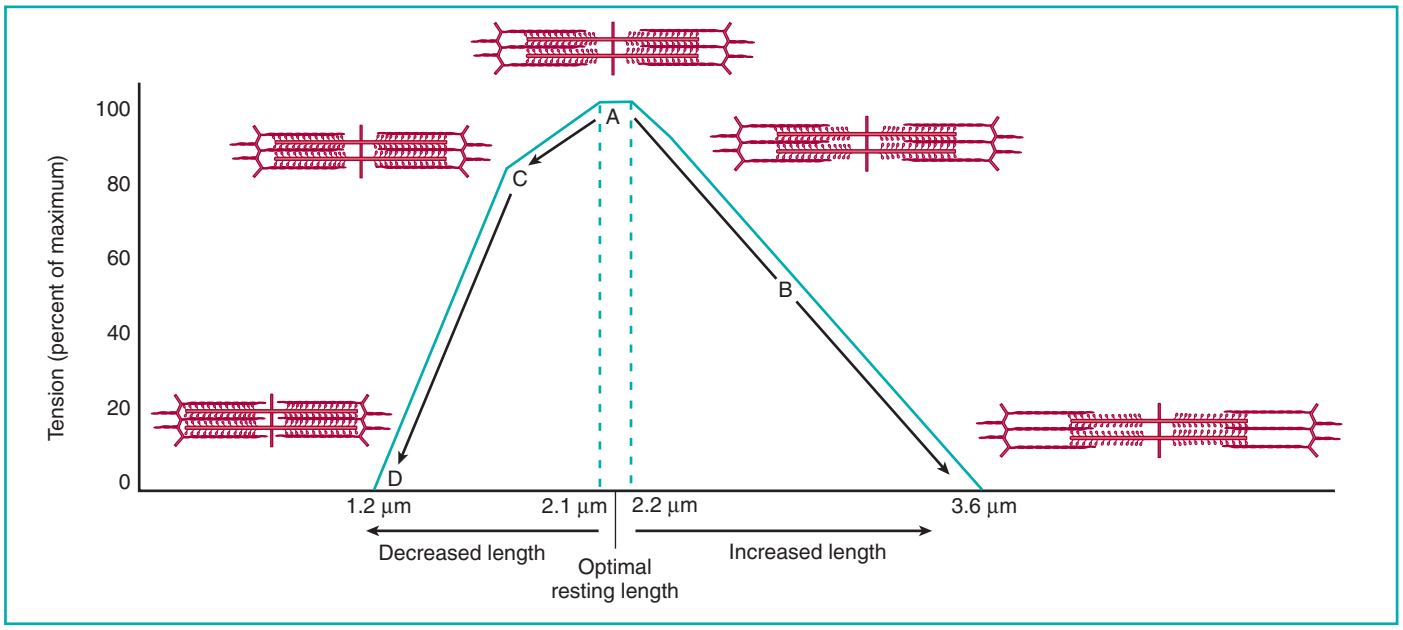

Figure 5-8. The optimal sarcomere length of 2.2 μm reflects the point at which there is a maximal overlap of the heads of the myosin filaments with the binding sites of the actin filaments. Any overstretching or understretching of the sarcomere decreases the maximum amount of tension that can be developed during contraction.

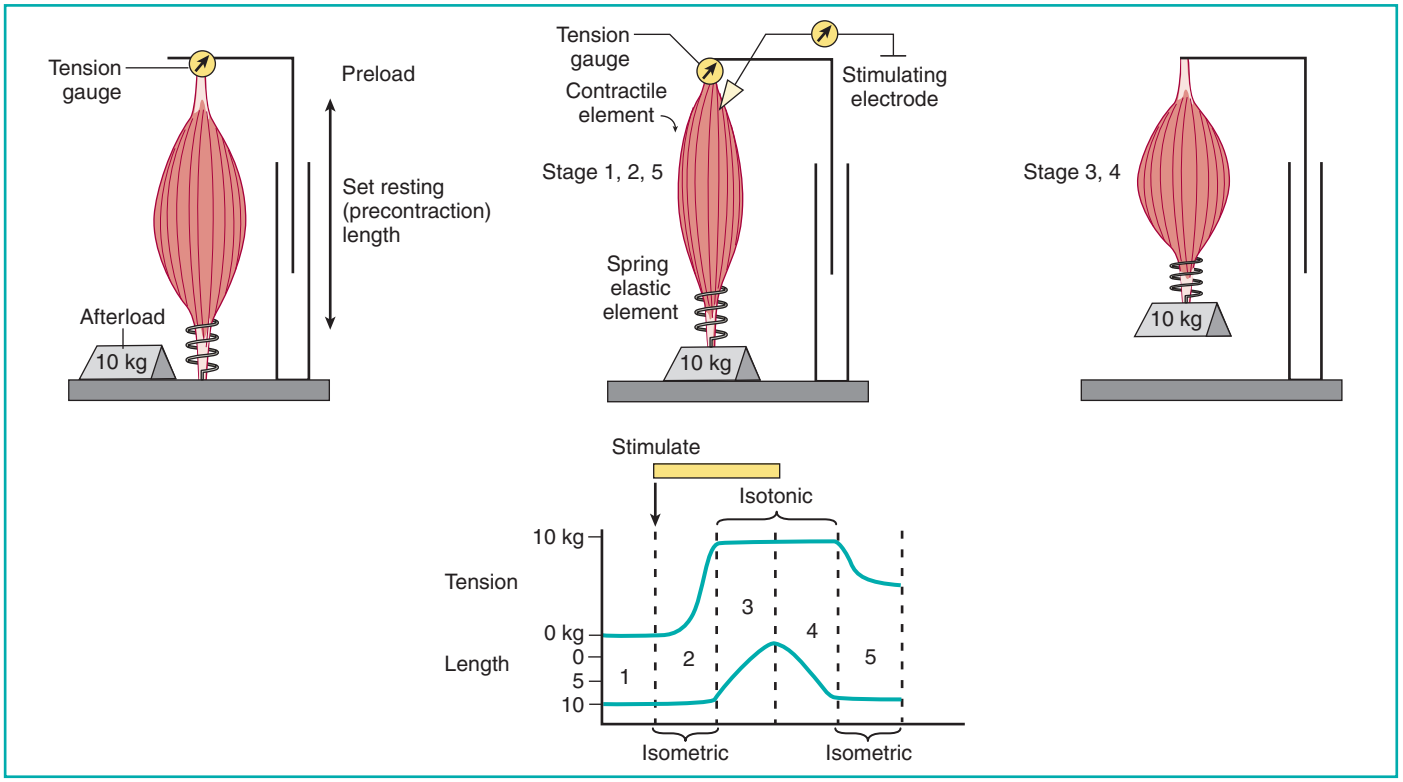

Figure 5-9. Contraction of the skeletal muscle causes a combination of an increase in tension and a shortening. The resting stretch on the skeletal muscle (preload) determines the overlap of the actin and myosin filaments and determines the peak tension that can be achieved during contraction. As contraction develops, tension in the muscle is increased until it is sufficient to move the weight (afterload). The afterload determines what portion of the total energy available during contraction will be used to develop tension, and what portion of the total energy available will be used to shorten the muscle.

the muscle. This is a muscle effect and should not be confused with facilitation of the presynaptic nerve terminal ACh release.

Skeletal muscle remodels based on the workload. Repetitive strong contractions increase muscle mass, which is called hypertrophy. Lack of muscle use decreases muscle mass, called atrophy. These changes reflect a change in the size of individual muscle cells and not a change in the number of muscle cells in the tissue.

SMOOTH MUSCLE

Smooth muscle is so named because it has no visible striations. Its contraction is involuntary. It is found in the walls of hollow organs (e.g., digestive tract, blood vessels, urinary bladder) and other areas (e.g., the iris). Smooth muscle is controlled by the autonomic nervous system, hormones, and intrinsic factors in the organ.

Smooth muscle fibers are smaller and shorter than skeletal muscle fibers. Multiunit smooth muscle is primarily under neural control. This is characteristic of vascular smooth muscle and ciliary muscles and iris of the eye. Single-unit smooth muscle is usually made up of cells that are coupled by gap junctions, allowing ions and action potentials to pass between adjacent cells. This arrangement allows the entire sheet of smooth muscle to function as a unit, or a syncytium, and is characteristic of GI smooth muscle.

Contraction

Smooth muscle uses actin and myosin filaments for contraction. The mechanism, illustrated in Figure 5-10, differs from that in skeletal muscle. Smooth muscle has tropomyosin but lacks troponin C. Calcium acts through calmodulin to activate myosin light-chain kinase to phosphorylate the myosin heads. This increases myosin ATPase activity. The calcium/calmodulin complex also uncovers the actin-binding site by binding to and phosphorylating calponin. Myosin hydrolyzes ATP, and the released energy causes the myosin head to pivot. Contraction develops more slowly but lasts longer than skeletal muscle. The actual rate varies greatly between groups of smooth muscle. ATP usage is much less than for a similar contraction of skeletal muscle.

Calcium flux is the primary ionic event, and sodium plays a smaller role in smooth muscle action potentials. Extracellular Ca^{++} directly activates smooth muscle actin, whereas the sarcoplasmic reticulum is the primary source of Ca^{++} in skeletal muscle. Some smooth muscle uses sarcoplasmic reticulum to enhance the contraction from extracellular Ca^{++}. Contraction ends when Ca^{++} is pumped out of the cell or back into the sarcoplasmic reticulum. Some smooth muscle shows spontaneous depolarization of the membrane potential, called a slow wave. Slow-wave depolarization can reach threshold and initiate an action potential. The rate of depolarization determines the frequency of action potentials. In regions such as the stomach, slow-wave generation can act as a pacemaker, setting the rate of contraction for the organ.

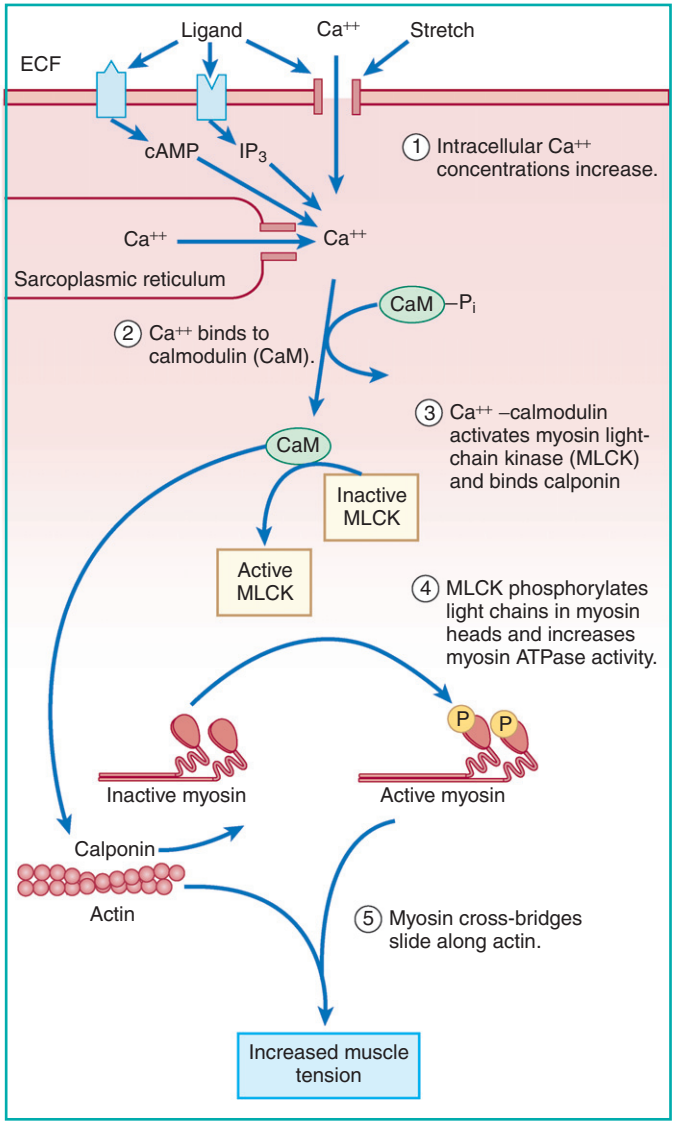

Figure 5-10. Smooth muscle excitation-contraction coupling depends on the calcium/calmodulin activation of kinases. The myosin light-chain kinase increases the activity of the myosin ATPase and moves calponin to expose the binding site on the actin protein.

Excitation

Multiple interacting mechanisms mediate the excitation-contraction coupling for smooth muscle. Stretch opens stretch-sensitive channels, depolarizes smooth muscle, and can initiate contraction. Cell membrane receptors respond to a variety of ligands, and working through inositol-1,4,5-trisphosphate (IP_3), stimulate sarcoplasmic Ca^{++} release and smooth muscle contraction. Hormones that increase cAMP can release Ca^{++} from intracellular stores and cause contraction without causing an action potential. Alternatively, some ligands promote the entry of extracellular Ca^{++}, directly stimulating contraction. The calcium/calmodulin contractile mechanism depends on protein phosphorylation and consequently is sensitive to modulation by multiple kinases.

In contrast to skeletal muscle, nerve activity can initiate smooth muscle contraction without causing action potentials. Neuromuscular junctions are more difficult to identify than in skeletal muscle. Neurotransmitters are released from axons and diffuse to the smooth muscle cell. The ability of nerves to initiate an action potential depends on the amount of neurotransmitter released and the amount of depolarization required to reach threshold. Acetylcholine stimulates contraction in some smooth muscle and relaxation in other smooth muscle types through the release of nitric oxide. Acetylcholine-mediated parasympathetic activity and norepinephrine-mediated sympathetic activity often have opposing effects on smooth muscle.

CARDIAC MUSCLE

The myocardium is a type of involuntary muscle that is found only in the heart. It is composed of branched, striated muscle cells connected by gap junctions. Cardiac muscle is controlled by intrinsic factors (e.g., the amount of venous return to the right atrium), hormones, and signals from the autonomic nervous system. Cardiac muscle is discussed in more detail in Chapter 7.

SKELETON

The adult body contains 206 bones, which together represent a tissue that is capable of growth, adaptation, and repair. Bone consists of an organic framework of proteins in collagen fibers. Hydroxyapatite crystals are embedded in this framework and provide a significant store that helps regulate plasma Ca^{++} levels (see Chapter 13).

Joints are articulations at the place of contact between two or more bones. Most of the joints in the body are synovial. They are freely movable, permitting position and motion changes. Ligaments and tendons reinforce the joint and help limit motion. Articular disks are located between the bones in some synovial joints and act to buffer forceful impact. Fibrous joints are articulations in which bones are held together by fibrous connective tissue. Cartilaginous joints are held together by cartilage, such as the ribs.

Bone marrow is the source of pluripotent blood cells (see Chapter 6). In adults, blood cells form in marrow cavities in the skull, vertebrae, ribs, sternum, shoulder, and pelvis. There are two types of bone marrow: yellow and red. Yellow marrow is composed mostly of fat cells and is found in the shafts of long bones. Yellow marrow does not normally produce blood cells. Red marrow has a hematopoietic function, manufacturing both red and white blood cells. It is located in the cancellous spaces of flat bones.

Bone contains three types of cells. Osteoblasts form bone by catalyzing the crystal formation of Ca^{++} and PO_4^- in a collagen meshwork. Osteocytes are osteoblasts that are encased in the bone matrix. Osteoclasts resorb damaged or old bone cells during periods of growth or repair. They are also crucial in returning Ca^{++} from bone to the bloodstream.

ANATOMY

Epiphyseal Plate

In children and young adults, the epiphyses are separated from the diaphysis by *epiphyseal cartilage* or plates, where bone grows in length. Estrogen and testosterone release at puberty initiates closure of the epiphyseal plates. When bone growth is complete, the epiphyseal cartilage is replaced with bone, which joins it to the diaphysis. Fractures of the epiphyseal plates in children can lead to slow bone growth or limb shortening.

The coordinated activity of these bone cells allows bone to grow, repair itself, and change shape. Even mature bone constantly changes, with new cells being formed and old cells being destroyed. The process of bone turnover is called remodeling, and it is one of the major mechanisms for maintaining Ca^{++} balance in the body. As much as 15% of the total bone mass normally turns over each year. Rebuilding of bone requires normal plasma concentrations of Ca^{++} and PO_4^- and is dependent on vitamin D.

Movement

Skeletal muscle contraction occurs when an α-motor neuron excites an individual muscle fiber. Outflow from the CNS motor cortex descends to the anterior horn of the spinal cord, where a synapse leads to activation of an α-motor neuron. The axon from the α-motor neuron transmits the action potential to the neuromuscular junction. ACh released at the neuromuscular junction binds to receptors on the muscle end plate, initiating an action potential in the muscle cell. The action potential spreads through the T tubules, causing release of Ca^{++} from the sarcoplasmic reticulum and contraction of the muscle.

Movement requires a shift of the position of the bones as they articulate across a joint. Skeletal muscle is attached to two different bones by fibrous tendons. Shortening of the skeletal muscle causes angles connecting the bones to decrease (for flexor muscles, i.e., biceps) or to increase (for extensor muscles, i.e., triceps). The musculoskeletal system functions as a unit to allow movement of the body.

Heat Production

The activity of skeletal muscle produces heat as a metabolic byproduct, which usually must be transmitted to the environment. Some of this heat can be used to maintain body temperature, as described in Chapter 1.

TOP 5 TAKE-HOME POINTS

1. Skeletal, cardiac, and smooth muscle all use the motor protein myosin, the structural protein actin, ATP, and Ca^{++}

for contraction. Muscle types differ in the source of Ca^{++}, arrangement of actin and myosin, excitation contraction coupling, and regulation of contraction.

2. Skeletal muscle contraction is initiated by the release of the neurotransmitter ACh from the α-motor neuron synapse, binding to cholinergic receptors on the muscle cell end plate region.
3. Skeletal muscle depolarization causes release of Ca^{++} from the sarcoplasmic reticulum, the binding of myosin to actin, and contraction of muscle.
4. The force developed during contraction is determined by the resting length of the muscle, the weight to be lifted, and the availability of ATP.
5. Smooth muscle contraction is initiated by membrane events that allow the influx of extracellular Ca^{++}. Calcium binds with calmodulin to phosphorylate a series of proteins, leading to the development of actin-myosin binding and contraction.