CHAPTER 9

Skeletal Muscle and Smooth Muscle

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CHAPTER OUTLINE

KEY CONCEPTS

1. The myoneural junction is a specialized synapse between the motor axon and a skeletal muscle fiber. A motor nerve and all of the muscle fibers it innervates is called a motor unit.
2. Neuromuscular transmission involves presynaptic transmitter release, diffusion of transmitter across the synaptic cleft, and binding to postsynaptic receptors.
3. The immediate postsynaptic electrical response to transmitter molecule binding is a local depolarization called the endplate potential, which is graded according to the relative number of channels that have been opened by the transmitter binding.
4. The endplate potential is localized to the endplate region and is not propagated. It causes current to flow into the muscle fiber at the endplate; the resulting outward current across adjacent areas of membrane leads to their depolarization and the generation of propagated nerve-like action potentials in the muscle cell membrane.
5. A twitch is a single muscle contraction, produced in response to a single action potential in the muscle cell membrane. A tetanus is a larger muscle contraction that results from repetitive stimulation (multiple action potentials) of the cell membrane. Its force represents the temporal summation of many twitch contractions.
6. Isometric contraction results when an activated muscle is prevented from shortening and force is produced without movement.
7. Isotonic contraction results when an activated muscle shortens against an external force (or load). The external load determines the force that the muscle will develop, and the developed force determines the velocity of shortening.
8. The length-tension curve describes the effect of the resting length of a muscle on the isometric force it can develop. This relationship, which passes through a maximum at the normal length of the muscle in the body, is determined largely by the molecular and cellular ultrastructure of the muscle.
9. The force-velocity curve describes the inverse relationship between the isotonic force and the shortening velocity in a fully activated muscle.
10. The power output of an isotonically contracting skeletal muscle is determined by the velocity of shortening, which is determined by the size of the load; it is maximal at approximately one-third of the maximal isometric force.
11. All muscles are arranged so that they may be extended by the action of antagonistic muscles or by an external force such as gravity. Muscles do not forcibly reextend themselves after shortening.
12. The control of skeletal muscle contraction is exercised through the thin filaments and is termed *actin-linked*. Smooth muscle contraction is controlled primarily via the thick filaments and is termed *myosin-linked*.
13. The links between cellular excitation and mechanical contraction in smooth muscle are varied and complex. In most of the pathways, the cellular concentration of free calcium ions is an important link in the process of activation and contraction.
14. The primary step in the regulation of smooth muscle contraction is the phosphorylation of the regulatory light chains of the myosin molecule, which is then free to interact with actin. Relaxation involves phosphatase-mediated dephosphorylation of the light chains.
15. The contractions of smooth muscle are considerably slower than those of skeletal muscle, but are much more economical in their use of cellular energy. A crossbridge mechanism called the "latch state" enables some smooth muscles to maintain contraction for extremely long periods of time.
16. Smooth muscle tissues, especially those in the walls of distensible organs, can operate over a wide range of lengths.

Chapter 8 dealt with the mechanics and activation of the internal cellular processes that produce muscle contraction. This chapter treats muscles as organized tissues, beginning with the events leading to membrane activation by nerve stimulation and continuing with the outward mechanical expression of internal processes.

ACTIVATION AND CONTRACTION OF SKELETAL MUSCLE

Skeletal muscle is controlled by the central nervous system (CNS), which provides a pattern of activation that is suited to the task at hand. The resulting contraction is further shaped by mechanical conditions external to the muscle. The connection between nerve and muscle has been studied for over a century, and a fairly clear picture of the process has emerged. While the process functions amazingly well, its complexity means that critical failures can lead to serious medical problems.

Impulse Transmission From Nerve to Muscle Occurs at the Neuromuscular Junction

The contraction of skeletal muscle occurs in response to action potentials that travel down somatic motor axons originating in the CNS. The transfer of the signal from nerve to muscle takes place at the **neuromuscular junction**, also called the **myoneural junction** or **motor endplate**. This special type of synapse has a close association between the membranes of nerve and muscle and a physiology much like that of excitatory neural synapses (see Chapter 3).

The Structure of the Neuromuscular Junction. On reaching a muscle cell, the axon of a motor neuron typically branches into several terminals, which constitute the **presynaptic portion** of the neuromuscular junction. The terminals lie in grooves or "gullies" in the surface of the muscle cell, outside the muscle cell membrane, and a Schwann cell covers them all (Fig. 9.1). Within the axoplasm of the nerve terminals are located numerous membrane-enclosed vesicles containing **acetylcholine** (**ACh**). Mitochondria, associated with the extra metabolic requirements of the terminal, are also plentiful.

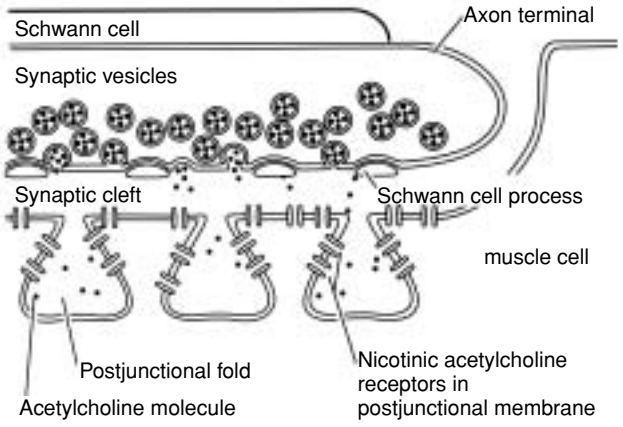

FIGURE 9.1 **Structural features of the neuromuscular junction.** Processes of the Schwann cell that overlie the axon terminal wrap around under it and divide the junctional area into active zones.

The postsynaptic portion of the junction or **endplate membrane** is that part of the muscle cell membrane lying immediately beneath the axon terminals. Here the membrane is formed into **postjunctional folds,** at the mouths of which are located many **nicotinic ACh receptor** molecules. These are *chemically gated* ion channels that increase the cation permeability of the postsynaptic membrane in response to the binding of ACh. Between the nerve and muscle is a narrow space called the **synaptic cleft.** Acetylcholine must diffuse across this gap to reach the receptors in the postsynaptic membrane. Also located in the synaptic cleft (and associated with the postsynaptic membrane) is the enzyme **acetylcholinesterase** (AChE).

Chemical Events at the Neuromuscular Junction. When the wave of depolarization associated with a nerve action potential spreads into the terminal of a motor axon, several processes are set in motion. The lowered membrane potential causes membrane channels to open and external calcium ions enter the axon. The rapid rise in intracellular calcium causes the cytoplasmic vesicles of ACh to migrate to the inner surface of the axon membrane, where they fuse with the membrane and release their contents. Because all the vesicles are of roughly the same size, they all release about the same amount—a **quantum**—of neurotransmitter. The transmitter release is called **quantal;** although so many vesicles are normally activated at once, their individual contributions are not separately identifiable.

When the ACh molecules arrive at the postsynaptic membrane after diffusing across the synaptic cleft, they bind to the ACh receptors. When two ACh molecules are bound to a receptor, it undergoes a configurational change that allows the relatively free passage of sodium and potassium ions down their respective electrochemical gradients. The binding of ACh to the receptor is reversible and rather loose. Soon ACh diffuses away and is hydrolyzed by AChE into choline and acetate, terminating its function as a transmitter molecule, and the membrane permeability returns to the resting state. The choline portion is taken up by the presynaptic terminal for resynthesis of ACh, and the acetate diffuses away into the extracellular fluid. These events take place over a few milliseconds and may be repeated many times per second without danger of fatigue.

Electrical Events at the Neuromuscular Junction. The binding of the ACh molecules to postsynaptic receptors initiates the electrical response of the muscle cell membrane, and what was a chemical signal becomes an electrical one. The stages of the development of the electrical signal are shown in Figure 9.2. With the opening of the postsynaptic ionic channels, sodium enters the muscle cell and potassium simultaneously leaves. Both ions share the same membrane channels; in this and several other respects, the endplate membrane is different from the general cell membrane of muscles and nerves. The opening of the channels depends only on the presence of neurotransmitter and not on mem-

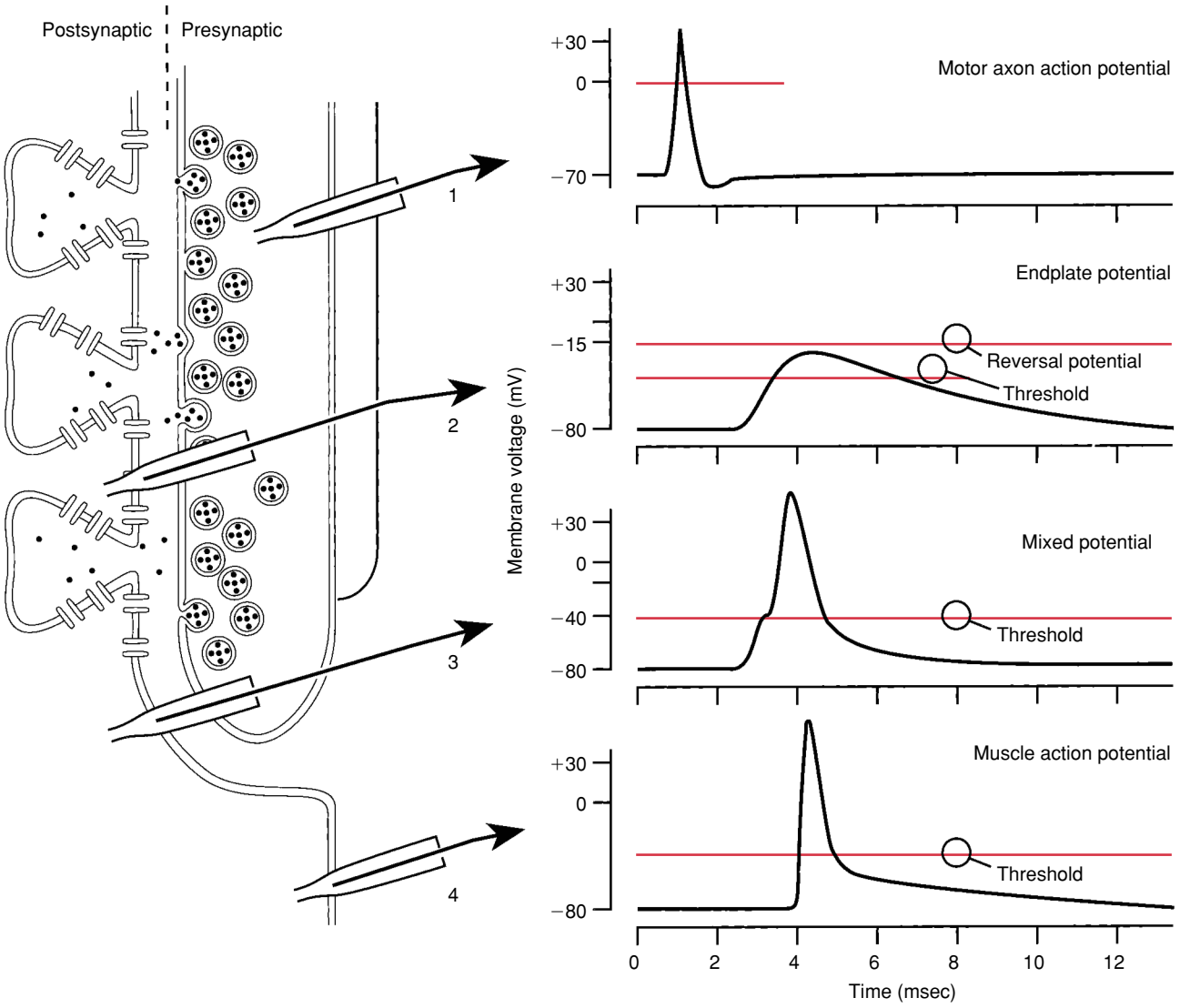

FIGURE 9.2 **Electrical activity at the neuromuscular junction.** The four microelectrodes sample membrane potentials at critical regions. (These are idealized records drawn to illustrate isolated portions of the response; in an actual recording, there would be considerable overlap of the responses because of the close spacing of the electrodes.) Note the time delays as a result of transmitter diffusion and endplate potential generation. The reversal potential is the membrane potential at which net current flow is zero (i.e., inward Na^+ and outward K^+ currents are equal).

brane voltage, and the sodium and potassium permeability changes occur simultaneously (rather than sequentially, as they do in nerve or in the general muscle membrane). As a result of the altered permeabilities, a net inward current, known as the **endplate current**, depolarizes the postsynaptic membrane. This voltage change is called the **endplate potential**. The voltage at which the net membrane current would become zero is called the **reversal potential** of the endplate (see Fig. 9.2), although time does not permit this condition to become established because the AChE is continuously inactivating transmitter molecules.

To complete the circuit, the current flowing inward at the postsynaptic membrane must be matched by a return current. This current flows through the local muscle cytoplasm (myoplasm), out across the adjacent muscle membrane and back through the extracellular fluid (Fig. 9.3). As this endplate current flows out across the muscle membrane in regions adjacent to the endplate, it depolarizes the membrane and causes voltage-gated sodium channels to open, bringing the membrane to threshold. This leads to an action potential in the muscle membrane. The muscle action potential is propagated along the muscle cell membrane by regenerative local currents similar to those in a nonmyelinated nerve fiber.

The endplate depolarization is **graded**, and its amplitude varies with the number of receptors with bound ACh. If some circumstance causes reduced ACh release, the amount of depolarization at the endplate could be correspondingly reduced. Under normal circumstances, however, the endplate potential is much more than sufficient to produce a muscle action potential; this reserve, referred to as a **safety factor**, can help preserve function under abnor-

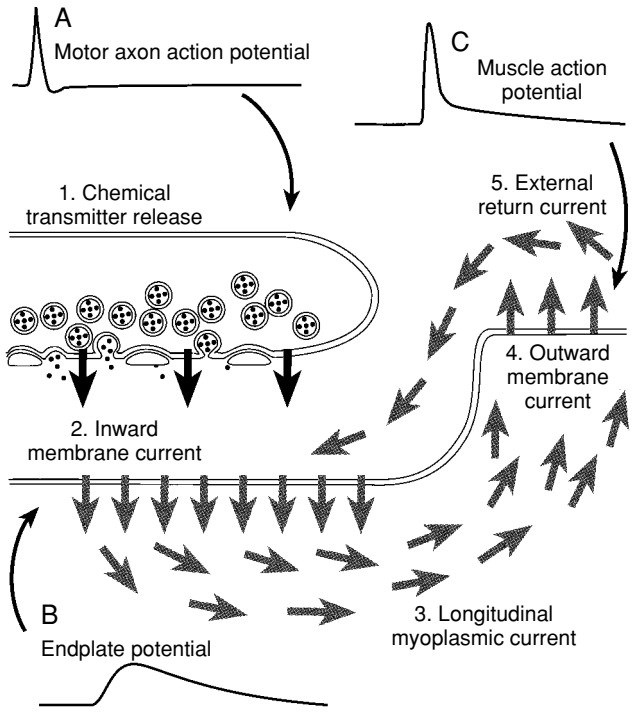

FIGURE 9.3 **Ionic currents at the neuromuscular junction. A**, The inward membrane current is carried by sodium ions through the channels associated with ACh receptors. The other currents are nonspecific and are carried by appropriately charged ions in the myoplasm and extracellular fluid. **B**, The endplate potential is localized to the endplate region. **C**, The muscle action potential is propagated along the surface of the muscle.

mal conditions. The rate of rise of the endplate potential is determined largely by the rate at which ACh binds to the receptors, and indirect clinical measurements of the size and rise time of the endplate potential are of considerable diagnostic importance. The rate of decay is determined by a combination of factors, including the rate at which the ACh diffuses away from the receptors, the rate of hydrolysis, and the electrical resistance and capacitance of the endplate membrane.

Neuromuscular Transmission Can Be Altered by Toxins, Drugs, and Trauma

The complex series of events making up neuromuscular transmission is subject to interference at several steps. **Presynaptic blockade** of the neuromuscular junction can occur if calcium does not enter the presynaptic terminal to participate in migration and emptying of the synaptic vesicles. The drug **hemicholinium** interferes with choline uptake by the presynaptic terminal and, thus, results in the depletion of ACh. **Botulinum toxin** interferes with ACh release. This bacterial toxin is used to treat focal dystonias (see Clinical Focus Box 9.1).

Postsynaptic blockade can result from a variety of circumstances. Drugs that partially mimic the action of ACh can be effective blockers. Derivatives of **curare**, originally used as arrow poison in South America, bind tightly to ACh receptors. This binding does not result in opening of the ion channels, however, and the endplate potential is reduced in proportion to the number of receptors occupied by curare. Muscle paralysis results. Although the muscle can be directly stimulated electrically, nerve stimulation is ineffective. The drug **succinylcholine** blocks the neuromuscular junction in a slightly different way; this molecule binds to the receptors and causes the channels to open. Because it is hydrolyzed very slowly by AChE, its action is long lasting and the channels remain open. This prevents resetting of the inactivation gates of muscle membrane sodium channels near the endplate region and blocks subsequent action potentials. Drugs that produce extremely long-lasting endplate potentials are referred to as **depolarizing blockers.**

Compounds such as **physostigmine** (**eserine**) are potent inhibitors of AChE and produce a depolarizing blockade. In carefully controlled doses, they can temporarily alleviate symptoms of **myasthenia gravis,** an autoimmune condition that results in a loss of postsynaptic ACh receptors. The principal symptom is muscular weakness caused by endplate potentials of insufficient amplitude. Partial inhibition of the enzymatic degradation of ACh allows ACh to remain effective longer and, thus, to compensate for the loss of receptor molecules.

Under normal conditions, ACh receptors are confined to the endplate region of a muscle. If accidental denervation occurs (e.g., by the severing of a motor nerve), the entire muscle becomes sensitive to direct application of ACh within several weeks. This extrasynaptic sensitivity is due to the synthesis of new ACh receptors, a process normally inhibited by the electrical activity of the motor axon. Artificial electrical stimulation has been shown experimentally to prevent the synthesis of new receptors, by regulating transcription of the genes involved. If reinnervation occurs, the extrasynaptic receptors gradually disappear. Muscle atrophy also occurs in the absence of functional innervation, which also can be at least partially reversed with artificial stimulation.

MECHANICAL PROPERTIES OF SKELETAL MUSCLE

The variety of controlled muscular movements that humans can make is remarkable, ranging from the powerful contractions of a weightlifter's biceps to the delicate movements of the muscles that position our eyes as we follow a moving object. In spite of this diversity, the fundamental mechanical events of the contraction process can be described by a relatively small set of specially defined functions that emphasize particular capabilities of muscle.

The Timing of Muscle Stimulation Is a Critical Determinant of Contractile Function

A skeletal muscle must be activated by the nervous system before it can begin contracting. Through the many processes previously described, a single nerve action potential arrives at each motor nerve axon terminal. A single muscle action potential then propagates along the length

CLINICAL FOCUS BOX 9.1

Focal Dystonias and Botulinum Toxin

Focal dystonias are neuromuscular disorders characterized by involuntary and repetitive or sustained skeletal muscle contractions that cause twisting, turning, or squeezing movements in a body part. Abnormal postures and considerable pain, as well as physical impairment, often result. Usually the abnormal contraction is limited to a small and specific region of muscles, hence, the term *focal* ("by itself"). *Dystonia* means "faulty contraction." **Spasmodic torticollis** and **cervical dystonia** (involving neck and shoulder muscles), **blepharospasm** (eyelid muscles), **strabismus** and **nystagmus** (extraocular muscles), **spasmodic dysphonia** (vocal muscles), **hemifacial spasm** (facial muscles), and **writer's cramp** (finger muscles in the forearm) are common dystonias. Such problems are neurological, not psychiatric, in origin, and sufferers can have severe impairment of daily social and occupational activities.

The specific cause is located somewhere in the central nervous system (CNS), but usually its exact nature is unknown. A genetic predisposition to the disorder may exist in some cases. Centrally acting drugs are of limited effectiveness, and surgical denervation, which carries a significant risk of permanent and irreversible paralysis, may provide only temporary relief. However, recent clinical trials using **botulinum toxin** to produce chemical denervation show significant promise in the treatment of these disorders.

Botulinum toxin is produced when the bacterium *Clostridium botulinum* grows anaerobically. It is one of the most potent natural toxins; a lethal dose for a human adult is about 2 to 3 μg. The active portion of the toxin is a protein with a molecular weight of about 150,000 that is conjugated with a variable number of accessory proteins. Type A toxin, the complex form most often used therapeutically, has a total molecular weight of 900,000 and is sold under the trade names Botox and Oculinum.

The toxin first binds to the cell membrane of presynaptic nerve terminals in skeletal muscles. The initial binding does not appear to produce paralysis until the toxin is actively transported into the cell, a process requiring more than an hour. Once inside the cell, the toxin disrupts calcium-mediated ACh release, producing an irreversible transmission block at the neuromuscular junction. The nerve terminals begin to degenerate, and the denervated muscle fibers atrophy. Eventually, new nerve terminals sprout from the axons of affected nerves and make new synaptic contact with the chemically denervated muscle fibers. During the period of denervation, which may be several months, the patient usually experiences considerable relief of symptoms. The relief is temporary, however, and the treatment must be repeated when reinnervation has occurred.

Clinically, highly diluted toxin is injected into the individual muscles involved in the dystonia. Often this is done in conjunction with electrical measurements of muscle activity (electromyography) to pinpoint the muscles involved. Patients typically begin to experience relief in a few days to a week. Depending on the specific disorder, relief may be dramatic and may last for several months or more. The abnormal contractions and associated pain are greatly reduced, speech can become clear again, eyes reopen and cease uncontrolled movements and, often, normal activities can be resumed.

The principal adverse effect is a temporary weakness of the injected muscles. A few patients develop antibodies to the toxin, which renders its further use ineffective. Studies have shown that the toxin's activity is confined to the injected muscles, with no toxic effects noted elsewhere. Long-term effects of the treatment, if any, are unknown.

of each muscle fiber innervated by that axon terminal. This leads to a single brief contraction of the muscle, a **twitch**. Though the contractile machinery may be fully activated (or nearly so) during a twitch, the amount of force produced is relatively low because the activation is so brief that the relaxation processes begin before contraction is fully established.

Effects of Repeated Stimulation. The duration of the action potential in a skeletal muscle fiber is short (about 5 msec) compared to the duration of a twitch (tens or hundreds of milliseconds, depending on muscle type, temperature, etc.). This means the absolute refractory period is also brief, and the muscle fiber membrane can be activated again long before the muscle has relaxed. Figure 9.4 shows the result of stimulating a muscle that is already active as a result of a prior stimulus. If the second stimulus is given during relaxation (Fig. 9.4B), well outside the refractory period caused by the first stimulus, significant additional force is developed. This additional force increment is associated with a second release of calcium ions from the SR, which adds to the calcium already there and reactivates actin and myosin interactions (see Chapter 8). When the second stimulus closely follows the first (even before force has begun to decline), the myoplasmic calcium concentration is still high (Fig. 9.4C), and the effect of the additional calcium ions is to increase the force and, to some extent, the duration of the twitch because a larger amount of calcium is present in the region of the myofilaments.

If stimuli are given repeatedly and rapidly, the result is a sustained contraction called a **tetanus**. When the contractions occur so close together that no fluctuations in force are observed, a fused tetanus results. The repetition rate at which this occurs is the **tetanic fusion frequency**, typically 20 to 60 stimuli per second, with the higher rates found in muscles that contract and relax rapidly. Figure 9.5 shows these effects in a special situation, in which the interval between successive stimuli is steadily reduced and the muscle responds at first with a series of twitches that become fused into a smooth tetanus at the highest stimulus frequency. Because it involves events that occur close together in time, a tetanus is a form of **temporal summation**.

Higher Forces Are Produced During a Tetanus. The amount of force produced in a tetanus is typically several times that of a twitch; the disparity is expressed as the

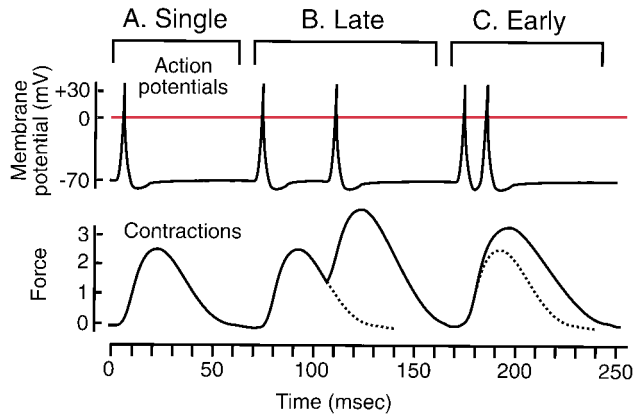

FIGURE 9.4 **Temporal summation of muscle twitches.** A, The first contraction is in response to a single action potential. B, The next contraction shows the summed response to a second stimulus given during relaxation; the two individual responses are evident. C, The last contraction is the result of two stimuli in quick succession. Though measured force was still rising when the second stimulus was given, the fact that there could be an added response shows that internal activation had begun to decline. In all cases, the solid line in the lower graph represents the actual summed tension.

tetanus-twitch ratio. The relaxation processes during a twitch, particularly the reuptake of calcium, begin to operate as soon as the muscle is activated, and full activation is brief (lasting less time than that required for the muscle to reach its peak force). Multiple stimuli, as in a tetanus, are needed for the full force to be expressed.

Another factor explaining the higher muscle force produced with repetitive stimulation is mechanical. Even if the ends of a muscle are held rigidly, internal dimensional changes take place on activation. Some of this internal motion is associated with the crossbridges, and the tendons at either end of the muscle make a considerable contribution.

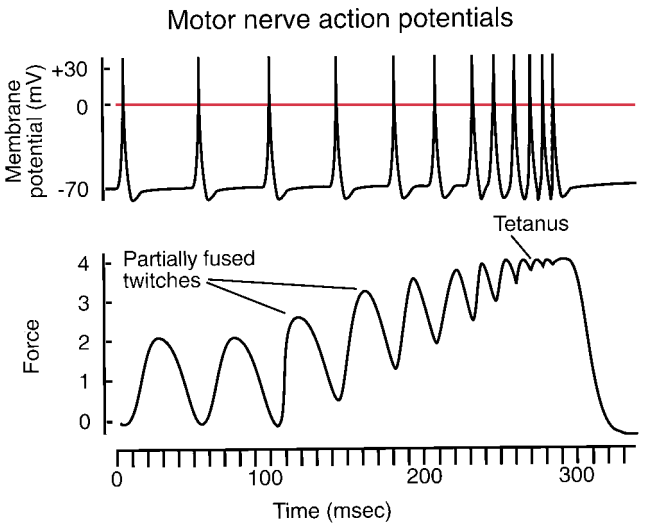

FIGURE 9.5 **Fusion of twitches into a smooth tetanus.** The interval between successive stimuli steadily decreases until no relaxation occurs between stimuli.

These deformable structures comprise the **series elastic component** of the muscle, and their extension takes a significant amount of time. The brief activation time of a twitch is not sufficient to extend the series elastic component fully, and not all of the potential force of the contraction is realized. Repeated activation in tetanus allows time for the internal "slack" to be more fully taken up, and more force is produced. Muscles with a large amount of series elasticity have a large tetanus-twitch ratio. The presence of series elasticity in human muscles provides some protection against sudden overloads of a muscle and allows for a small amount of mechanical energy storage. In jumping animals, such as kangaroos, a large fraction of muscular energy is stored in the elastic tendons and contributes significantly to the economy of locomotion.

Partial Activation of a Whole Muscle. Since a skeletal muscle consists of many fibers, each supplied by its own branch of a motor axon, it is possible (and usual) that only a portion of the muscle will be activated at any one time. The pattern of activation is determined by the CNS and by the distribution of the motor axons among the muscle fibers. A typical motor axon branches as it courses through the muscle, and each of its terminal branches innervates a single muscle fiber. All the fibers supplied by a single motor axon will contract together when a nerve action potential travels from the central nervous system and divides among the branches.

A single motor axon and all of the fibers it innervates are called a **motor unit.** Contractions in only some of the fibers in a motor unit are impossible, so the motor unit is normally the smallest functional unit of a muscle. In muscles adapted for fine and precise control, only a few muscle fibers are associated with a given motor axon; in muscles in which high force is more important, a single motor axon controls many more muscle fibers. The total force produced by a muscle is determined by the number of motor units active at any one time; as more motor units are brought into play, the force increases. This phenomenon, called **motor unit summation,** is illustrated in Figure 9.6. The force of contraction of the whole muscle is further modified by the degree of activation of each motor unit in the muscle; some may be fully tetanized, while others may be at rest or produce only a series of twitches. During a sustained contraction, the pattern of activity is continually changed by the CNS, and the burden of contraction is shared among the motor units. This results in a smooth contraction, with the force precisely controlled to produce the desired movement (or lack of it).

Externally Imposed Conditions Also Affect Contraction

Mechanical factors external to the muscle also influence the force and speed of contraction. For example, if a muscle is not allowed to shorten when it is stimulated, it will develop more force than it would if its length were allowed to change. If a muscle is in the process of lifting a load, its force of contraction is determined by the size of the load, not by the capabilities of the muscle. The speed with which a muscle shortens is likewise determined, at least in part, by external conditions.

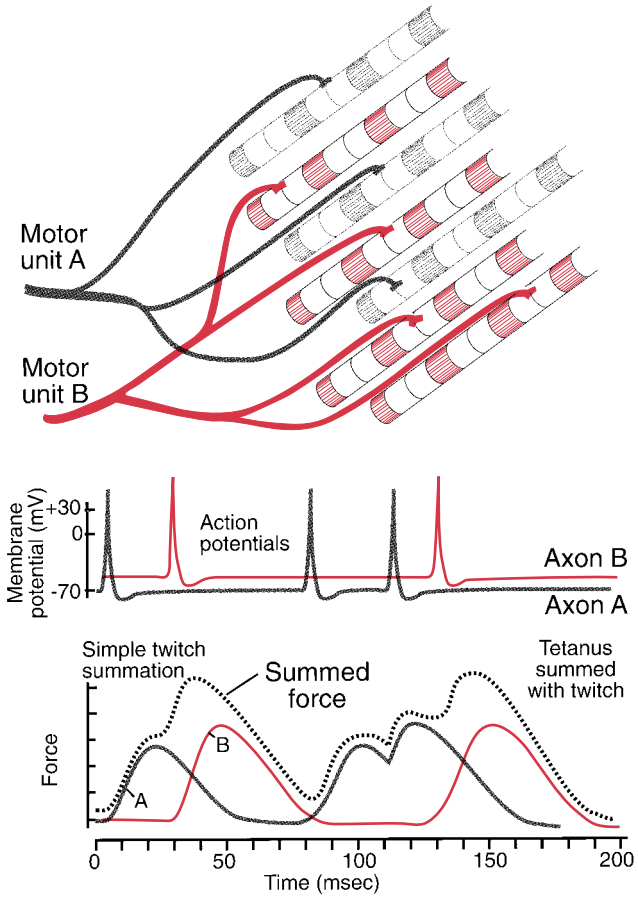

FIGURE 9.6 **Motor unit summation.** Two units are shown above; their motor nerve action potentials and muscle twitches are shown below. In the first contraction, there is a simple summation of two twitches; in the second, a brief tetanus in one motor unit sums with a twitch in the other.

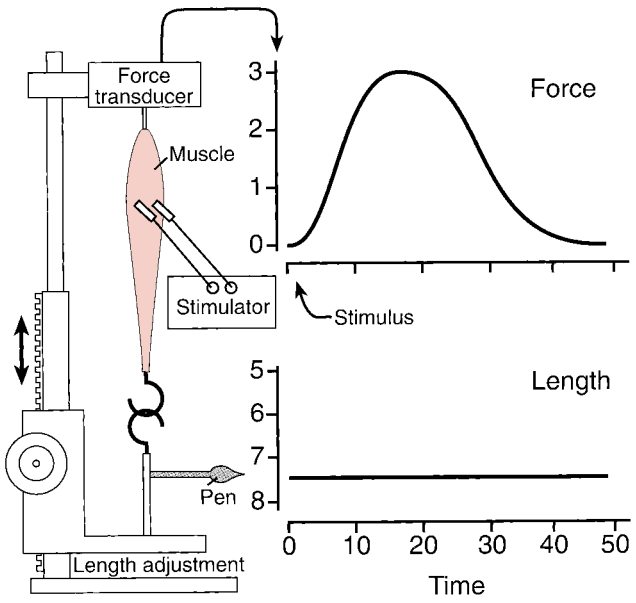

FIGURE 9.7 **A simple apparatus for recording isometric contractions.** The length of the muscle (marked on the graph by the pen attached near its lower end) is adjustable at rest but is held constant during contraction. The force transducer provides a record of the isometric force response to a single stimulus at a fixed length (isometric by definition). (Force, length, and time units are arbitrary.)

Isometric Contraction. If a muscle is prevented from shortening when activated, the muscle will express its contractile activity by pulling against its attachments and developing force. This type of contraction is termed **isometric** (meaning "same length"). The forces developed during an isometric contraction can be studied by attaching a dissected muscle to an apparatus similar to that shown in Figure 9.7. This arrangement provides for setting the length of the muscle and tracing a record of force versus time. In a twitch, isometric force develops relatively rapidly, and subsequent isometric relaxation is somewhat slower. The durations of both contraction time and relaxation time are related to the rate at which calcium ions can be delivered to and removed from the region of the crossbridges, the actual sites of force development. During an isometric contraction, no actual physical work is done on the external environment because no movement takes place while the force is developed. The muscle, however, still consumes energy to fuel the processes that generate and maintain force.

Isotonic Contraction. When conditions are arranged so the muscle can shorten and exert a constant force while doing so, the contraction is called **isotonic** (meaning "same force"). In the simplest conditions, this constant force is provided by the load a muscle lifts. This load is called an **afterload,** since its magnitude and presence are not apparent to the muscle until after it has begun to shorten.

Recording an isotonic contraction requires modification of the apparatus used to study isometric contraction (Fig. 9.8). Here the muscle is allowed to shorten while lifting an afterload, which is provided by the attached weight. This weight is chosen to present somewhat less than the peak force capability of the muscle. When the muscle is stimulated, it will begin to develop force without shortening, since it takes some time to build up enough force to begin to lift the weight. This means that early on, the contraction is isometric (phase 1; Fig. 9.8). After sufficient force has been generated, the muscle will begin to shorten and lift the load (phase 2). The contraction then becomes isotonic because the force exerted by the muscle exactly matches that of the weight, and the mass of the weight does not vary. Therefore, the upper tracing in Figure 9.8 shows a flat line representing constant force, while the muscle length (lower tracing) is free to change. As relaxation begins (phase 3), the muscle lengthens at constant force because it is still supporting the load; this phase of relaxation is isotonic, and the muscle is reextended by the weight. When the muscle has been extended sufficiently to return to its original length, conditions again become isometric (phase 4), and the remaining force in the muscle declines as it would in a purely isometric twitch. In almost all situations encountered in daily life, isotonic contraction is preceded by isometric force development; such contractions are called **mixed contractions** (isometric-isotonic-isometric).

The duration of the early isometric portion of the contraction varies, depending on the afterload. At low after-

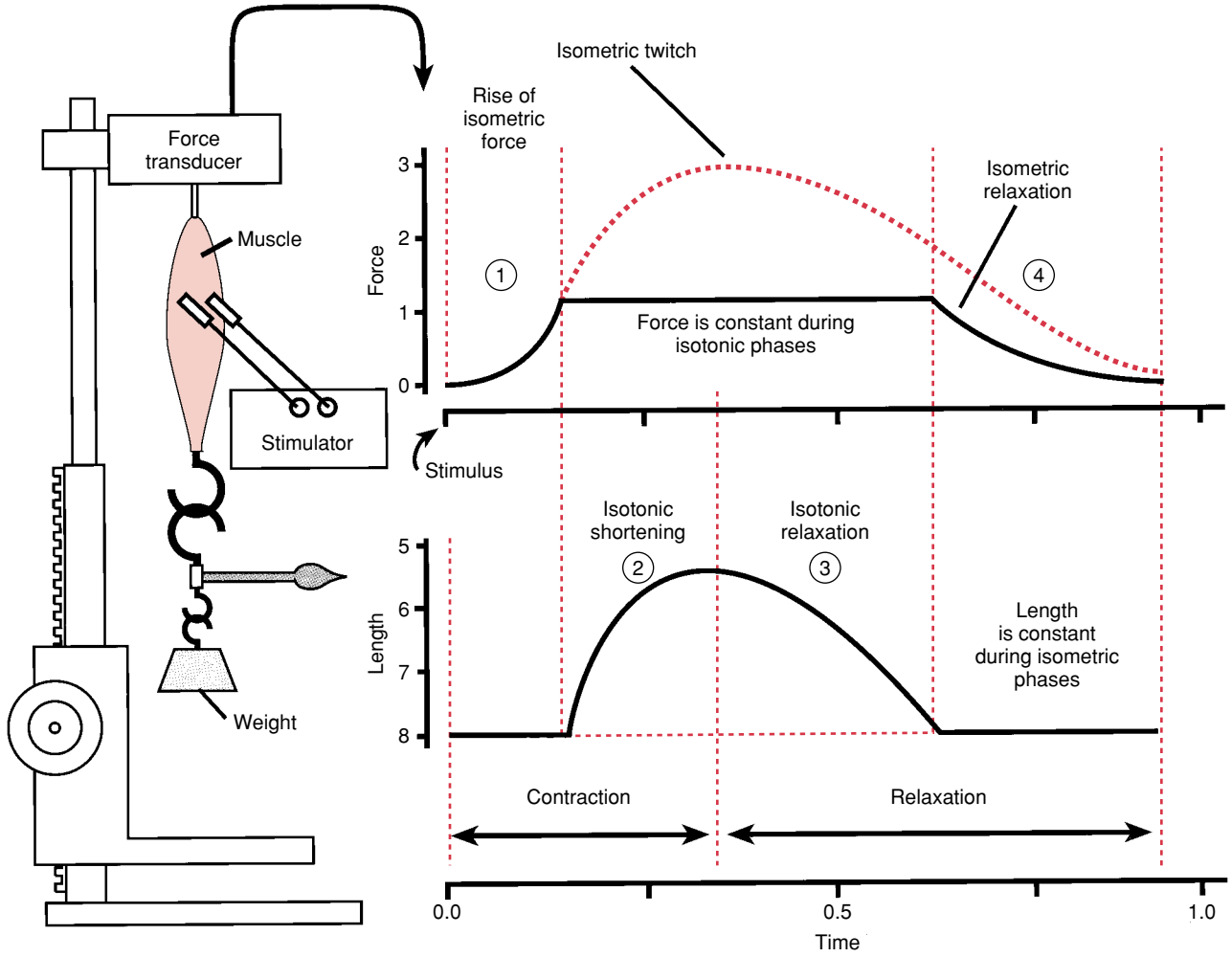

FIGURE 9.8 A modified apparatus showing the recording of a single isotonic switch. The pen at the lower end of the muscle marks its length, and the weight attached to the muscle provides the afterload, while the platform beneath the weight prevents the muscle from being overstretched at rest. The first part of the contraction, until sufficient force has developed to lift the weight, is isometric. During shortening and isotonic relaxation the force is constant (isotonic conditions), and during the final relaxation, conditions are again isometric because the muscle no longer lifts the weight. The dotted lines in the force and length traces show the isometric twitch that would have resulted if the force had been too large (greater than 3 units) for the muscle to lift. (Force, length, and time units are arbitrary.) (See text for details.)

loads, the muscle requires little time to develop sufficient force to begin to shorten, and conditions will be isotonic for a longer time. Figure 9.9 presents a series of three twitches. At the lowest afterload (weight A only), the isometric phase is the briefest and the isotonic phase is the longest with the lowest force. With the addition of weight B, the afterload is doubled and the isometric phase is longer, while the isotonic phase is shorter with twice the force. If weight C is added, the combined afterload represents more force that the muscle can exert, and the contraction is isometric for its entire duration. The speed and extent of shortening depend on the afterload in unique ways described shortly.

Other Types of Contraction. Other physical situations are sometimes encountered that modify the type of muscle contraction. When the force exerted by a shortening muscle continuously increases as it shortens, the contraction is said to be **auxotonic**. Drawing back a bowstring is an example of this type of contraction. If the force of contraction decreases as the muscle shortens, the contraction is called **meiotonic**.

In the body, a **concentric** contraction is one in which shortening (not necessarily isotonic) takes place. In an **eccentric** contraction, a muscle is extended (while active) by an external force. Activities such as descending stairs or landing from a jump utilize this type of contraction. Such contractions are potentially dangerous because the muscle can experience forces that are larger than it could develop on its own, and tearing (strain) injuries can result. A **static** contraction results in no movement, but this may be due to partial activation (fewer motor units active) opposing a load that is not maximal. (This is different from a true isometric contraction, in which shortening is physically impossible regardless of the degree of activation.)

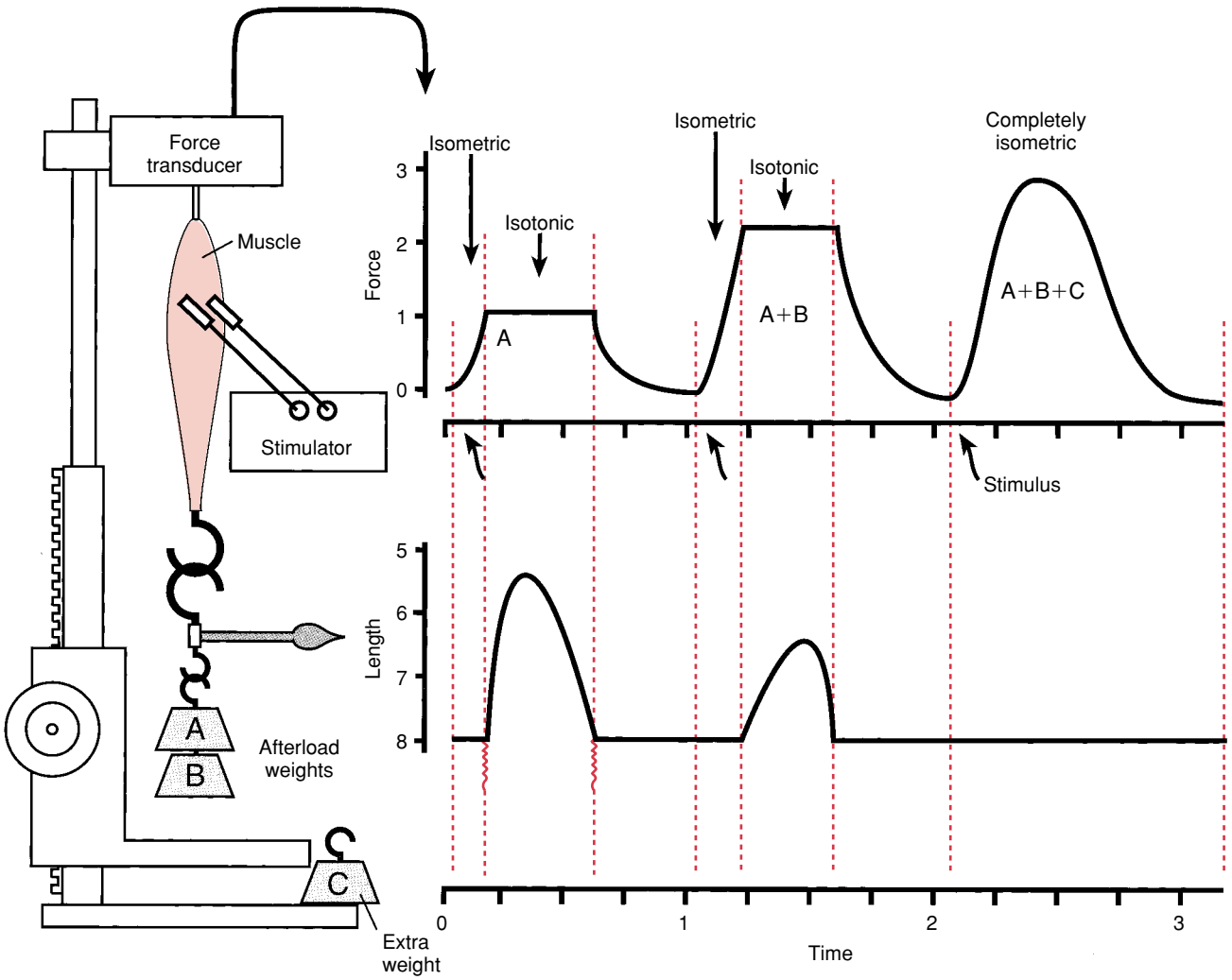

FIGURE 9.9 **A series of afterloaded isotonic contractions.** The curves labeled A and A + B correspond to the force and shortening records during the lifting of those weights. In each case, the adjustable platform prevents the muscle from being stretched by the attached weight, and all contractions start from the same muscle length. Note the lower force and greater shortening with the lower weight (A). If weight C (total weight = A + B + C) is added to the afterload, the muscle cannot lift it, and the entire contraction remains isometric. (Force, length, and time units are arbitrary.)

Special Mechanical Arrangements Allow a More Precise Analysis of Muscle Function

The types of contraction described above provide a basis for a better understanding of muscle function. The isometric and isotonic mechanical behavior of muscle can be described in terms of two important relationships:

- The length-tension curve, treating isometric contraction at different muscle lengths
- The force-velocity curve, concerned with muscle performance during isotonic contraction

Isometric Contraction and the Length-Tension Curve.

Because it is made of contractile proteins and connective tissue, an isolated muscle can resist being stretched at rest. When it is very short, it is slack and will not resist passive extension. As it is made longer and longer, however, its resisting force increases more and more. Normally a muscle is protected against overextension by attachments to the skeleton or by other anatomic structures. If the muscle has not been stimulated, this resisting force is called **passive force** or **resting force**.

The relationship between force and length is much different in a stimulated muscle. The amount of active force or **active tension** a muscle can produce during an isometric contraction depends on the length at which the muscle is held. At a length roughly corresponding to the natural length in the body, the **resting length,** the maximum force is produced. If the muscle is set to a shorter length and then stimulated, it produces less force. At an extremely short length, it produces no force at all. If the muscle is made longer than its optimal length, it produces less force when stimulated. This behavior is summarized in the **length-tension curve** (Fig. 9.10).

In Figure 9.10, the left side of the top graph shows the force produced by a series of twitches made over the range

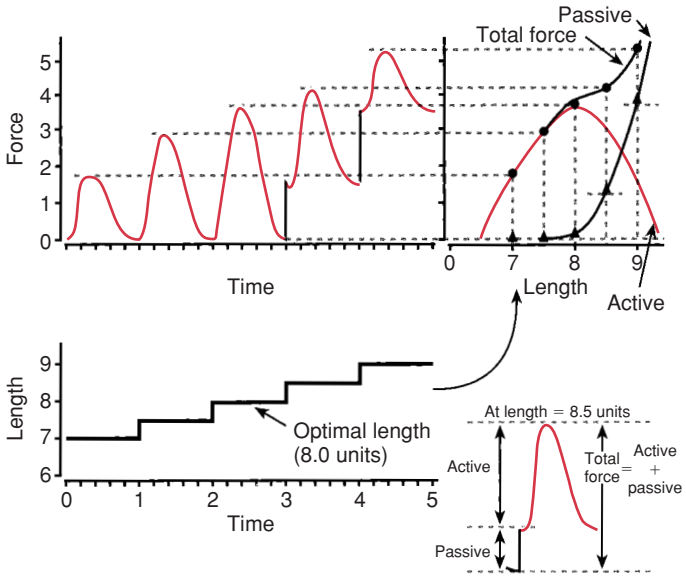

FIGURE 9.10 **A length-tension curve for skeletal muscle.** Contractions are made at several resting lengths, and the resting (passive) and peak (total) forces for each twitch are transferred to the graph at the right. Subtraction of the passive curve from the total curve yields the active force curve. These curves are further illustrated in the lower right corner of the figure. (Force, length, and time units are arbitrary.) (See text for details.)

of muscle lengths indicated at the left side of the bottom graph. Information from these traces is plotted at the right. The total peak force from each twitch is related to each length (dotted lines). The muscle length is changed only when the muscle is not stimulated, and it is held constant (isometric) during contraction. The difference between the total force and the passive force is called the active force (see inset; Fig. 9.10). The active force results directly from the active contraction of the muscle.

The length-tension curve shows that when the muscle is either longer or shorter than optimal length, it produces less force. Myofilament overlap is a primary factor in determining the active length-tension curve (see Chapter 8). However, studies have demonstrated that at very short lengths, the effectiveness of some steps in the excitation-contraction coupling process is reduced—binding of calcium to troponin is less and there is some loss of action potential conduction in the T tubule system.

The functional significance of the length-tension curve varies among the different muscle types. Many skeletal muscles are confined by their skeletal attachments to a relatively short region of the curve that is near the optimal length. In these cases, the lever action of the skeletal system, not the length-tension relationship, is of primary importance in determining the maximal force the muscle can exert. Cardiac muscle, however, normally works at lengths significantly less than optimal for force production, but its passive length-tension curve is shifted to shorter lengths (see Chapter 10). The length-tension relationship is, therefore, very important when considering the ability of cardiac muscle to adjust to changes in length (related to the volume of blood contained in the heart) to meet the body's changing needs. The role of the length-tension curve in smooth muscle is less clearly understood because of the great diversity among smooth muscles and their physiological roles. For all muscle types, however, the length-tension curve has provided important information about the cellular and molecular mechanisms of contraction.

Isotonic Contraction and the Force-Velocity Curve.

Everyday experience shows that the speed at which a muscle can shorten depends on the load that must be moved. Simply stated, light loads are lifted faster than heavy ones. Detailed analysis of this observation can provide insight into how the force and shortening of muscles are matched to the external tasks they perform, as well as how muscles function internally to liberate mechanical energy from their metabolic stores. The analysis is performed by arranging a muscle so that it can be presented with a series of afterloads (see Fig. 9.9; Fig. 9.11). When the muscle is maximally stimulated, lighter loads are lifted quickly and heavier loads more slowly. If the applied load is greater than the maximal force capability of the muscle, known as $\mathbf{F_{max}}$, no shortening will result and the contraction will be isometric. If no load is applied, the muscle will shorten at its greatest possible speed, a velocity known as $\mathbf{V_{max}}$.

The **initial velocity**—the speed with which the muscle begins to shorten—is measured at various loads. Initial velocity is measured because the muscle soon begins to slow down; as it gets shorter, it moves down its length-tension curve and is capable of less force and speed of shortening. When all the initial velocity measurements are related to each corresponding afterload lifted, an inverse relationship known as the **force-velocity curve** is obtained. The curve is steeper at low forces. When the measurements are made on a fully activated muscle, the force-velocity curve defines the upper limits of the muscle's isotonic capability. In practice, a completely unloaded contraction is very difficult to arrange, but mathematical extrapolation provides an accurate V_{max} value.

Figure 9.11 shows a force-velocity curve made from such a series of isotonic contractions. The initial velocity points (A–D) correspond to the contractions shown at the top. Factors that modify muscle performance, such as fatigue or incomplete stimulation (e.g., fewer motor units activated), result in operation *below* the limits defined by the force-velocity curve.

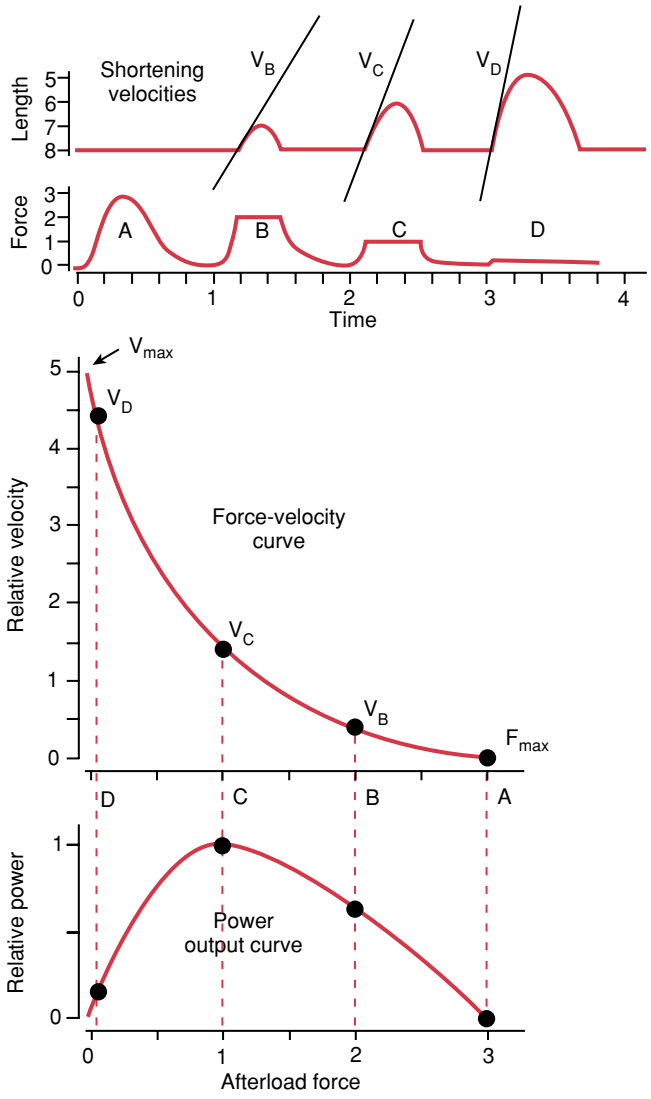

FIGURE 9.11 **Force-velocity and power output curves for skeletal muscle.** Contractions at four different afterloads (decreasing left to right) are shown in the top graphs. Note the differences in the amounts of shortening. The initial shortening velocity (slope) is measured (V_B, V_C, V_D) and the corresponding force and velocity points plotted on the axes in the bottom graph. Also shown is power output, the product of force and velocity. Note that it reaches a maximum at an afterload of about one-third of the maximal force. (Force, length, and time units are arbitrary.)

Consideration of the force-velocity relationship of muscle can provide insight into how it functions as a biological motor, its primary physiological role. For instance, V_{max} represents the maximal rate of crossbridge cycling; it is directly related to the biochemistry of the actin-myosin ATPase activity in a particular muscle type and can be used to compare the properties of different muscles.

Because isotonic contraction involves moving a force (the afterload) through a distance, the muscle does physical work. The rate at which it does this work is its **power output** (see Figure 9.11). The factors represented in the force-velocity curve are thus relevant to questions of muscle work and power. At the two extremes of the force-velocity curve (zero force, maximal velocity and maximal force, zero velocity), no work is done because, by definition, work requires moving a force through a distance. Between these two extremes, work and power output pass through a maximum at a point where the force is approximately one-third of its maximal value. The peak of the curve represents the combination of force and velocity at which the greatest power output is produced; at any afterload force greater or smaller than this, less power can be produced. It also appears in skeletal muscle that the optimal power output occurs under nearly the same conditions at which muscle **efficiency**, the amount of power produced for a given metabolic energy input, is greatest.

In terms of mechanical work, the chemical reactions of muscle are about 20% efficient; the energy from the remaining 80% of the fuel consumed (ATP) appears as heat. In some forms of locomotion, such as running, the measured efficiency is higher, approaching 40% in some cases. This apparent increase is probably due to the storage of mechanical energy (between strides) in elastic elements of the muscle and in the potential and kinetic energy of the moving body. This energy is then partly returned as work during the subsequent contraction. It has also been shown that stretching an active muscle (e.g., during running or descending stairs) can greatly reduce the breakdown of ATP, since the crossbridge cycle is disrupted when myofilaments are forced to slide in the lengthening direction.

These force-velocity and efficiency relationships are important when endurance is a significant concern. Athletes who are successful in long-term physical activity have learned to optimize their power output by "pacing" themselves and adjusting the velocity of contraction of their muscles to extend the duration of exercise. Such adjustments obviously involve compromises, as not all of the many muscles involved in a particular task can be used at optimal loading and rate and subjective factors, such as experience and training, enter into performance.

In rapid, short-term exercise, it is possible to work at an inefficient force-velocity combination to produce the most rapid or forceful movements possible. Such activity must necessarily be of more limited duration than that carried out under conditions of maximal efficiency. Examples of attempts at optimal matching of human muscles to varying loads can be found in the design of human-powered machinery, pedestrian ramps, and similar devices.

Interactions Between Isometric and Isotonic Contractions.

The length-tension curve represents the effect of length on the isometric contraction of skeletal muscle. During isotonic shortening, however, muscle length does change while the force is constant. The limit of this shortening is also described by the length-tension curve. For example, a lightly loaded muscle will shorten farther than one starting from the same length and bearing a heavier load. If the muscle begins its shortening from a reduced length, its subsequent shortening will be reduced. These relationships are diagrammed in Figure 9.12. In the case of day-to-day skeletal muscle activity, these limits are not usually encountered because voluntary adjustments of the contracting muscle are usually made to accomplish a specific task. In the case of cardiac muscle, however, such interrelationships between force

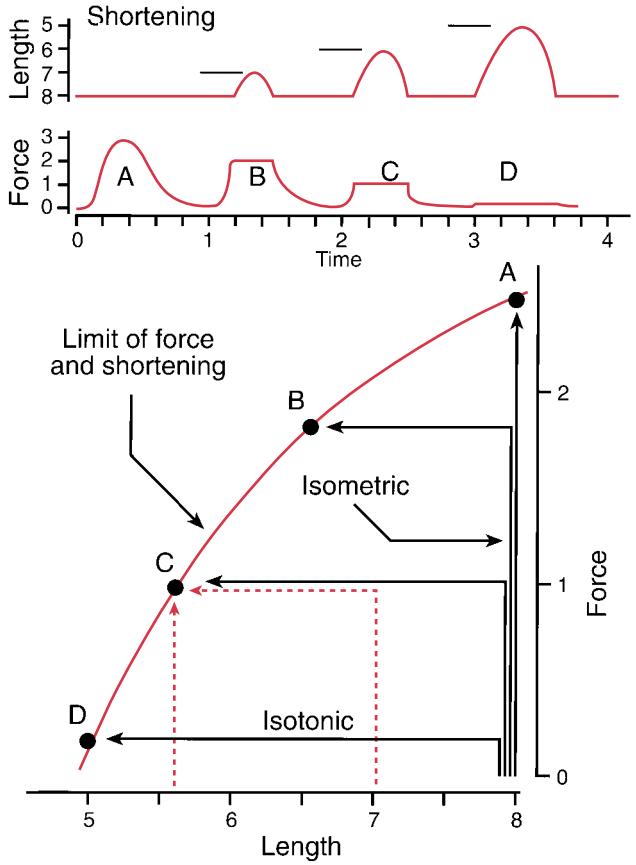

FIGURE 9.12 **The relationship between isotonic and isometric contractions.** The top graphs show the contractions from Figure 9.11, with different amounts of shortening. The bottom graph shows, for contractions B, C, and D, the initial portion is isometric (the line moves upward at constant length) until the afterload force is reached. The muscle then shortens at the afterload force (the line moves to the left) until its length reaches a limit determined (at least approximately) by the isometric length-tension curve. The dotted lines show that the same final force/length point can be reached by several different approaches. Relaxation data, not shown on the graph, would trace out the same pathways in reverse. (Force, length, and time units are arbitrary.)

and length are of critical importance in functional adjustment of the beating heart (see Chapter 10).

The Anatomic Arrangement of Muscle Is a Prime Determinant of Function

Anatomic location places restrictions on muscle function by limiting the amount of shortening or determining the kinds of loads encountered. Skeletal muscle is generally attached to bone, and bones are attached to each other. Because of the way the muscles are attached and the skeleton is articulated, the bones and muscles together constitute a **lever system**. This arrangement influences the physiology of the muscles and the functioning of the body as a whole. In most cases, the system works at a **mechanical disadvantage** with respect to the force exerted. The shortening capability of skeletal muscle by itself is rather limited, and the

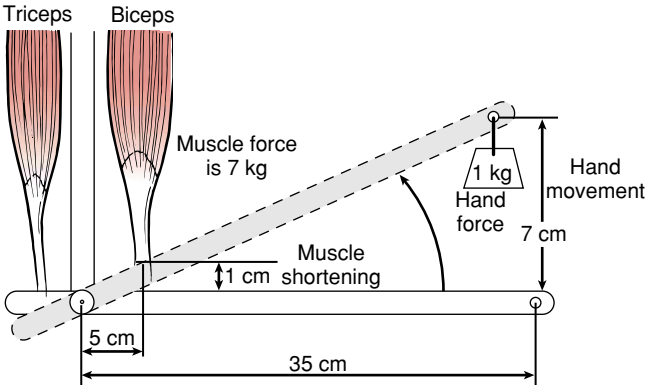

FIGURE 9.13 **Antagonistic pairs and the lever system of skeletal muscle.** Contraction of the biceps muscle lifts the lower arm (flexion) and elongates the triceps, while contraction of the triceps lowers the arm and hand (extension) and elongates the biceps. The bones of the lower arm are pivoted at the elbow joint (the fulcrum of the lever); the force of the biceps is applied through its tendon close to the fulcrum; the hand is 7 times as far away from the elbow joint. Thus, the hand will move 7 times as far (and fast) as the biceps shortens (lever ratio, 7:1), but the biceps will have to exert 7 times as much force as the hand is supporting.

skeletal lever system multiplies the distance over which an extremity can be moved (Fig. 9.13). However, this means the muscle must exert a much greater force than the actual weight of the load being lifted (the muscle force is increased by the same ratio that the length change at the end of the extremity is increased). In the case of the human forearm, the biceps brachii, when moving a force applied to the hand, must exert a force at its insertion on the radius that is approximately 7 times as great. However, the resulting movement of the hand is approximately 7 times as far and 7 times as rapid as the shortening of the muscle itself. Muscles may be subject to large forces and this can lead to muscle injury (see Clinical Focus Box 9.2).

Acting independently, a muscle can only shorten, and the force to relengthen it must be provided externally. These actions are achieved by the arrangement of muscles into **antagonistic pairs** of **flexors** and **extensors**. For example, the shortening of the biceps is countered by the action of the triceps; the triceps, in turn, is relengthened by contraction of the biceps. In some cases, gravity provides the restoring force.

Metabolic and Structural Adaptations Fit Skeletal Muscle for a Variety of Roles

Specific skeletal muscles are adapted for specialized functions. These adaptations involve primarily the structures and chemical reactions that supply the contractile system with energy. The enzymatic properties (i.e., the rate of ATP hydrolysis) of actomyosin ATPase also vary. The basic structural features of the sarcomeres and the thick/thin filament interactions are, however, essentially the same among the types of skeletal muscle.

Chapter 8 detailed the biochemical reactions responsible for providing ATP to the contractile system. Recall that

CLINICAL FOCUS BOX 9.2

Strain Injuries to Muscle

Skeletal muscle is subject to being damaged in several ways. In accidents that result in crushing or laceration, considerable muscle damage can occur. However, damage directly related to the contractile function of muscle is also possible. Such injuries are incidental to the muscle's primary function of exerting force and causing motion. In the areas of sports or physical labor, muscle strain is the most common type of injury.

The muscles most susceptible to injury are those of the limbs, especially those that go from joint to joint (e.g., the gastrocnemius or the rectus femoris) or that have a complex architecture (e.g., the adductor longus and, again, the rectus femoris). Often the injury will be confined to one muscle of a group used to perform a specific action. Injury can occur to a muscle that is overstretched while unstimulated, but most injuries occur during eccentric contraction, that is, during the forced extension of an activated muscle. Under such circumstances, the force in the muscle may rise to a level considerably higher than could be attained in an isometric contraction; relatively few injuries occur under isometric or isotonic (concentric) contraction conditions. The site of injury is most often at the myotendinous junction, a location that can be determined by physical examination and confirmed by magnetic resonance imaging (MRI) or by a computed tomography (CT) scan. There may also be extensive damage throughout the muscle itself. In some cases, there is complete disruption of the muscle (avulsion), although usually separation is not complete. Symptoms of a muscle strain injury include obvious soreness, weakness, delayed swelling, and "bunching up" in extreme cases.

Several predisposing factors may cause a muscle strain injury, including relative weakness of a given muscle, resulting from a lack of training early in a sports season, and fatigue, which leads to increased injury late in an athletic event. In general, factors that make a muscle less able to contract also predispose it to strain injury; laboratory experiments have shown that muscles in better physical condition are better able to safely absorb the energy that leads to injury. Retraining too rapidly or too soon after an injury or returning to activity too soon also make reinjury more likely.

Delayed-onset muscle soreness, as often experienced after unaccustomed exercise, also results from strain injury, but on a smaller scale. Muscle subjected to overload during eccentric contraction shows reduced contractile ability and ultrastructural damage to the contractile elements, especially at the Z lines. The pain peaks 1 to 2 days after exercise; as the healing progresses, the muscle becomes more able to withstand microinjury. Repeated bouts of exercise are tolerated increasingly well and are associated with the hypertrophy of the muscle; hence, the familiar phrase, "No pain, no gain."

Treatments for muscle strain injury are rather limited. They include the application of ice packs and enforced rest of the injured muscle. Nonsteroidal anti-inflammatory drugs (NSAIDs) can lessen the pain, but they also appear to delay healing somewhat. For injuries in which an actual separation of the muscle and tendon occurs, surgical repair is necessary. Massaging of an injured muscle does not appear to be as beneficial as light exercise, which may help to increase blood flow and promote healing. Recovery from strain injury is associated with the gradual regaining of strength, which will eventually reach near-normal levels if reinjury is avoided. Some muscle tissue is permanently replaced with scar tissue, which may change the geometry of the muscle. Most recovered muscles will have a somewhat increased susceptibility to injury for an extended period of time.

Precautions for avoiding strain injury include adequate physical conditioning and practiced expertise at the task at hand. Preexercise stretching and warm-up may be of some value in preventing strain injury, although the experimental evidence is equivocal.

muscle fibers contain both **glycolytic** (anaerobic) and **oxidative** (aerobic) metabolic pathways, which differ in their ability to produce ATP from metabolic fuels, particularly glucose and fatty acids. Among muscle fibers, the relative importance of each pathway and the presence or absence of associated supporting organelles and structures vary. These variations form the basis for the classification of skeletal muscle fiber types (Table 9.1). A typical skeletal muscle usually contains a mixture of fiber types, but in most muscles a particular type predominates. The major classification criteria are derived from mechanical measurements of muscle function and histochemical staining techniques in which dyes for specific enzymatic reactions are used to identify individual fibers in a muscle cross section.

Red Muscle Fibers and Aerobic Metabolism. The color differences of skeletal muscles arise from differences in the amount of **myoglobin** they contain. Similar to the related red blood cell protein hemoglobin, myoglobin can bind, store, and release oxygen. It is abundant in muscle fibers that depend heavily on aerobic metabolism for their ATP supply, where it facilitates oxygen diffusion (and serves as a minor auxiliary oxygen source) in times of heavy demand. Red muscle fibers are divided into **slow-twitch fibers** and **fast-twitch fibers** on the basis of their contraction speed (see Table 9.1). The differences in rates of contraction (shortening velocity or force development) arise from differences in actomyosin ATPase activity (i.e., in the basic crossbridge cycling rate). Mitochondria are abundant in these fibers because they contain the enzymes involved in aerobic metabolism.

White Muscle Fibers and Anaerobic Metabolism. White muscle fibers, which contain little myoglobin, are fast-twitch fibers that rely primarily on glycolytic metabolism. They contain significant amounts of stored **glycogen**, which can be broken down rapidly to provide a quick source of energy. Although they contract rapidly and powerfully, their endurance is limited by their ability to sustain an oxygen deficit (i.e., to tolerate the buildup of lactic acid). They require a period of recovery (and a supply of oxygen) after heavy use. White muscle fibers have fewer

TABLE 9.1 Classification of Skeletal Muscle Fiber Types

	Fast Twitch		Slow Twitch
Metabolic Type	Fast Glycolytic (White)	Fast Oxidative-Glycolytic (Red)	Slow Oxidative (Red)
Metabolic properties			
ATPase activity	High	High	Low
ATP source(s)	Anaerobic glycolysis	Anaerobic glycolysis/ Oxidative phosphorylation	Oxidative phosphorylation
Glycolytic enzyme content	High	Moderate	Low
Number of mitochondria	Low	High	High
Myoglobin content	Low	High	High
Glycogen content	High	Moderate	Low
Fatigue resistance	Low	Moderate	High
Mechanical properties			
Contraction speed	Fast	Fast	Slow
Force capability	High	Medium	Low
SR Ca^{2+}-ATPase activity	High	High	Moderate
Motor axon velocity	100 m/sec	100 m/sec	85 m/sec
Structural properties			
Fiber diameter	Large	Moderate	Small
Number of capillaries	Few	Many	Many
Functional role in body	Rapid and powerful movements	Medium endurance	Postural/endurance
Typical example	Latissimus dorsi	Mixed-fiber muscle, such as vastus lateralis	Soleus

mitochondria than red muscle fibers because the reactions of glycolysis take place in the myoplasm. There are indications that enzymes of the glycolytic pathway may be closely associated with the thin filament array.

Red and White Fibers and Muscle Function. The relative proportions of red and white muscle fibers fit muscles for different uses in the body. Muscles containing primarily slow-twitch oxidative red fibers are specialized for functions requiring slow movements and endurance, such as the maintenance of posture. Muscles containing a preponderance of fast-twitch red fibers support faster and more powerful contractions. They also typically contain varying numbers of fast-twitch white fibers; their resulting ability to use both aerobic and anaerobic metabolism increases their power and speed. Muscles containing primarily fast-twitch white fibers are suited for rapid, short, powerful contractions.

Fast muscles, both white and red, not only contract rapidly but also relax rapidly. Rapid relaxation requires a high rate of calcium pumping by the SR, which is abundant in these muscles. In such muscles, the energy used for calcium pumping can be as much as 30% of the total consumed. Fast muscles are supplied by large motor axons with high conduction velocities; this correlates with their ability to make quick and rapidly repeated contractions.

Muscle Fatigue. During a period of heavy exercise, especially when working above 70% of maximal aerobic capacity, skeletal muscle is subject to **fatigue.** The speed and force of contraction are diminished, relaxation time is prolonged, and a period of rest is required to restore normal function. While there is a close correlation between the oxidative capacity of a particular muscle fiber type and its fatigue resistance, chemical measurements of fatigued skeletal muscle specimens have shown that the ATP content, while reduced, is not completely exhausted. In well-motivated subjects, CNS factors do not appear to play an important role in fatigue, and transmission at the neuromuscular junction has such a large safety factor that impaired transmission also does not contribute to fatigue.

Studies on isolated muscle have distinguished two different mechanisms producing fatigue. Stimulation of the muscle at a rate far above that necessary for a fused tetanus quickly produces **high-frequency stimulation fatigue;** recovery from this condition is rapid (a few tens of seconds). In this type of fatigue, the principal defect seems to be a failure in T tubule action potential conduction, which leads to less Ca^{2+} release from the SR. Under most *in vivo* circumstances, feedback mechanisms in neural motor pathways work to reduce the stimulation to the minimum necessary for a smooth tetanus, and this type of fatigue is probably not often encountered.

Prolonged or repeated tetanic stimulation produces a longer-lasting fatigue with a longer recovery time. This type of fatigue—**low-frequency stimulation fatigue**—is related to the muscle's metabolic activities. The buildup of metabolites produced by crossbridge cycling, especially inorganic phosphate (P_i) and H^+ ions, reduces calcium sensitivity of the myofilaments and the contractile force generated per crossbridge. The reduced amount of metabolic energy available to the calcium transport system in the SR leads to reduced Ca^{2+} pumping. As a result, relaxation time increases and there is less Ca^{2+} available to activate the contraction with each stimulus, resulting in lowered peak force.

PROPERTIES OF SMOOTH MUSCLE

The properties of skeletal muscle described thus far apply in a general way to smooth muscle. Many of the basic muscle properties are highly modified in smooth muscle, however, because of the very different functional roles it plays in the body. The adaptations of smooth muscle structure and function are best understood in the context of the special requirements of the organs and systems of which smooth muscle is an integral component. Of particular importance are the high metabolic economy of smooth muscle, which allows it to remain contracted for long periods with little energy consumption, and the small size of its cells, which allows precise control of very small structures, such as blood vessels. Most smooth muscles are not discrete organs (like individual skeletal muscles) but are intimate components of larger organs. It is in the context of these specializations that the physiology of smooth muscle is best understood.

Structural Arrangements Equip Smooth Muscle for Its Special Roles

While there are major differences among the organs and systems in which smooth muscle plays a major part, the structure of smooth muscle is quite consistent at the tissue level and even more similar at the cellular level. Several typical arrangements of smooth muscle occur in a variety of locations.

The variety of smooth muscle tasks—regulating and promoting movement of fluids, expelling the contents of organs, moving visceral structures—is accomplished by a few basic types of tissue structures. All of these structures are subject, like skeletal muscle, to the requirement for antagonistic actions: If smooth muscle contracts, an external force must lengthen it again. The structures described below provide these restoring forces in a variety of ways.

Circular Organization: Blood Vessels. The simplest smooth muscle arrangement is found in the arteries and veins of the circulatory system. Smooth muscle cells are oriented in the circumference of a vessel so that shortening of the fibers results in reducing the vessel's diameter. This reduction may range from a slight narrowing to a complete obstruction of the vessel lumen, depending on the physiological needs of the body or organ. The orientation of the cells in the vessel walls is helical, with a very shallow pitch. In the larger muscular vessels, particularly arteries, there may be many layers of cells and the force of contraction may be quite high; in small arterioles, the muscle layer may consist of single cells wrapped around the vessel. The blood pressure provides the force to relengthen the cells in the vessel walls. This type of muscle organization is extremely important because the narrowing of a blood vessel has a powerful influence on the rate of blood flow through it (see Chapters 12 and 15). This circular arrangement is also prominent in the airways of the lungs, where it regulates the flow of air.

A further specialization of the circular muscle arrangement is a **sphincter,** a thickening of the muscular portion of the wall of a hollow or tubular organ, whose contraction has the effect of restricting flow or stopping it completely. Many sphincters, such as those in the gastrointestinal and urogenital tracts, have a special nerve supply and participate in complex reflex behavior. The muscle in sphincters is characterized by the ability to remain contracted for long periods with little metabolic cost.

Circular and Longitudinal Layers: The Small Intestine. Next, in order of complexity, is the combination of circular and longitudinal layers, as in the muscle of the small intestine. The outermost muscle layer, which is relatively thin, runs along the length of the intestine. The inner muscle layer, thicker and more powerful, has a circular arrangement. Coordinated alternating contractions and relaxations of these two layers propel the contents of the intestine, although most of the motive power is provided by circular muscle (see Chapter 26).

Complex Fiber Arrangements. The most complex arrangement of smooth muscle is found in organs such as the urinary bladder and uterus. Numerous layers and orientations of muscle fibers are present and the effect of their contraction is an overall reduction of the volume of the organ. Even with such a complex arrangement of fibers, coordinated and organized contractions take place. The relengthening force, in the case of these hollow organs, is provided by the gradual accumulation of contents. In the urinary bladder, for example, the muscle is gradually stretched as the emptied organ fills again.

In a few instances, smooth muscles are structurally similar to skeletal muscles in their arrangement. Some of the structures supporting the uterus, for example, are called ligaments; however, they contain large amounts of smooth muscle and are capable of considerable shortening. **Pilomotor muscles**, the small cutaneous muscles that erect the hairs, are also discrete structures whose shortening is basically unidirectional. Certain areas of mesentery also contain regions of linearly oriented smooth muscle fibers.

Small Cell Size Facilitates Precise Control

The most notable feature of smooth muscle tissue organization, in contrast to that of skeletal muscle, is the small size of the cells compared to the tissue they make up. Individual smooth muscle cells (depending somewhat on the type of tissue they compose) are 100 to 300 μm long and 5 to 10 μm in diameter. When isolated from the tissue, the cells are roughly cylindrical along most of their length and taper at the ends. The single nucleus is elongated and centrally located. Electron microscopy reveals that the cell margins contain many areas of small membrane invaginations, called **caveoli**, which may play a role in increasing the surface area of the cell (Fig. 9.14). Mitochondria are located at the ends of the nucleus and near the surface membrane. In some smooth muscle cells, the SR is abundant, although not to the extent found in skeletal muscle. In some cases, it closely approaches the cell membrane, but there is no organized T tubular system as in other types of muscle.

The bulk of the cell interior is occupied by three types of myofilaments: thick, thin, and intermediate. The thin filaments are similar to those of skeletal muscle but lack the

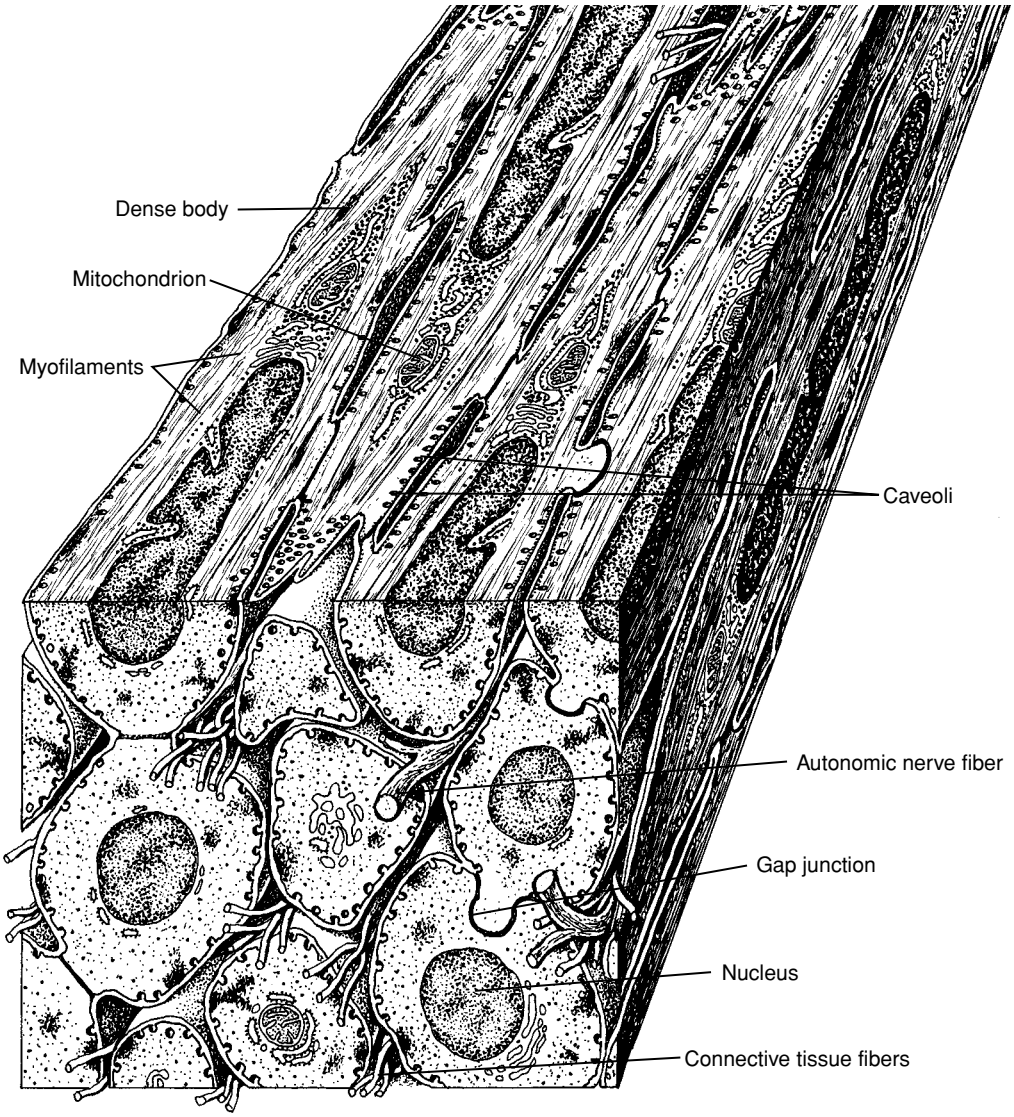

FIGURE 9.14 **A drawing from electron micrographs of smooth muscle, showing cells in cross section and longitudinal section.** (Adapted from Krstic RV. General Histology of the Mammal. New York, Springer-Verlag, 1984.)

troponin protein complex. The length of the individual filaments is not known with certainty because of their irregular organization. The thick filaments are composed of myosin molecules, as in skeletal muscle, but the details of the exact arrangement of the individual molecules into filaments are not completely understood. The thick filaments appear to be approximately 2.2 μm long, somewhat longer than in skeletal muscle (1.6 μm). The **intermediate filaments** are so named because their diameter of 10 nm is between that of the thick and thin filaments. Intermediate filaments appear to have a cytoskeletal, rather than a contractile, function. Prominent throughout the cytoplasm are small, dark-staining areas called **dense bodies.** They are associated with the thin and intermediate filaments and are considered analogous to the Z lines of skeletal muscle. Dense bodies associated with the cell margins are often called **membrane-associated dense bodies** (or **patches**) or **focal adhesions.** They appear to serve as anchors for thin filaments and to transmit the force of contraction to adjacent cells.

Smooth muscle lacks the regular sarcomere structure of skeletal muscle. Studies have shown some association among dense bodies down the length of a cell and a tendency of thick filaments to show a degree of lateral grouping. However, it appears that the lack of a strongly periodic arrangement of the contractile apparatus is an adaptation of smooth muscle associated with its ability to function over a wide range of lengths and to develop high forces despite a smaller cellular myosin content.

Mechanical Coupling. Because smooth muscle cells are so small compared to the whole tissue, some mechanical and electrical communication among them is necessary. Individual cells are coupled mechanically in several ways. A proposed arrangement of the smooth muscle contractile and force transmission system is shown in Figure 9.15. This

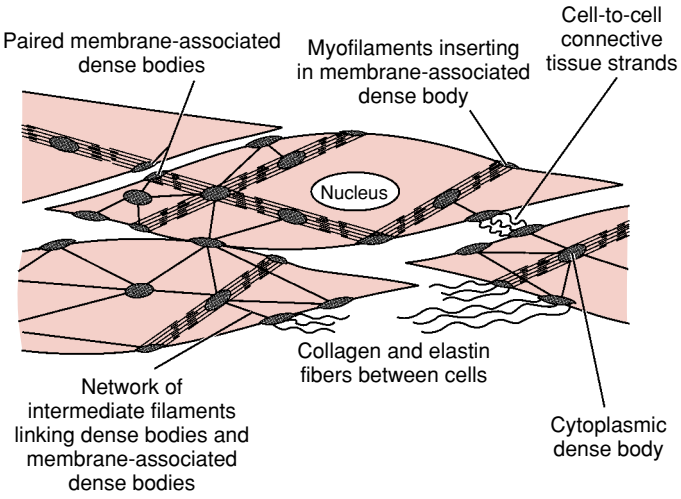

FIGURE 9.15 **The contractile system and cell-to-cell connections in smooth muscle.** Note regions of association between thick and thin filaments that are anchored by the cytoplasmic and membrane-associated dense bodies. A network of intermediate filaments provides some spatial organization (see, especially, the left side). Several types of cell-to-cell mechanical connections are shown, including direct connections and connections to the extracellular connective tissue matrix. Structures are not necessarily drawn to scale. (See text for details.)

picture represents a consensus from many researchers and areas of investigation. Note that assemblies of myofilaments are anchored within the cell by the dense bodies and at the cell margins by the membrane-associated dense bodies. The contractile apparatus lies oblique to the long axis of the cell. When single isolated smooth muscle cells contract, they undergo a "corkscrew" motion that is thought to reflect the off-axis orientation of the contractile filaments. In intact tissues, the connections to adjacent cells prevent this rotation.

Force appears to be transmitted from cell to cell and throughout the tissue in several ways. Many of the membrane-associated dense bodies are opposite one another in adjacent cells and may provide continuity of force transmission between the contractile apparatus in each cell. There are also areas of cell-to-cell contact, both lateral and end to end, where myofilament insertions are not apparent but where a direct transmission of force could occur. In some places, short strands of connective tissue link adjacent cells; in other places, cells are joined to the collagen and elastin fibers running throughout the tissue. These fibers, along with reticular connective tissue, comprise the **connective tissue matrix** or **stroma** found in all smooth muscle tissues. It serves to connect the cells and to give integrity to the whole tissue. In tissues that can resist considerable external force, this connective tissue matrix is well developed and may be organized into **septa**, which transmit the force of many cells.

Electrical Coupling. Smooth muscle cells are also coupled electrically. The structure most effective in this coupling is the **gap junction** (see Chapter 1). Gap junctions in smooth muscle appear to be somewhat transient structures that can form and disappear over time. In some tissues, this phenomenon is under hormonal control; in the uterus, for example, gap junctions are rare during most of pregnancy, and the contractions of the muscle are weak and lack coordination. However, just prior to the onset of labor, the number and size of gap junctions increase dramatically and the contractions become strong and well coordinated. Shortly after the cessation of labor, these gap junctions disappear and tissue function again becomes less coordinated.

Electrical coupling among smooth muscle cells is the basis for classifying smooth muscle into two major types:

- **Multiunit smooth muscle**, which has little cell-to-cell communication and depends directly on nerve stimulation for activation (like skeletal muscle). An example is the iris of the eye.
- **Unitary** or **single-unit smooth muscle**, which has a high degree of coupling among cells, so that large regions of tissue act as if they were a single cell. Its cells form a **functional syncytium** (an arrangement in which many cells behave as one). This type of smooth muscle makes up the bulk of the muscle in the visceral organs.

The Regulation and Control of Smooth Muscle Involve Many Factors

Smooth muscle is subject to a much more complex system of controls than skeletal muscle. In addition to contraction in response to nerve stimulation, smooth muscle responds to hormonal and pharmacological stimuli, the presence or lack of metabolites, cold, pressure, and stretch, or touch, and it may be spontaneously active as well. This multiplicity of controlling factors is vital for the integration of smooth muscle into overall body function. Skeletal muscle is primarily controlled by the CNS and by a relatively straightforward cellular control mechanism. The control of smooth muscle is much more closely related to the many factors that regulate the internal environment. It is not surprising, therefore, that many internal and external pathways have as their final effect the control of the interaction of smooth muscle contractile proteins.

Innervation of Smooth Muscle. Most smooth muscles have a nerve supply, usually from both divisions of the autonomic nervous system. There is much diversity in this area; the muscle response to a given neurotransmitter substance depends on the type of tissue and its physiological state. Smooth muscle does not contain the highly structured neuromuscular junctions found in skeletal muscle. Autonomic nerve axons run throughout the tissue; along the length of the axons are many swellings or **varicosities**, which are the sites of release of transmitter substances in response to nerve action potentials. Released molecules of excitatory or inhibitory transmitter diffuse from the nerve to the nearby smooth muscle cells, where they take effect. Since the cells are so small and numerous, relatively few are directly reached by the transmitters; those that are not reached are stimulated by cell-to-cell communication, as described above. Neuromuscular transmission in smooth muscle is a relatively slow process, and in many tissues, nerve stimulation serves mainly to modify (increase or decrease) spontaneous rhythmic mechanical activity.

Activation of Smooth Muscle Contraction. Chemical factors that control the function of smooth muscle cells most often have their first influence at the cell membrane. Some factors act by opening or closing cell membrane ion channels. Others result in production of a second messenger that diffuses to the interior of the cell, where it causes further changes (see Chapter 1). The final result of both mechanisms is usually a change in the intracellular concentration of Ca^{2+}, which, in turn, controls the contractile process itself.

The membrane potential of smooth muscle is subject to many external and internal influences, in contrast to the case in skeletal and cardiac muscle. In smooth muscle, the linkage between the electrical activity of the cell membrane and cellular functions, particularly contraction, is much more subtle and complex than in the other types of muscle.

The resting potential of most smooth muscles is approximately −50 mV. This is less negative than the resting potential of nerve and other muscle types, but here too it is determined primarily by the transmembrane potassium ion gradient. The smaller potential is due primarily to a greater resting permeability to sodium ions. In many smooth muscles, the resting potential varies periodically with time, producing a rhythmic potential change called a **slow wave** (see Chapter 26). Action potentials in smooth muscle also have a variety of forms. In many smooth muscles the action potential is a transient depolarization event lasting approximately 50 msec. At times, such action potentials will occur in rapid groups and produce repetitive membrane depolarizations that last for some time. Relatively rapid twitch-like contractions are usually the result of one or more action potentials. Sustained, low-level, partial contraction is often only loosely related to the electrical activity of the membrane.

The ionic basis of smooth muscle action potentials is complex because of the great variety of tissues, physiological conditions, and types of membrane channels. As a resting membrane potential of −50 mV results in the inactivation of typical fast sodium channels, sodium is usually not the major carrier of inward current during the action potential. In most cases, it has been shown that the rising (depolarizing) phase of a smooth muscle action potential is dominated by calcium, which enters through voltage-gated membrane channels. Repolarization current is carried by potassium ions, which leave through several types of channels, some voltage-controlled and others sensitive to the internal calcium concentration. These general ionic properties are typical of most smooth muscle types, although specific tissues may have variations within this general framework. The most important common feature is the entry of calcium ions during the action potential, since this inward flux is an important source of the calcium that controls the contractile process.

In addition to voltage-gated calcium channels, smooth muscle also contains receptor-activated calcium channels that are opened by the binding of hormones or neurotransmitters. One such ligand-gated channel in arterial smooth muscle is controlled by ATP, which acts as a transmitter substance in some types of smooth muscle tissues.

Smooth muscle can also be activated via the generation of second messengers, such as inositol 1,4,5-trisphosphate (IP_3) (see Chapter 1). This form of control involves chemical and hormonal activators and does not depend on membrane depolarization. The IP_3 causes the release of calcium from the SR, which initiates contraction.

The Role of Calcium in Smooth Muscle Contraction. All of the processes described above are ultimately concerned with the control of muscle contraction via the pool of intracellular calcium. Figure 9.16 summarizes these mechanisms in an overall picture of calcium regulation in smooth

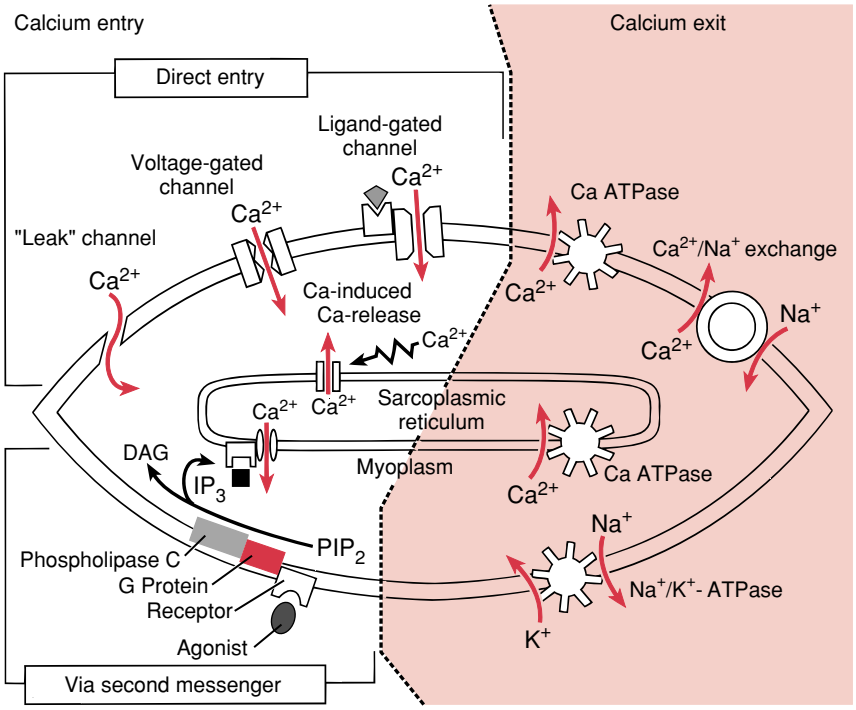

FIGURE 9.16 Major routes of calcium entry and exit from the cytoplasm of smooth muscle. The ATPase reactions are energy-consuming ion pumps. The processes on the left side increase cytoplasmic calcium and promote contraction; those on the right decrease internal calcium and cause relaxation. PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol.

muscle. These processes may be grouped into those concerned with **calcium entry**, intracellular **calcium liberation**, and **calcium exit** from the cell. Calcium enters the cell through several pathways, including voltage-gated and ligand-gated channels and a relatively small number of unregulated "**leak**" **channels** that permit the continual passive entry of small amounts of extracellular calcium. Within the cell, the major storage site of calcium is the SR; in some types of smooth muscle, its capacity is quite small and these tissues are strongly dependent on extracellular calcium for their function. Calcium is released from the SR by at least two mechanisms, including IP_3-induced release and via **calcium-induced calcium release**. In this latter mechanism, calcium that has entered the cell via a membrane channel causes additional calcium release from the SR, amplifying its activating effect.

Studies in which internal calcium is continuously measured while the muscle is stimulated to contract typically reveal a high level of internal calcium early in the contraction; this activating burst most likely originates from internal SR storage. The level then decreases somewhat, although during the entire contraction it is maintained at a significantly elevated level. This sustained calcium level is the result of a balance between mechanisms allowing calcium entry and those favoring its removal from the cytoplasm. Calcium leaves the myoplasm in two directions: A portion of it is returned to storage in the SR by an active transport system (a Ca^{2+}-ATPase); and the rest is ejected from the cell by two principal means. The most important of these is another ATP-dependent active transport system located in the cell membrane. The second mechanism, also located in the plasma membrane, is sodium-calcium exchange, a process in which the entry of three sodium ions is coupled to the extrusion of one calcium ion. This mechanism derives its energy from the large sodium gradient across the plasma membrane; thus, it depends critically on the operation of the cell membrane Na^+/K^+-ATPase. (The sodium-calcium exchange mechanism, relatively unimportant in smooth muscle, is of much greater consequence in cardiac muscle; see Chapter 10.)

Biochemical Control of Contraction and Relaxation. The contractile proteins of smooth muscle, like those of skeletal and cardiac muscle, are controlled by changes in the intracellular concentration of calcium ions. Likewise, the general features of the actin-myosin contraction system are similar in all muscle types. It is in the control of the contractile proteins themselves that important differences exist. Because the control of contraction in skeletal and cardiac muscle is associated with thin filament proteins, it is called **actin-linked regulation**. The thin filaments of smooth muscle lack troponin; control of smooth muscle contraction relies instead on the thick filaments and is, therefore, called **myosin-linked regulation**. In actin-linked regulation, the contractile system is in a constant state of **inhibited readiness** and calcium ions remove the inhibition. In the myosin-linked regulation of smooth muscle, the role of calcium is to cause **activation** of a resting state of the contractile system. The general outlines of this process are well understood and appear to apply to all types of smooth muscle, although a variety of secondary regulatory mechanisms are being found in different tissue types. This general scheme is shown in Figure 9.17.

When smooth muscle is at rest, there is little cyclic interaction between the myosin and actin filaments because of a special feature of its myosin molecules. As in skeletal muscle, the S2 portion of each myosin molecule (the paired "head" portion) contains four protein **light chains**. Two of these have a molecular weight of 16,000 and are called **essential light chains**; their presence is necessary for actin-myosin interaction, but they do not appear to participate in the regulatory process. The other two light chains have a molecular weight of 20,000 and are called **regulatory light chains**; their role in smooth muscle is critical. These chains contain specific locations (amino acid residues) to which the terminal phosphate group of an ATP molecule can be attached via the process of **phosphorylation**; the enzyme responsible for promoting this reaction is **myosin light-chain kinase** (MLCK). When the regulatory light chains are phosphorylated, the myosin heads can interact in a cyclic fashion with actin, and the reactions of the **crossbridge cycle** (and its mechanical events) take place much as in skeletal muscle. It is important to note that the ATP molecule that phosphorylates a myosin light chain is separate and distinct from the one consumed as an energy source by the mechanochemical reactions of the crossbridge cycle.

For myosin phosphorylation to occur, the MLCK must be activated, and this step is also subject to control. Closely associated with the MLCK is **calmodulin** (CaM), a smaller protein that binds calcium ions. When four calcium ions are bound, the CaM protein activates its associated MLCK and light-chain phosphorylation can proceed. It is this MLCK-activating step that is sensitive to the cytoplasmic calcium concentration; at levels below 10^{-7} M Ca^{2+}, no calcium is bound to calmodulin and no contraction can take place. When cytoplasmic calcium concentration is greater than 10^{-4} M, the binding sites on calmodulin are fully occupied, light-chain phosphorylation proceeds at maximal rate, and contraction occurs. Between these extreme limits, variations in the internal calcium concentration can cause corresponding gradations in the contractile force. Such modulation of smooth muscle contraction is essential for its regulatory functions, especially in the vascular system.

Smooth Muscle Relaxation. The biochemical processes controlling relaxation in smooth muscle also differ from those in skeletal and cardiac muscle, in which a state of inhibition returns as calcium ions are withdrawn from being bound to troponin. In smooth muscle, the phosphorylation of myosin is reversed by the enzyme **myosin light-chain phosphatase** (MLCP). The activity of this phosphatase appears to be only partially regulated; that is, there is always some enzymatic activity, even while the muscle is contracting. During contraction, however, MLCK-catalyzed phosphorylation proceeds at a significantly higher rate, and phosphorylated myosin predominates. When the cytoplasmic calcium concentration falls, MLCK activity is reduced because the calcium dissociates from the calmodulin, and myosin dephosphorylation (catalyzed by the phosphatase) predominates. Because dephosphorylated myosin has a low affinity for actin, the reactions of the crossbridge cycle can no longer take place. Relaxation is, thus, brought about by mechanisms that lower cytoplasmic calcium concentrations

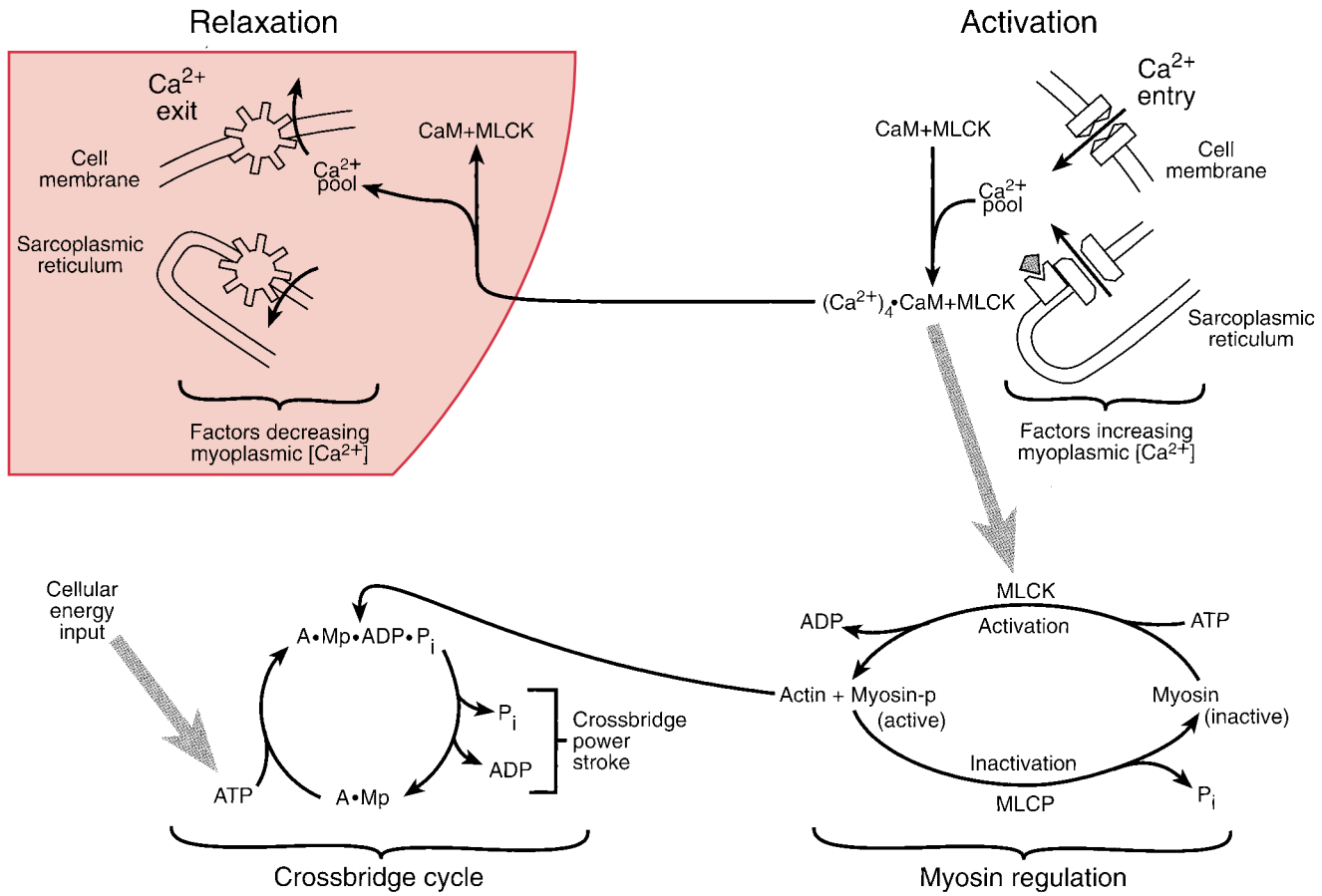

FIGURE 9.17 Reaction pathways involved in the basic regulation of smooth muscle contraction and relaxation. Activation begins (upper right) when cytoplasmic calcium levels are increased and calcium binds to calmodulin (CaM), activating the myosin light-chain kinase (MLCK). The kinase (lower right) catalyzes the phosphorylation of myosin, changing it to an active form (myosin-P or Mp). The phosphorylated myosin can then participate in a mechanical crossbridge cycle (lower left) much like that in skeletal muscle, although much slower. When calcium levels are reduced (upper left), calcium leaves calmodulin, the kinase is inactivated, and the myosin light-chain phosphatase (MLCP) dephosphorylates the myosin, making it inactive. The crossbridge cycle stops, and the muscle relaxes.

or decrease MLCK activity. Because of the importance of smooth muscle relaxation in physiological processes, this subject will be treated fully later in the chapter.

Secondary Mechanisms. In addition to myosin phosphorylation to control smooth muscle activation, secondary regulatory mechanisms are present in some types of smooth muscle. One of these provides long-term regulation of contraction in some tissues after the initial calcium-dependent myosin phosphorylation has activated the contractile system. For example, in vascular smooth muscle, the force of contraction may be maintained for long periods. This extended maintenance of force capability, called the **latch state,** appears to be related to a reduction in the cycling rate of crossbridges (possibly related to reduced phosphorylation) so that each remains attached for a longer portion of its total cycle. Even during the latch state, increased cytoplasmic calcium appears to be necessary for force to be maintained. Not all smooth muscle tissue can enter a latch state, however, and the details of the process are not completely understood.

Another possible secondary mechanism in some smooth muscle tissues involves the protein **caldesmon.** This molecule, also sensitive to the concentration of cytoplasmic calcium, is capable of binding to myosin at one of its ends and to actin and calmodulin at the other. While the process is not well understood, it is possible that caldesmon, under the control of calcium, could form crosslinks between actin and myosin filaments and, thus, aid in bearing force during a long-maintained contraction.

Other secondary regulatory mechanisms have been proposed. It is likely that several such mechanisms exist in various tissues, but the calcium-dependent phosphorylation of myosin light chains is the primary event in the activation of smooth muscle contraction.

Mechanical Activity in Smooth Muscle Is Adapted for Its Specialized Physiological Roles

The contraction of smooth muscle is much slower than that of skeletal or cardiac muscle; it can maintain contraction far

longer and relaxes much more slowly. The source of these differences lies largely in the chemistry of the interaction between actin and myosin of smooth muscle. Recall that the crossbridges of muscle form an actin-myosin enzyme system (actomyosin ATPase) that releases energy from ATP so that it may be converted into a mechanical contraction (i.e., tension or shortening). The inherent rate of this ATPase correlates strongly with the velocity of shortening of the intact muscle. Most smooth muscles require several seconds (or even minutes) to develop maximal isometric force. A smooth muscle that contracts 100 times more slowly than a skeletal muscle will have an actomyosin ATPase that is 100 times as slow. The major source of this difference in rates is the myosin molecules; the actin found in smooth and skeletal muscles is rather similar. There is a close association in smooth muscle between maximal shortening velocity and degree of myosin light-chain phosphorylation.

A high economy of tension maintenance, typically 300 to 500 times greater than that in skeletal muscle, is vital to the physiological function of smooth muscle. Economy, as used here, means the amount of metabolic energy input compared to the tension produced. In smooth muscle, there is a direct relationship between isometric tension and the consumption of ATP. The economy is related to the basic cycling rate of the crossbridges: Early in a contraction (while tension is being developed and the crossbridges are cycling more rapidly), energy consumption is about 4 times as high as in the later steady-state phase of the contraction. Compared with skeletal muscle, the crossbridge cycle in smooth muscle is hundreds of times slower, and much more time is spent with the crossbridges in the attached phase of the cycle.

The cycling crossbridges are not the only energy-utilizing system in smooth muscle. Because the cells are so small and numerous, smooth muscle tissue contains a large cell membrane area. Maintenance of the proper ionic concentrations inside the cells requires the activity of the membrane-based ion pumps for sodium/potassium and calcium, and this ion pumping requires a significant portion of the cell's energy supply. Internal pumping of calcium ions into the SR during relaxation also requires energy, and the processes that result in phosphorylation of the myosin light chains consume a further portion of the cellular energy, as do the other processes of cellular maintenance and repair. Smooth muscle contains both glycolytic and oxidative metabolic pathways, with the oxidative pathway usually the most important; under some conditions, a transition may temporarily be made from oxidative to glycolytic metabolism. In terms of the entire body economy, the energy requirements of smooth muscle are small compared with those of skeletal muscle, but the critical regulatory functions of smooth muscle require that its energy supply not be interrupted.

Modes of Contraction. Smooth muscle contractile activity cannot be divided clearly into twitch and tetanus, as in skeletal muscle. In some cases, smooth muscle makes rapid **phasic contractions**, followed by complete relaxation. In other cases, smooth muscle can maintain a low level of active tension for long periods without cyclic contraction and relaxation; a long-maintained contraction is called **tonus** (rather than tetanus) or a **tonic contraction**. This is typical of smooth muscle activated by hormonal, pharmacological, or metabolic factors, whereas phasic activity is more closely associated with stimulation by neural activity.

Comparison With Skeletal Muscle. The force-velocity curve for smooth muscle reflects the differences in crossbridge functions described previously. Although smooth muscle contains one-third to one-fifth as much myosin as skeletal muscle, the longer smooth muscle myofilaments and the slower crossbridge cycling rate allow it to produce as much force per unit of cross-sectional area as does skeletal muscle. Thus, the maximum values for smooth muscle on the force axis would be similar, while the maximum (and intermediate) velocity values are very different (Fig. 9.18). Furthermore, smooth muscle can have a set of

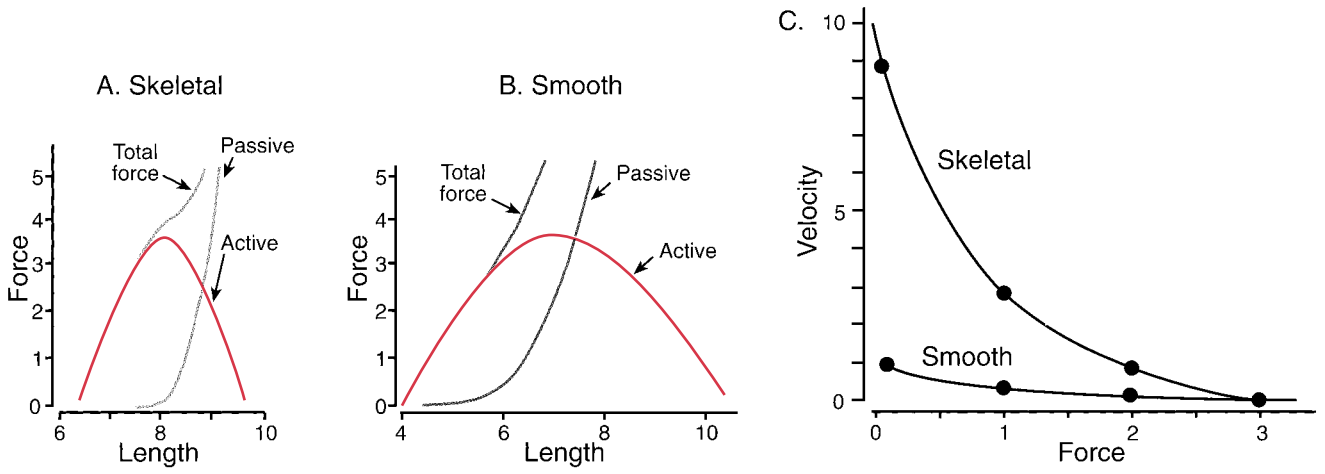

FIGURE 9.18 **Smooth and skeletal muscle mechanical characteristics compared.** A and B, Typical length-tension curves from skeletal and smooth muscle. Note the greater range of operating lengths for smooth muscle and the leftward shift of the passive (resting) tension curve. C, Skeletal and smooth muscle force-velocity curves. While the peak forces may be similar, the maximum shortening velocity of smooth muscle is typically 100 times lower than that of skeletal muscle. (Force and length units are arbitrary.)

force-velocity curves, each corresponding to a different level of myosin light-chain phosphorylation.

Other mechanical properties of smooth muscle are also related to its physiological roles. While its underlying cellular basis is uncertain, smooth muscle has a length-tension curve somewhat similar to that of skeletal muscle, although there are some significant differences (Fig. 9.18). At lengths at which the maximal isometric force is developed, many smooth muscles bear a substantial passive force. This is mostly a result of the network of connective tissue that supports the smooth muscle cells and resists overextension; in some cases, it may be partly a result of residual interaction between actin and attached but noncycling myosin crossbridges. Compared to skeletal and cardiac muscle, smooth muscle can function over a significantly greater range of lengths. It is not constrained by skeletal attachments, and it makes up several organs that vary greatly in volume during the course of their normal functioning. The shape of the length-tension curve can also vary with time and the degree of distension. For example, when the urinary bladder is highly distended by its contents, the peak of the active length-tension curve can be displaced to longer muscle lengths. This means that as the muscle shortens to expel the organ's contents, it can reach lengths at which it can no longer exert active force. After a period of recovery at this shorter length, the muscle can again exert sufficient force to expel the contents.

Stress Relaxation and Viscoelasticity. These reversible changes in the length-tension relationship are, at least in part, the result of **stress relaxation,** which characterizes **viscoelastic materials** such as smooth muscle. When a viscoelastic material is stretched to a new length, it responds initially with a significant increase in force; this is an **elastic response**, and it is followed by a decline in force that is initially rapid and then continuously slows until a new steady force is reached. If a viscoelastic material is subjected to a constant force, it will elongate slowly until it reaches a new length. This phenomenon, the complement of stress relaxation, is called **creep.** In smooth muscle organs, the abundant connective tissue prevents overextension.

The viscoelastic properties of smooth muscle allow it to function well as a reservoir for fluids or other materials; if an organ is filled slowly, stress relaxation allows the internal pressure to adjust gradually, so that it rises much less than if the final volume had been introduced rapidly. This process is illustrated in Figure 9.19 for the case of a hollow smooth muscle organ subjected to both rapid and slow infusions of liquid (since this is a hollow structure, internal pressure and volume are directly related to the force and length of the muscle fibers in the walls). The dashed lines in the top graphs denote the pressure that would result if the material were simply elastic rather than having the additional property of viscosity.

Some of the viscoelasticity of smooth muscle is a property of the extracellular connective tissue and other materials, such as the hyaluronic acid gel, present between the cells; some of it is inherent in the smooth muscle cells, probably because of the presence of noncycling crossbridges in resting tissue. One important feature of smooth muscle viscoelasticity is the tissue's ability to return to its original state following extreme extension. This capability

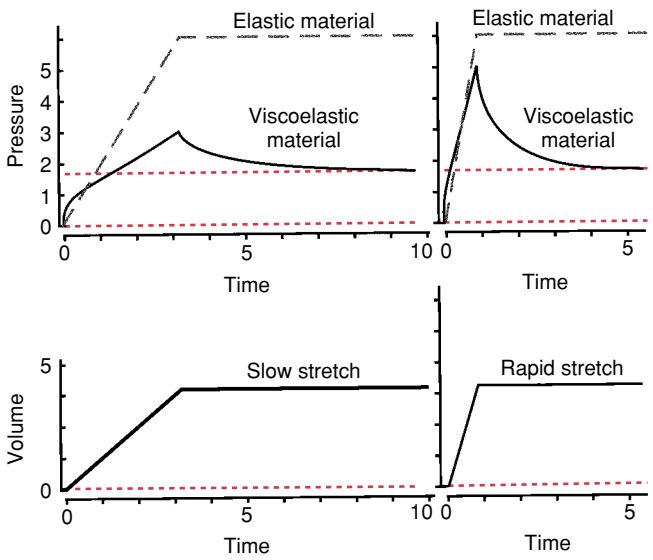

FIGURE 9.19 **Viscoelasticity.** The behavior of a viscoelastic material (e.g., the walls of a hollow, smooth muscle-containing organ) are subjected to slow (left) and rapid (right) elongation. The increase in force (or pressure) is proportional to the rate of extension, and at the end of the stretch, the force decays exponentially to a steady level. A purely elastic material (dashed line) maintains its force without stress relaxation.

is a result of the tonic contractile activity present in most smooth muscles under normal physiological conditions.

Other processes that are not yet well understood may also account for some of the length-dependent behavior of smooth muscle. In some smooth muscles, mechanical behavior in the later stages of a contraction depends strongly on the length at which the contraction began. This effect, called **plasticity** (not to be confused with nonrecoverable deformation), appears to arise from molecular rearrangements within the contractile protein array and may form the basis for both long- and short-term mechanical adaptation.

Modes of Relaxation. Relaxation is a complex process in smooth muscle. The central cause of relaxation is a reduction in the internal (cytoplasmic) calcium concentration, a process that is itself the result of several mechanisms. Electrical repolarization of the plasma membrane leads to a decrease in the influx of calcium ions, while the plasma membrane calcium pump and the sodium-calcium exchange mechanism (to a lesser extent) actively promote calcium efflux. Most important quantitatively is the uptake of calcium back into the SR. The net result of lowering the calcium concentration is a reduction in MLCK activity so that dephosphorylation of myosin can predominate over phosphorylation.

Biochemical Mechanisms. Both calcium uptake by the SR and the MLCK activity may be subject to another control mechanism called **β-adrenergic relaxation.** In some vascular smooth muscles, relaxation occurs in response to the presence of the hormone **norepinephrine.** Binding of this substance to cell membrane receptors causes the activation of **adenylyl cyclase** and the formation of cAMP (see

Chapter 1). Increased intracellular cAMP concentration is an effective promoter of relaxation in at least two major ways. The activity of the enzyme **cAMP-dependent protein kinase** increases as the concentration of cAMP rises. This enzyme (and perhaps also cAMP acting directly) enhances calcium uptake by the SR, resulting in a further lowering of the cytoplasmic calcium. At the same time, phosphorylation of MLCK (by the action of cAMP-dependent protein kinase) reduces its catalytic effectiveness, and myosin light-chain phosphorylation is decreased as if intracellular calcium had been lowered. Since many vascular muscles are continuously in a state of partial contraction, β-adrenergic relaxation is a physiologically important process in the adjustment of blood flow and pressure.

Another important relaxation pathway is present in the smooth muscle of small arteries (as well as other smooth muscle tissues). The lumen of arteries is lined with **endothelial cells**. In addition to their structural role, they serve as a controllable source of **nitric oxide** (NO), which was formerly known as endothelium-derived relaxing factor (EDRF) (see Chapter 1). The mechanical shearing effect of the flowing blood causes the endothelial cells to release NO; it is a small and highly diffusible molecule, and it quickly binds to membrane receptors on the vascular smooth muscle cells. This action results in a cascade of effects, the first of which is the stimulation of the enzyme **guanylyl cyclase**, which catalyzes the formation of **cyclic guanosine 3′,5′-monophosphate** (cGMP). By mechanisms similar to those in the case of cAMP, this leads to the activation of **cGMP-dependent protein kinase** (PKG), which affects several processes leading to relaxation. PKG promotes the reuptake of calcium ions, and it causes the opening of calcium-activated potassium ion channels in the cell membrane, leading to hyperpolarization and subsequent relaxation. PKG also blocks the activity of agonist-evoked **phospholipase C** (PLC), and this action reduces the liberation of stored calcium ions by IP_3. By mechanisms not well understood, cGMP reduces the calcium sensitivity of the myosin light-chain phosphorylation process, further promoting relaxation. Some drugs that relax vascular smooth muscle, such as **sodium nitroprusside**, work by mimicking the action of NO and causing similar intracellular events.

Mechanical Factors. Relaxation is obviously also a mechanical process. Contractile force decreases as cross-bridges detach and myofilaments become free again to slide past one another. Because most smooth muscle activity involves at least some shortening, relaxation must require elongation. As with other types of muscle, an external force must be applied for lengthening to occur. In the intestine, for example, material being propelled into a recently contracted region provides the extending force. Smooth muscle relaxation (or its absence) may have important indirect consequences. Hypertension, for example, can be caused by a failure of smooth muscle relaxation. In the uterus during labor, adequate relaxation between contractions is essential for the well-being of the fetus. During the contractions of labor, the muscular walls of the uterus become quite rigid and tend to compress the blood vessels that run through them. As a result, blood flow to the fetus is restricted, and failure of the muscle to relax adequately between contractions can result in fetal distress.

Adaptation to Changing Conditions.

Several external influences, some not well understood, affect the growth and functional adaptation of smooth muscle. Some of these changes are vital for normal body function, while others can be part of a disease process.

Hormone-Induced Hypertrophy. The uterus and associated tissues are under the influence of the female sex hormones (see Chapters 38 and 39). During pregnancy, high levels of progesterone, later followed by high estrogen levels, promote significant changes in uterine growth and control. The mass of muscle layers, known as the **myometrium**, increases as much as 70-fold, primarily through an increase in muscle cell size—**hypertrophy**—associated with a large increase in content of contractile proteins and associated regulatory proteins. The distension caused by the growing fetus also promotes hypertrophy. Extracellular connective tissue also increases. The number of cells increases as well, a condition called **hyperplasia.**

Throughout most of pregnancy the cells are poorly coupled electrically and contractile activity is not well coordinated. As pregnancy nears term, the large increase in the number of gap junctions permits coordinated contractions that culminate in the birth process. Following delivery and the consequent hormonal and mechanical changes, the processes leading to hypertrophy are reversed and the muscle reverts to its nonpregnant state.

Other Forms of Hypertrophy. Chronic obstruction of hollow smooth muscle organs (e.g., the urinary bladder, small intestine, portal vein) produces a chronically elevated internal pressure. This acts as a stimulus for smooth muscle hypertrophy, although the cellular mechanisms involved are not well understood. In addition to structural changes, there may be alterations of the metabolic activities, contractile properties, and response to agonists. Hyperplasia is also present to some degree in these muscle adaptations, but its relative contribution is difficult to ascertain experimentally. Nonmuscular components of the organ wall (e.g., connective tissue) are also increased. These changes, especially those involving the muscle cells, usually revert to near normal when the mechanical cause of the hypertrophy is removed.

Vascular smooth muscle, especially of the arteries, is also subject to hypertrophy (and hyperplasia) when it encounters a sustained pressure overload. This is an important factor in **hypertension** or high blood pressure. An increase in blood pressure, perhaps a result of chronically elevated sympathetic nervous system activity, may be present before smooth muscle hypertrophy occurs. Enlargement of the smooth muscle layer is a response to this stimulus, and there may be a trophic effect of the sympathetic nervous system activity as well. The resulting thickening of the vascular wall further reduces the lumen diameter, aggravating the hypertension. Lowering the blood pressure by therapeutic means can result in a return of the vessel walls to a near-normal state. Hypertension in the pulmonary vasculature is also associated with increased smooth muscle growth and with the development of smooth muscle cells in areas of the arterial system that do not normally have smooth muscle in their walls.

Under some circumstances, smooth muscle cells can

lose most of their contractile function and become synthesizers of collagen and accumulators of low-density lipoproteins. The loss of contractile activity is accompanied by a significant loss in the number of myofilaments. Such a **phenotypic transformation** takes place, for example, in the formation of atherosclerotic lesions in artery linings. While the factors involved in initiating and sustaining this reversible transition are not well understood, they appear to involve growth-promoting substances released from platelets following endothelial injury, while circulating heparin-like substances block the transformation.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

1. The endplate potential at the neuromuscular junction is the result of increased postsynaptic membrane permeability to
   (A) Sodium first, then potassium
   (B) Sodium and potassium simultaneously
   (C) Sodium only
   (D) Potassium only
2. The endplate potential differs from a muscle action potential in several ways. In which one of the following ways are they similar?
   (A) They are both actively propagated down the length of the muscle fiber
   (B) They both arise from changes in the permeability to sodium and potassium ions
   (C) They are both initiated by the flow of electrical (ionic) current
   (D) In both cases, the membrane potential becomes inside-positive
3. If transmission at the neuromuscular junction were blocked by the application of curare, which one of the events listed below would fail to occur when a motor nerve impulse arrived?
   (A) Depolarization of the postsynaptic membrane
   (B) Depolarization of the presynaptic membrane
   (C) Entry of calcium ions into the presynaptic terminal
   (D) Presynaptic release of transmitter substance
4. In a certain muscle, it takes 25 msec for a single twitch to develop its peak force in response to a single stimulus. If this muscle were stimulated with two stimuli spaced 15 msec apart, the result would be
   (A) A single twitch identical to the one-stimulus twitch
   (B) A contraction similar to a single twitch, but of higher amplitude
   (C) Two distinct contractions of very short duration
   (D) A failure of the muscle to contract at all
5. The factor most important in producing an isometric contraction is
   (A) Keeping the muscle from changing its length
   (B) Providing a stimulus adequate to activate all motor units
   (C) Determining the resting length of the muscle
   (D) Stimulating in a tetanic fashion to produce the maximal force
6. If a muscle is arranged so as to lift an afterload equal to one-half its maximal isometric capabilities, the ultimate force it develops is determined by the
   (A) Length of the muscle
   (B) Size of the afterload
   (C) Strength of the stimulation
   (D) Number of motor units activated
7. In a series of afterloaded isotonic twitches, as the load is increased, the
   (A) Force developed by the muscle increases and the shortening velocity decreases
   (B) Force developed by the muscle increases, while the velocity remains the same
   (C) Velocity increases to compensate for the increased afterload
   (D) Force developed is determined by the velocity of shortening
8. At which point along the isotonic force-velocity curve is the power output maximal?
   (A) At the lowest force and highest velocity (V_{max})
   (B) At the highest force and lowest velocity (F_{max})
   (C) At a force that is about one third of F_{max}
   (D) At a velocity that is about two thirds of V_{max}
9. Consider a load being lifted by a human hand. Because of the mechanical effects of the skeletal lever system, the biceps muscle exerts a force
   (A) Less than the load, but shortens at a higher velocity
   (B) Equal to the load, and shortens at a velocity equal to the load
   (C) Greater than the load, but shortens at a lower velocity
   (D) Independent of the load, and shortens at a velocity independent of the load
10. Muscles that are best suited for brief high-intensity exercise would contain which of the following types of fibers?
    (A) Mostly glycolytic (white)
    (B) Mostly slow-twitch oxidative (red)
    (C) A mix of slow twitch (red) and fast twitch (red)
    (D) A mix of glycolytic (white) and fast twitch (red)
11. Smooth muscles that are in the walls of hollow organs
    (A) Can shorten without developing force
    (B) Can develop force isometrically
    (C) Have no contractile function, but resist lengthening
    (D) Shorten as the volume of the organ increases
12. The relaxation of smooth muscle is associated with a reduction in free intracellular calcium ion concentration. The effect of the reduction is
    (A) Reestablishment of the inhibition of the actin-myosin interaction
    (B) Deactivation of the enzymatic activity of the individual actin molecules
    (C) Decreased phosphorylation of myosin molecules
    (D) Reduced contractile interaction by blocking the active sites of the myosin molecules
13. Which statement below most closely describes the role of calcium ions in the control of smooth muscle contraction?
    (A) Binding of calcium ions to regulatory proteins on thin filaments removes the inhibition of actin-myosin interaction
    (B) Binding of calcium ions to regulatory proteins associated with thick filaments, specifically calmodulin, activates the enzymatic activity of myosin molecules
    (C) Calcium ions serve as a direct inhibitor of the interaction of thick and thin filaments
    (D) A high concentration of calcium ions in the myofilament space is

(continued)

required to maintain muscle in a relaxed state

14. Compared with skeletal muscle, smooth muscle
    (A) Contracts more slowly, but exerts considerably more force
    (B) Contracts more rapidly, but exerts considerably less force
    (C) Maintains long-duration contractions economically
    (D) Exerts considerable force but can do little shortening
15. Compared with that of skeletal muscle, the crossbridge cycle of smooth muscle
    (A) Is similar, but runs in the reverse direction
    (B) Contains the same steps, but some of them are slower
    (C) Does not have a step in which actin and myosin are bound together
    (D) Can proceed without the consumption of ATP
16. Receptors in the smooth muscle cell membrane
    (A) Function only in combination with electrical activation
    (B) Cannot function if the cell is relaxed
    (C) Play a variety of regulatory roles
    (D) Control chemical activation, but do not affect electrical activation

SUGGESTED READING

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