Neuromuscular junctions (SEM)

CHAPTER 11

Muscular Tissue

CHAPTER OUTLINE

INSIGHTS

Brushing Up

To understand this chapter, it is important that you understand or brush up on the following concepts:

- Aerobic and anaerobic metabolism (p. 86)
- The functions of membrane proteins, especially receptors and ion gates (p. 100)
- Structure of a neuron (p. 175)
- General histology of the three types of muscle (p. 176)
- Desmosomes and gap junctions (p. 179)
- Connective tissues of a muscle (p. 326)

Movement is a fundamental characteristic of all living things, but reaches its highest development in animals because of their muscular tissue. Muscular tissue is composed of elongated cells that contract when stimulated. A muscle cell is essentially a device for converting the chemical energy of ATP into the mechanical energy of contraction. This chapter discusses contraction at the cellular and molecular levels and explains the basis of such aspects of muscle performance as warm-up, strength, endurance, and fatigue. These phenomena have obvious relevance to athletic performance, and they become very important when old age or lack of physical conditioning interferes with a person's ability to carry out everyday motor tasks. The effects of old age on the muscular system are discussed in chapter 29.

The three types of muscle tissue—*skeletal, cardiac,* and *smooth*—were described and compared in chapter 5. The expression "muscular system" refers only to skeletal muscle. This chapter is concerned primarily with the microscopic anatomy and physiology of skeletal muscle. Cardiac and smooth muscle are discussed more briefly to compare their properties and functions with skeletal muscle. Cardiac muscle is discussed more extensively in chapter 19.

Types and Characteristics of Muscular Tissue

Objectives

When you have completed this section, you should be able to

- describe the physiological properties that all muscle types have in common;
- list the defining characteristics of skeletal muscle; and
- describe the elastic functions of the connective tissue components of a muscle.

Universal Characteristics of Muscle

The functions of muscular tissue were detailed in the preceding chapter: movement, stability, communication, control of body openings and passages, and heat production. To carry out those functions, all muscular tissue has the following characteristics:

- **Responsiveness (excitability).** Responsiveness is a property of all living cells, but muscle and nerve cells have developed this property to the highest degree. When stimulated by chemical signals (neurotransmitters), stretch, and other stimuli, muscle cells respond with electrical changes across the plasma membrane.
- **Conductivity.** Stimulation of a muscle fiber produces more than a local effect. The local electrical change triggers a wave of excitation that travels rapidly along the muscle fiber and initiates processes leading to muscle contraction.
- **Contractility.** Muscle fibers are unique in their ability to shorten substantially when stimulated. This enables them to pull on bones and other tissues and create movement of the body and its parts.
- **Extensibility.** In order to contract, a muscle cell must also be extensible—able to stretch again between contractions. Most cells rupture if they are stretched even a little, but skeletal muscle fibers can stretch to as much as three times their contracted length.
- **Elasticity.** When a muscle cell is stretched and the tension is then released, it recoils to its original resting length. Elasticity, commonly misunderstood as the ability to stretch, refers to this tendency of a muscle cell (or other structures) to return to the original length when tension is released.

Skeletal Muscle

Skeletal muscle may be defined as voluntary striated muscle that is usually attached to one or more bones. A typical skeletal muscle cell is about 100 μm in diameter and 3 cm long; some are as thick as 500 μm and as long as 30 cm. Because of their extraordinary length, skeletal muscle cells are usually called *muscle fibers* or *myofibers.* A skeletal muscle fiber exhibits alternating light and dark transverse bands, or **striations,** that reflect the overlapping arrangement of the internal contractile proteins (fig. 11.1). Skeletal muscle is called **voluntary** because it is usually subject to conscious control. The other types of muscle are **involuntary** (not usually under conscious control), and they are never attached to bones.

Recall from chapter 10 that a skeletal muscle is composed not only of muscular tissue, but also of fibrous connective tissue: the *endomysium* that surrounds each muscle fiber, the *perimysium* that bundles muscle fibers together into fascicles, and the *epimysium* that encloses the entire muscle. These connective tissues are continuous with the collagen fibers of tendons and those, in turn,

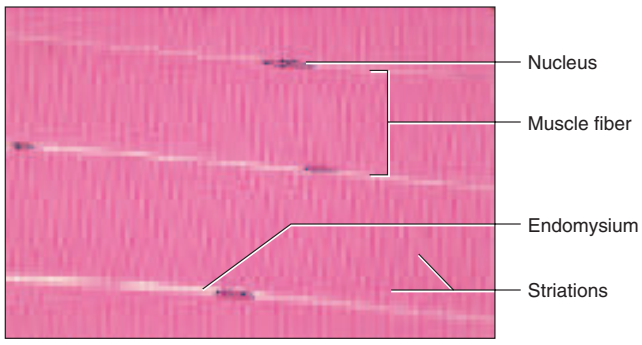


Figure 11.1 Skeletal Muscle Fibers. Note the striations.

with the collagen of the bone matrix. Thus, when a muscle fiber contracts, it pulls on these collagen fibers and moves a bone.

Collagen is not excitable or contractile, but it is somewhat extensible and elastic. It stretches slightly under tension and recoils when released. Because of this elasticity and because the connective tissue components are connected to each other in a linear series, the connective tissues are called the *series-elastic components* of a muscle. Their elasticity helps to return muscles to their resting lengths when contraction ceases. Elastic recoil of the tendons adds significantly to the power output and efficiency of the muscles.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. Define *responsiveness, conductivity, contractility, extensibility,* and *elasticity.* State why each of these properties is necessary for muscle function.
2. How is skeletal muscle different from the other types of muscle?
3. Why would the skeletal muscles perform poorly without their series-elastic components?

Microscopic Anatomy of Skeletal Muscle

Objectives

When you have completed this section, you should be able to

- describe the structural components of a muscle fiber;
- relate the striations of a muscle fiber to the overlapping arrangement of its protein filaments; and
- name the major proteins of a muscle fiber and state the function of each.

The Muscle Fiber

In order to understand muscle function, you must know how the organelles and macromolecules of a muscle fiber are arranged. Perhaps more than any other cell, a muscle fiber exemplifies the adage, Form follows function. It has a complex, tightly organized internal structure in which even the spatial arrangement of protein molecules is closely tied to its contractile function.

Muscle fibers have multiple flattened or sausage-shaped nuclei pressed against the inside of the plasma membrane. This unusual condition results from their embryonic development—several stem cells called **myoblasts**[1] fuse to produce each muscle fiber, with each myoblast contributing a nucleus to the mature fiber. Some myoblasts remain as unspecialized **satellite cells** between the muscle fiber and endomysium. When a muscle is injured, satellite cells can multiply and produce new muscle fibers to some degree. Most muscle repair, however, is by fibrosis rather than regeneration of functional muscle.

The plasma membrane, called the **sarcolemma,**[2] has tunnel-like infoldings called **transverse (T) tubules** that penetrate through the fiber and emerge on the other side. The function of a T tubule is to carry an electrical current from the surface of the cell to the interior when the cell is stimulated. The cytoplasm, called **sarcoplasm,** is occupied mainly by long protein bundles called **myofibrils** about 1 μm in diameter (fig. 11.2). Most other organelles of the cell, such as mitochondria and smooth endoplasmic reticulum (ER), are located between adjacent myofibrils. The sarcoplasm also contains an abundance of **glycogen,** which provides stored energy for the muscle to use during exercise, and a red pigment called **myoglobin,** which binds oxygen until it is needed for muscular activity.

The smooth ER of a muscle fiber is called **sarcoplasmic reticulum (SR).** It forms a network around each myofibril, and alongside the T tubules it exhibits dilated sacs called **terminal cisternae.** The SR is a reservoir for calcium ions; it has gated channels in its membrane that can release a flood of calcium into the cytosol, where the calcium activates the muscle contraction process.

Myofilaments

Let's return to the myofibrils just mentioned—the long protein cords that fill most of the muscle cell—and look at their structure at a finer, molecular level. It is here that the key to muscle contraction lies. Each myofibril is a bundle of parallel protein microfilaments called **myofilaments.** There are three kinds of myofilaments:

1. **Thick filaments** (fig. 11.3*a, b*) are about 15 nm in diameter. Each is made of several hundred molecules of a protein called **myosin.** A myosin molecule is shaped like a golf club, with two polypeptides intertwined to form a shaftlike *tail* and a double globular *head,* or *cross-bridge,* projecting from it at an angle. A thick filament may be likened to a bundle of 200 to 500 such "golf clubs," with their heads directed outward in a spiral array around the bundle. The heads on one half of the thick filament angle to the left, and the heads on the other half angle to the right; in the middle is a *bare zone* with no heads.
2. **Thin filaments** (fig. 11.3*c, d*), 7 nm in diameter, are composed primarily of two intertwined strands of a protein called **fibrous (F) actin.** Each F actin is like

[1] *myo* = muscle + *blast* = precursor

[2] *sarco* = flesh, muscle + *lemma* = husk

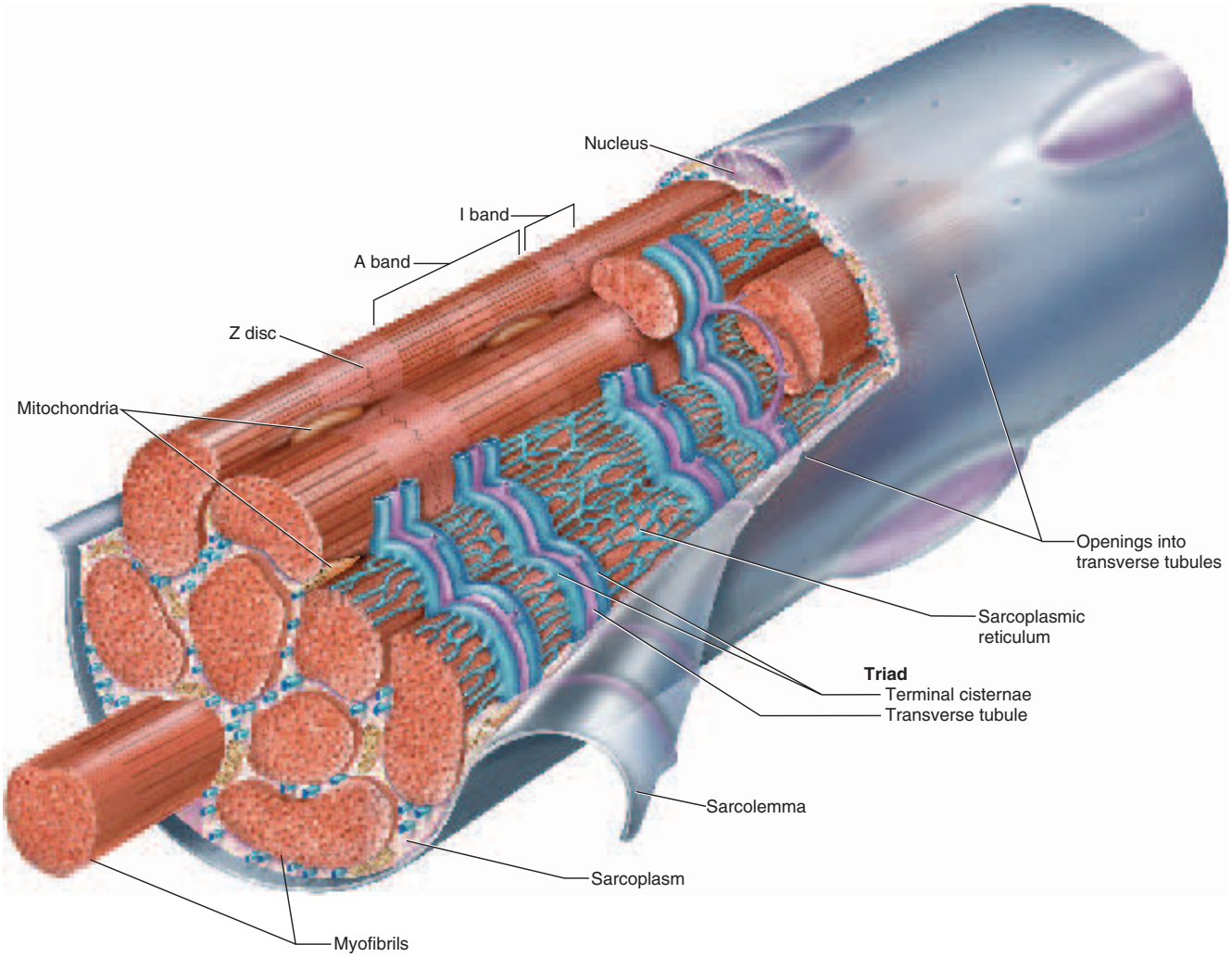


Figure 11.2 Structure of a Skeletal Muscle Fiber. This is a single cell containing 11 myofibrils (9 shown at the *left end* and 2 cut off at midfiber).

a bead necklace—a string of subunits called **globular (G) actin.** Each G actin has an **active site** that can bind to the head of a myosin molecule.

A thin filament also has 40 to 60 molecules of yet another protein called **tropomyosin.** When a muscle fiber is relaxed, tropomyosin blocks the active sites of six or seven G actins, and prevents myosin cross-bridges from binding to them. Each tropomyosin molecule, in turn, has a smaller calcium-binding protein called **troponin** bound to it.

3. **Elastic filaments** (fig. 11.4*b, c*), 1 nm in diameter, are made of a huge springy protein called **titin**[3] **(connectin).** They run through the core of a thick filament, emerge from the end of it, and connect it to a structure called the *Z disc,* explained shortly. They help to keep thick and thin filaments aligned with each other, resist overstretching of a muscle, and help the cell recoil to resting length after it is stretched.

Myosin and actin are called the **contractile proteins** of muscle because they do the work of shortening the muscle fiber. Tropomyosin and troponin are called the **regulatory proteins** because they act like a switch to determine when it can contract and when it cannot. Several clues as to how they do this may be apparent from what has already been said—calcium ions are released into the sarcoplasm to activate contraction; calcium binds to troponin; troponin is

[3] *tit* = giant + *in* = protein

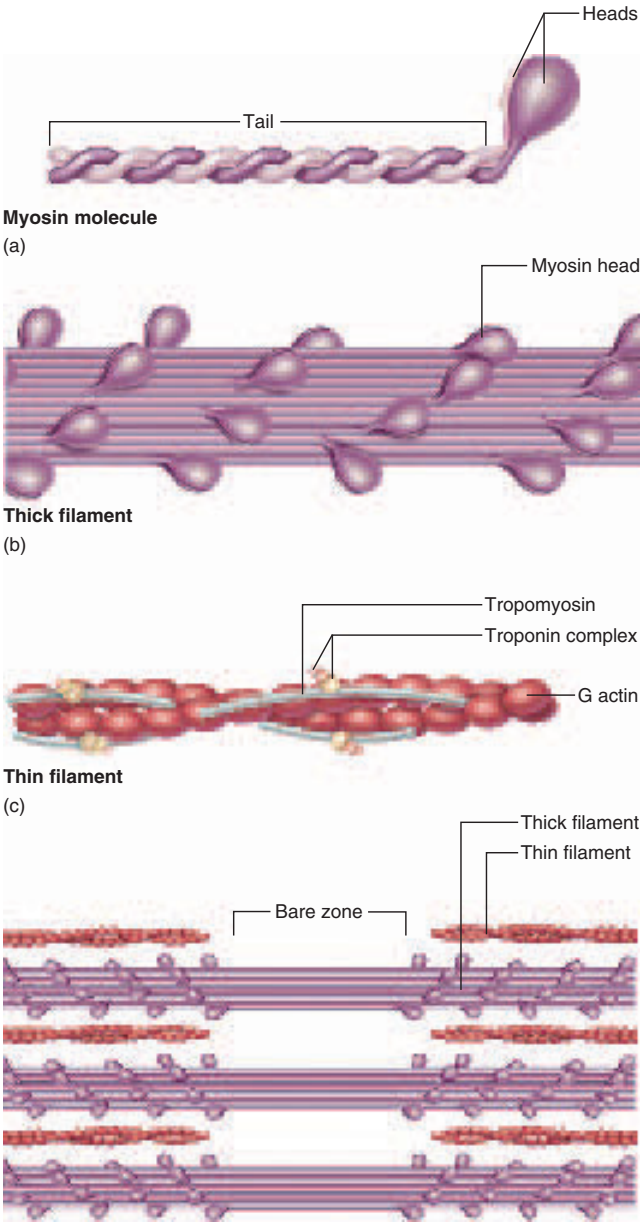


Figure 11.3 Molecular Structure of Thick and Thin Filaments. (*a*) A single myosin molecule consists of two intertwined polypeptides forming a filamentous tail and a double globular head. (*b*) A thick filament consists of 200 to 500 myosin molecules bundled together with the heads projecting outward in a spiral array. (*c*) A thin filament consists of two intertwined chains of G actin molecules, smaller filamentous tropomyosin molecules, and a three-part protein called troponin associated with the tropomyosin. (*d*) A region of overlap between the thick and thin filaments.

also bound to tropomyosin; and tropomyosin blocks the active sites of actin, so that myosin cannot bind to it when the muscle is not stimulated. Perhaps you are already forming some idea of the contraction mechanism to be explained shortly.

Striations

Myosin and actin are not unique to muscle; these proteins occur in all cells, where they function in cellular motility, mitosis, and transport of intracellular materials. In skeletal and cardiac muscle they are especially abundant, however, and are organized in a precise array that accounts for the striations of these two muscle types (fig. 11.4).

Striated muscle has dark **A bands** alternating with lighter **I bands.** (*A* stands for *anisotropic* and *I* for *isotropic,* which refers to the way these bands affect polarized light. To help remember which band is which, think "d*A*rk" and "l*I*ght.") Each A band consists of thick filaments lying side by side. Part of the A band, where thick and thin filaments overlap, is especially dark. In this region, each thick filament is surrounded by thin filaments. In the middle of the A band, there is a lighter region called the **H band,**[4] into which the thin filaments do not reach.

Each light I band is bisected by a dark narrow **Z disc**[5] (Z line) composed of the protein connectin. The Z disc provides anchorage for the thin filaments and elastic filaments. Each segment of a myofibril from one Z disc to the next is called a **sarcomere**[6] (SAR-co-meer), the functional contractile unit of the muscle fiber. A muscle shortens because its individual sarcomeres shorten and pull the Z discs closer to each other, and the Z discs are connected to the sarcolemma by way of the cytoskeleton. As the Z discs are pulled closer together during contraction, they pull on the sarcolemma to achieve overall shortening of the cell.

The terminology of muscle fiber structure is reviewed in table 11.1; this table may be a useful reference as you study the mechanism of contraction.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

4. What special terms are given to the plasma membrane, cytoplasm, and smooth ER of a muscle cell?
5. What is the difference between a myofilament and a myofibril?
6. List five proteins of the myofilaments and describe their physical arrangement.
7. Sketch the overlapping pattern of myofilaments to explain how they account for the A bands, I bands, H bands, and Z discs.

[4] H = *helle* = bright
[5] Z = *Zwichenscheibe* = "between disc"
[6] *sarco* = muscle + *mere* = part, segment

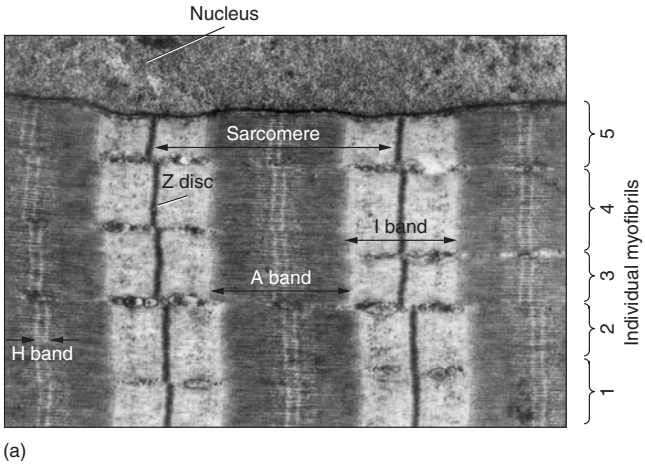


Figure 11.4 Muscle Striations and Their Molecular Basis. (*a*) Five myofibrils of a single muscle fiber, showing the striations in the relaxed state. (*b*) The overlapping pattern of thick and thin myofilaments that accounts for the striations seen in figure *a*. (*c*) The pattern of myofilaments in a contracting muscle fiber. Note that all myofilaments are the same length as before, but they overlap to a greater extent.

Which band narrows or disappears when muscle contracts?

The Nerve-Muscle Relationship

Objectives

When you have completed this section, you should be able to

- explain what a motor unit is and how it relates to muscle contraction;
- describe the structure of a junction where a nerve fiber meets a muscle fiber; and
- explain why a cell has an electrical charge difference across its plasma membrane and, in general terms, how this relates to muscle contraction.

Skeletal muscle never contracts unless it is stimulated by a nerve (or artificially with electrodes). If its nerve connections are severed or poisoned, a muscle is paralyzed. If innervation is not restored, the paralyzed muscle undergoes a shrinkage called *denervation atrophy.* Thus, muscle contraction cannot be understood without first understanding the relationship between nerve and muscle cells.

Motor Neurons

Skeletal muscles are innervated by *somatic motor neurons.* The cell bodies of these neurons are in the brainstem and spinal cord. Their axons, called **somatic motor fibers,** lead to the skeletal muscles. At its distal end, each somatic motor fiber branches about 200 times, with each branch leading to a different muscle fiber (fig. 11.5). Each muscle fiber is innervated by only one motor neuron.

The Motor Unit

When a nerve signal approaches the end of an axon, it spreads out over all of its terminal branches and stimulates all the muscle fibers supplied by them. Thus, these muscle fibers contract in unison. Since they behave as a single functional unit, one nerve fiber and all the muscle fibers innervated by it are called a **motor unit.** The muscle fibers of a single motor unit are not all clustered together but are dispersed throughout a muscle (fig. 11.6). Thus, when they are stimulated, they cause a weak contraction over a wide area—not just a localized twitch in one small region.

Earlier it was stated that a motor nerve fiber supplies about 200 muscle fibers, but this is just a representative number. Where fine control is needed, we have *small motor units.* In the muscles of eye movement, for example, there are only 3 to 6 muscle fibers per nerve fiber. Small motor units are not very strong, but they provide the fine degree of control needed for subtle movements. They also have small neurons that are easily stimulated. Where strength is more important than fine control, we have large motor units. The gastrocnemius muscle of the calf, for example, has about 1,000 muscle fibers per nerve fiber.

Table 11.1 Structural Components of a Muscle Fiber

Term	Definition
General Structure and Contents of the Muscle Fiber	
Sarcolemma	The plasma membrane of a muscle fiber
Sarcoplasm	The cytoplasm of a muscle fiber
Glycogen	An energy-storage polysaccharide abundant in muscle
Myoglobin	An oxygen-storing red pigment of muscle
T tubule	A tunnel-like extension of the sarcolemma extending from one side of the muscle fiber to the other; conveys electrical signals from the cell surface to its interior
Sarcoplasmic reticulum	The smooth ER of a muscle fiber; a Ca^{2+} reservoir
Terminal cisternae	The dilated ends of sarcoplasmic reticulum adjacent to a T tubule
Myofibrils	
Myofibril	A bundle of protein microfilaments (myofilaments)
Myofilament	A threadlike complex of several hundred contractile protein molecules
Thick filament	A myofilament about 11 nm in diameter composed of bundled myosin molecules
Elastic filament	A myofilament about 1 nm in diameter composed of a giant protein, titin, that emerges from the core of a thick filament and links it to a Z disc
Thin filament	A myofilament about 5 to 6 nm in diameter composed of actin, troponin, and tropomyosin
Myosin	A protein with a long shaftlike tail and a globular head; constitutes the thick myofilament
F actin	A fibrous protein made of a long chain of G actin molecules twisted into a helix; main protein of the thin myofilament
G actin	A globular subunit of F actin with an active site for binding a myosin head
Regulatory proteins	Troponin and tropomyosin, proteins that do not directly engage in the sliding filament process of muscle contraction but regulate myosin-actin binding
Tropomyosin	A regulatory protein that lies in the groove of F actin and, in relaxed muscle, blocks the myosin-binding active sites
Troponin	A regulatory protein associated with tropomyosin that acts as a calcium receptor
Titin	A springy protein that forms the elastic filaments and Z discs
Striations and Sarcomeres	
Striations	Alternating light and dark transverse bands across a myofibril
A band	Dark band formed by parallel thick filaments that partly overlap the thin filaments
H band	A lighter region in the middle of an A band that contains thick filaments only; thin filaments do not reach this far into the A band in relaxed muscle
I band	A light band composed of thin filaments only
Z disc	A protein disc to which thin filaments and elastic filaments are anchored at each end of a sarcomere; appears as a narrow dark line in the middle of the I band
Sarcomere	The distance from one Z disc to the next; the contractile unit of a muscle fiber

Large motor units are much stronger, but have larger neurons that are harder to stimulate, and they do not produce such fine control.

One advantage of having multiple motor units in a muscle is that they are able to "work in shifts." Muscle fibers fatigue when subjected to continual stimulation. If all of the fibers in one of your postural muscles fatigued at once, for example, you might collapse. To prevent this, other motor units take over while the fatigued ones rest, and the muscle as a whole can sustain long-term contraction. The role of motor units in muscular strength is discussed later in the chapter.

The Neuromuscular Junction

The functional connection between a nerve fiber and its target cell is called a **synapse** (SIN-aps). When the second cell is a muscle fiber, the synapse is called a **neuromuscular**

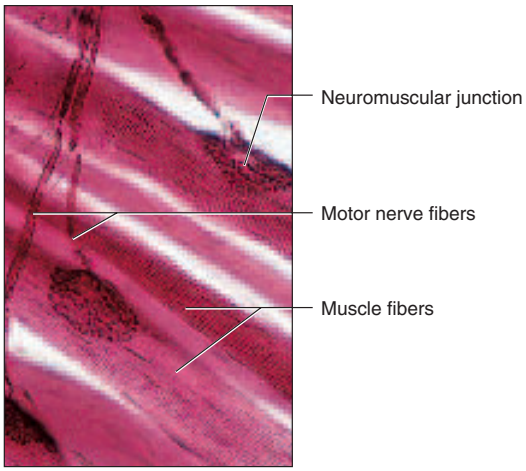


Figure 11.5 **Innervation of Skeletal Muscle.**

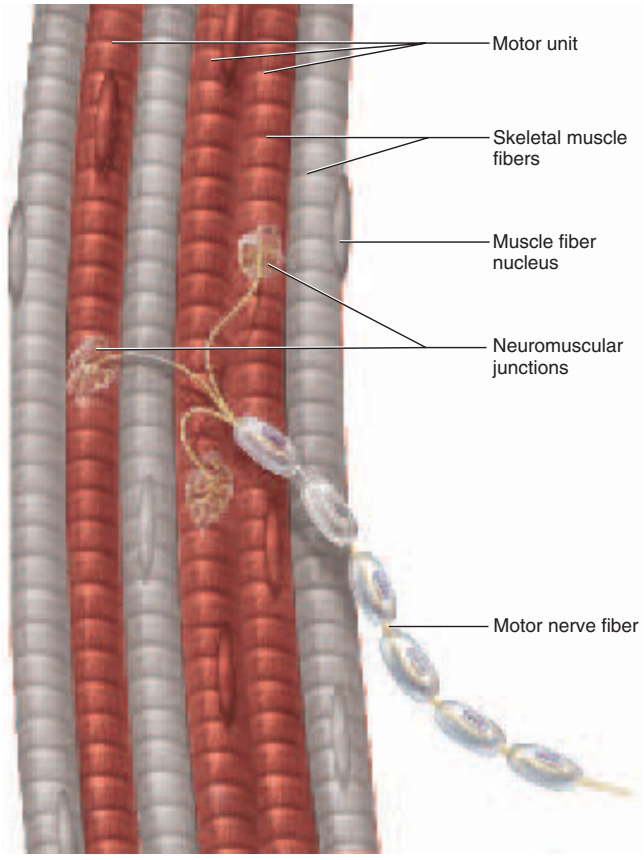


Figure 11.6 **A Motor Unit.** The motor nerve fiber shown here branches to supply those muscle fibers shown in color. The other muscle fibers *(gray)* belong to other motor units.

junction (fig. 11.7). Each branch of a motor nerve fiber ends in a bulbous swelling called a **synaptic** (sih-NAP-tic) **knob,** which is nestled in a depression on the sarcolemma called the **motor end plate.** The two cells do not actually touch each other but are separated by a tiny gap, the **synaptic cleft,** about 60 to 100 nm wide. A third cell, called a *Schwann cell,* envelops the entire neuromuscular junction and isolates it from the surrounding tissue fluid.

The electrical signal (nerve impulse) traveling down a nerve fiber cannot cross the synaptic cleft like a spark jumping between two electrodes—rather, it causes the nerve fiber to release a neurotransmitter that stimulates the next cell. Although many chemicals function as neurotransmitters, the one released at the neuromuscular junction is **acetylcholine** (ASS-eh-till-CO-leen) **(ACh).** ACh is stored in spherical organelles called **synaptic vesicles.**

Directly across from the synaptic vesicles, the sarcolemma of the muscle cell exhibits infoldings called *junctional folds,* about 1 μm deep. The muscle fiber has about 50 million membrane proteins called **ACh receptors,** which bind the acetylcholine release by the nerve fiber. Most ACh receptors are concentrated in and near these junctional folds. Very few ACh receptors are found anywhere else on a muscle fiber. Junctional folds increase the surface area for receptor sites and ensure a more effective response to ACh. The muscle nuclei beneath the junctional folds are specifically dedicated to the synthesis of ACh receptors and other proteins of the motor end plate. A deficiency of ACh receptors leads to muscle paralysis in the disease *myasthenia gravis* (see insight 11.4, p. 437).

The entire muscle fiber is surrounded by a *basal lamina* that passes through the synaptic cleft and virtually fills it. Both the sarcolemma and that part of the basal lamina in the cleft contain an enzyme called **acetylcholinesterase** (ASS-eh-till-CO-lin-ESS-ter-ase) **(AChE),** which breaks down ACh, shuts down the stimulation of muscle fibers, and allows a muscle to relax (see insight 11.1).

Insight 11.1 Clinical Application

Neuromuscular Toxins and Paralysis

Toxins that interfere with synaptic function can paralyze the muscles. Some pesticides, for example, contain *cholinesterase inhibitors* that bind to acetylcholinesterase and prevent it from degrading ACh. This causes *spastic paralysis,* a state of continual contraction of the muscle that poses the danger of suffocation if the laryngeal and respiratory muscles are affected. A person poisoned by a cholinesterase inhibitor must be kept lying down and calm, and sudden noises or other disturbances must be avoided. A minor startle response can escalate to dangerous muscle spasms in a poisoned individual.

Tetanus ("lockjaw") is a form of spastic paralysis caused by a toxin from the bacterium *Clostridium tetani.* In the spinal cord, an inhibitory neurotransmitter called glycine stops motor neurons from producing unwanted muscle contractions. The tetanus toxin blocks glycine release and thus allows overstimulation of the muscles. (At the cost of

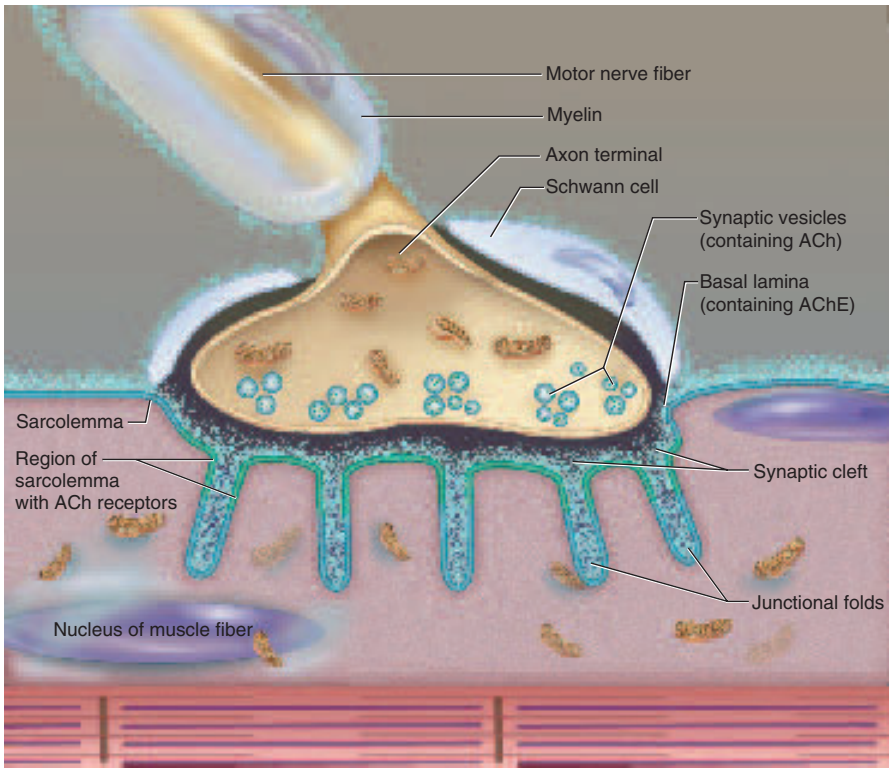


Figure 11.7 **A Neuromuscular Junction.**

some confusion, the word *tetanus* also refers to a completely different and normal muscle phenomenon discussed later in this chapter.)

Flaccid paralysis is a state in which the muscles are limp and cannot contract. It can cause respiratory arrest when it affects the thoracic muscles. Flaccid paralysis can be caused by poisons such as curare (cue-RAH-ree) that compete with ACh for receptor sites but do not stimulate the muscle. Curare is extracted from certain plants and used by some South American natives to poison blowgun darts. It has been used to treat muscle spasms in some neurological disorders and to relax abdominal muscles for surgery, but other muscle relaxants have now replaced curare for most purposes.

You must be very familiar with the foregoing terms to understand how a nerve stimulates a muscle fiber and how the fiber contracts. They are summarized in table 11.2 for your later reference.

Electrically Excitable Cells

Muscle fibers and neurons are regarded as *electrically excitable cells* because their plasma membranes exhibit voltage changes in response to stimulation. The study of the electrical activity of cells, called **electrophysiology,** is a key to understanding nervous activity, muscle contraction, the heartbeat, and other physiological phenomena. The details of electrophysiology are presented in chapter 12, but a few fundamental principles must be introduced here so you can understand muscle excitation.

In an unstimulated (resting) cell, there are more anions (negative ions) on the inside of the plasma membrane than on the outside. Thus, the plasma membrane is electrically **polarized,** or charged, like a little battery. In a resting muscle cell, there is an excess of sodium ions (Na^+) in the extracellular fluid (ECF) outside the cell and an excess of potassium ions (K^+) in the intracellular fluid (ICF) within the cell. Also in the ICF, and unable to penetrate the plasma membrane, are anions such as proteins, nucleic acids, and phosphates. These anions make the inside of the plasma membrane negatively charged by comparison to its outer surface.

A difference in electrical charge from one point to another is called an electrical potential, or voltage. The difference is typically 12 volts (V) for a car battery and 1.5 V

Table 11.2 Components of the Neuromuscular Junction

Term	Definition
Neuromuscular junction	A functional connection between the distal end of a nerve fiber and the middle of a muscle fiber; consists of a synaptic knob and motor end plate
Synaptic knob	The dilated tip of a nerve fiber that contains synaptic vesicles
Motor end plate	A depression in the sarcolemma, near the middle of the muscle fiber, that receives the synaptic knob; contains acetylcholine receptors
Synaptic cleft	A gap of about 60 to 100 nm between the synaptic knob and motor end plate
Synaptic vesicle	A secretory vesicle in the synaptic knob that contains acetylcholine
Junctional folds	Invaginations of the membrane of the motor end plate where ACh receptors are especially concentrated; located across from the active zones
Acetylcholine (ACh)	The neurotransmitter released by a somatic motor fiber that stimulates a skeletal muscle fiber (also used elsewhere in the nervous system)
ACh receptor	An integral protein in the sarcolemma of the motor end plate that binds to ACh
Acetylcholinesterase (AChE)	An enzyme in the sarcolemma and basal lamina of the muscle fiber in the synaptic region; responsible for degrading ACh and stopping the stimulation of the muscle fiber

for a flashlight battery, for example. On a sarcolemma of a muscle cell, the voltage is much smaller, about −90 millivolts (mV), but critically important to life. (The negative sign refers to the relative charge on the intracellular side of the membrane.) This voltage is called the **resting membrane potential (RMP).** It is maintained by the sodium-potassium pump, as explained in chapter 3.

When a nerve or muscle cell is stimulated, dramatic things happen electrically, as we shall soon see in our study of the excitation of muscle. Ion gates in the plasma membrane open and Na^+ instantly diffuses down its concentration gradient into the cell. These cations override the negative charges in the ICF, so the inside of the plasma membrane briefly becomes positive. Immediately, Na^+ gates close and K^+ gates open. K^+ rushes out of the cell, partly because it is repelled by the positive sodium charge and partly because it is more concentrated in the ICF than in the ECF, so it diffuses down its concentration gradient when it has the opportunity. The loss of positive potassium ions from the cell turns the inside of the membrane negative again. This quick up-and-down voltage shift, from the negative RMP to a positive value and then back to a negative value again, is called an **action potential.** The RMP is a stable voltage seen in a "waiting" cell, whereas the action potential is a quickly fluctuating voltage seen in an active, stimulated cell.

Action potentials have a way of perpetuating themselves—an action potential at one point on a plasma membrane causes another one to happen immediately in front of it, which triggers another one a little farther along, and so forth. A wave of action potentials spreading along a nerve fiber like this is called a *nerve impulse* or *nerve signal.* Such signals also travel along the sarcolemma of a muscle fiber. We will see shortly how this leads to muscle contraction. Chapter 12 explains the mechanism of action potentials more fully.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

8. What differences would you expect to see between one motor unit where muscular strength is more important than fine control and another motor unit where fine control is more important?
9. Distinguish between acetylcholine, an acetylcholine receptor, and acetylcholinesterase. State where each is found and describe the function it serves.
10. What accounts for the resting membrane potential seen in unstimulated nerve and muscle cells?
11. What is the difference between a resting membrane potential and an action potential?

Behavior of Skeletal Muscle Fibers

Objectives

When you have completed this section, you should be able to

- explain how a nerve fiber stimulates a skeletal muscle fiber;
- explain how stimulation of a muscle fiber activates its contractile mechanism;
- explain the mechanism of muscle contraction;
- explain how a muscle fiber relaxes; and
- explain why the force of a muscle contraction depends on its length prior to stimulation.

The process of muscle contraction and relaxation can be viewed as occurring in four major phases: (1) excitation, (2) excitation-contraction coupling, (3) contraction, and (4) relaxation. Each phase occurs in several smaller steps, which we now examine in detail. The steps are numbered in the following descriptions to correspond to those in figures 11.8 to 11.11.

Excitation

Excitation is the process in which action potentials in the nerve fiber lead to action potentials in the muscle fiber. The steps in excitation are shown in figure 11.8.

1. A nerve signal arrives at the synaptic knob and stimulates voltage-gated calcium channels to open. Calcium ions enter the synaptic knob.
2. Calcium ions stimulate exocytosis of the synaptic vesicles, which release acetylcholine (ACh) into the synaptic cleft. One action potential causes exocytosis of about 60 synaptic vesicles, and each vesicle releases about 10,000 molecules of ACh.
3. ACh diffuses across the synaptic cleft and binds to receptor proteins on the sarcolemma.
4. These receptors are *ligand-gated ion channels.* When ACh (the ligand) binds to them, they change shape and open an ion channel through the middle of the receptor protein. Each channel allows Na^+ to diffuse quickly into the cell and K^+ to diffuse outward. As a result of these ion movements, the sarcolemma reverses polarity—its voltage quickly jumps from the RMP of −90 mV to a peak of +75 mV as Na^+ enters, and then falls back to a level close to the RMP as K^+ diffuses out. This rapid fluctuation in membrane voltage at the motor end plate is called the **end-plate potential (EPP).**
5. Areas of sarcolemma next to the end plate have *voltage-gated ion channels* that open in response to the EPP. Some of the voltage-gated channels are specific for Na^+ and admit it to the cell, while others are specific for K^+ and allow it to leave. These ion movements create an *action potential.* The muscle fiber is now excited.

Think About It

An impulse begins at the middle of a 100-mm-long muscle fiber and travels 5 m/sec. How long would it take to reach the ends of the muscle fiber?

Excitation-Contraction Coupling

Excitation-contraction coupling refers to the events that link the action potentials on the sarcolemma to activation of the myofilaments, thereby preparing them to contract. The steps in the coupling process are shown in figure 11.9.

6. A wave of action potentials spreads from the end plate in all directions, like ripples on a pond. When this wave of excitation reaches the T tubules, it continues down them into the sarcoplasm.
7. Action potentials open voltage-regulated ion gates in the T tubules. These are physically linked to calcium channels in the terminal cisternae of the sarcoplasmic reticulum (SR), so gates in the SR open as well and calcium ions diffuse out of the SR, down their concentration gradient and into the cytosol.
8. The calcium ions bind to the troponin of the thin filaments.
9. The troponin-tropomyosin complex changes shape and shifts to a new position. This exposes the active sites on the actin filaments and makes them available for binding to myosin heads.

Contraction

Contraction is the step in which the muscle fiber develops tension and may shorten. (Muscles often "contract," or develop tension, without shortening, as we see later.) How a muscle fiber shortens remained a mystery until sophisticated techniques in electron microscopy enabled cytologists to see the molecular organization of muscle fibers. In 1954, two researchers at the Massachusetts Institute of Technology, Jean Hanson and Hugh Huxley, found evidence for a model now called the **sliding filament theory.** This theory holds that the thin filaments slide over the thick ones and pull the Z discs behind them, causing the cell as a whole to shorten. The individual steps in this mechanism are shown in figure 11.10.

10. The myosin head must have an ATP molecule bound to it to initiate the contraction process. **Myosin ATPase,** an enzyme in the head, hydrolyzes this ATP. The energy released by this process activates the head, which "cocks" into an extended, high-energy position. The head temporarily keeps the ADP and phosphate group bound to it.
11. The cocked myosin binds to an active site on the thin filament.
12. Myosin releases the ADP and phosphate and flexes into a bent, low-energy position, tugging the thin filament along with it. This is called the **power stroke.** The head remains bound to actin until it binds a new ATP.
13. Upon binding more ATP, myosin releases the actin. It is now prepared to repeat the whole process—it will hydrolyze the ATP, recock (the **recovery stroke**), attach to a new active site farther down the thin filament, and produce another power stroke.

It might seem as if releasing the thin filament at step 13 would simply allow it to slide back to its previous position, so that nothing would have been accomplished. Think of the sliding filament mechanism, however, as

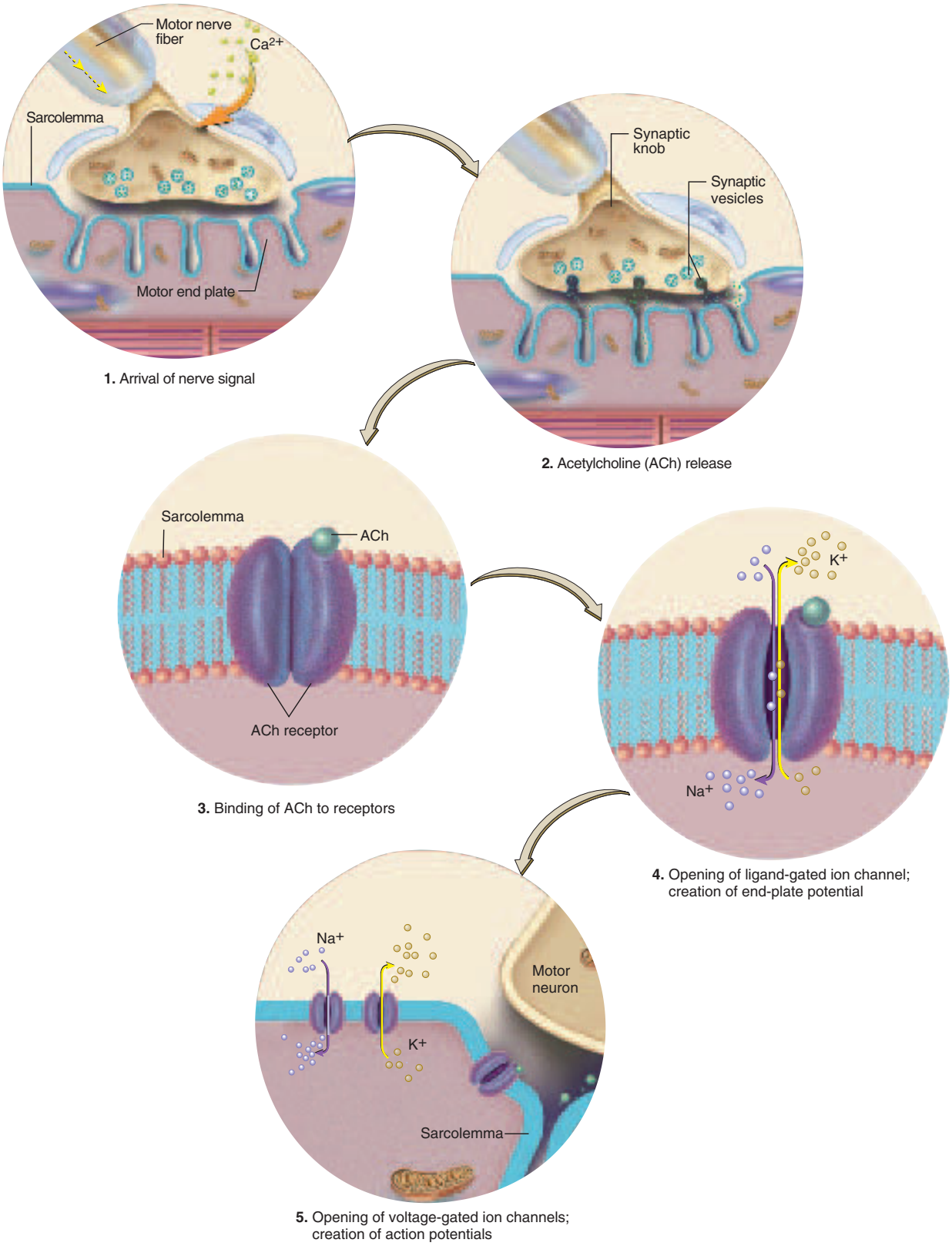


Figure 11.8 **Excitation of a Muscle Fiber.** These events link action potentials in a nerve fiber to the generation of action potentials in the muscle fiber.

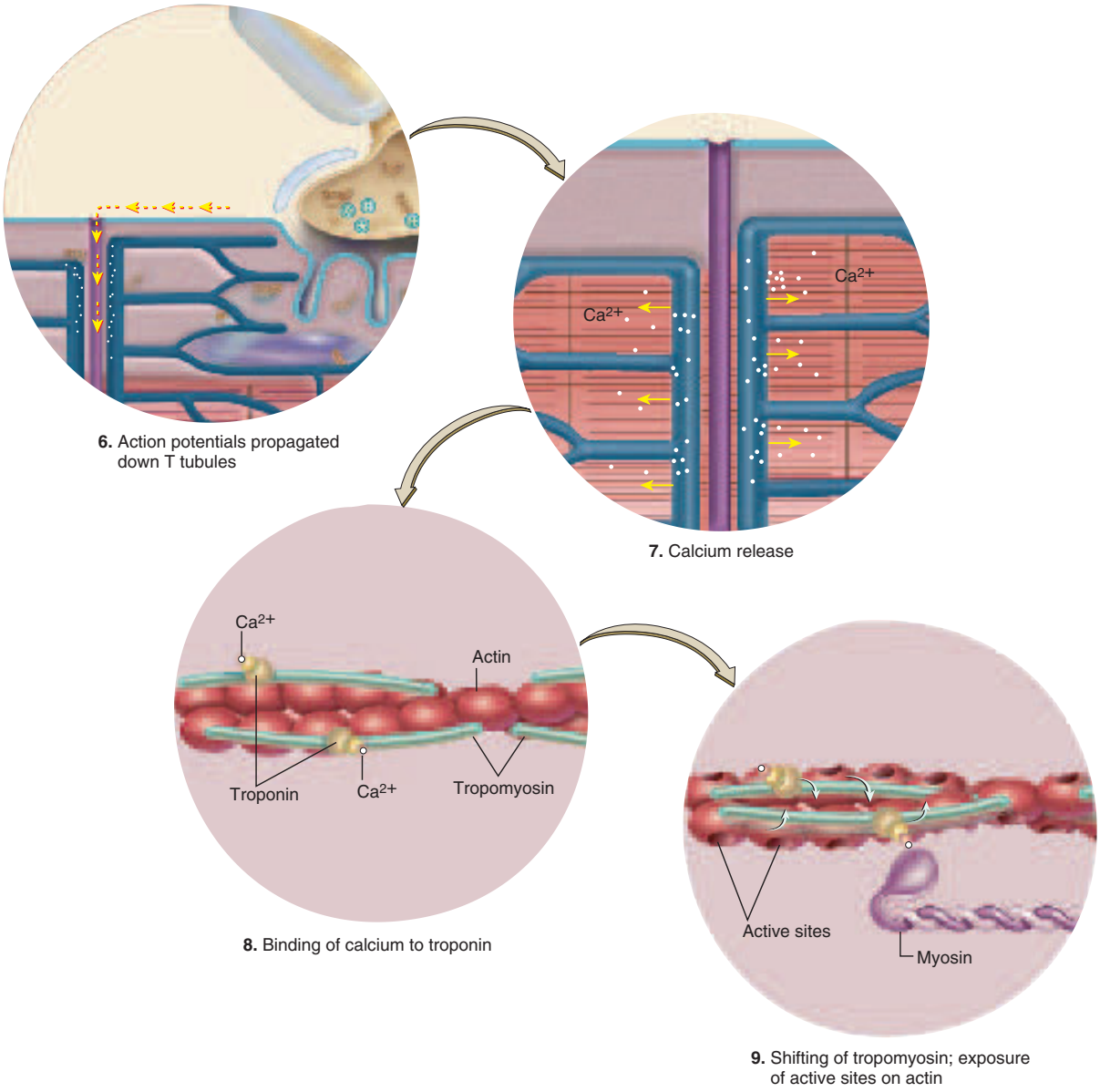


Figure 11.9 Excitation-Contraction Coupling. These events link action potentials in the muscle fiber to the release and binding of calcium ions. The numbered steps in this figure begin where the previous figure left off.

being similar to the way you would pull in a boat anchor hand over hand. When the myosin head cocks, it is like your hand reaching out to grasp the anchor rope. When it flexes back into the low-energy position, it is like your elbow flexing to pull on the rope and draw the anchor up a little bit. When you let go of the rope with one hand, you hold onto it with the other, alternating hands until the anchor is pulled in. Similarly, when one myosin head releases the actin in preparation for the recovery stroke, there are many other heads on the same thick filament holding onto the thin filament so that it doesn't slide back. At any given moment during contraction, about half of the heads are bound to the thin filament and the other half are extending forward to grasp the filament farther down. That is, the myosin heads of a thick filament do not all stroke at once but contract sequentially.

As another analogy, consider a millipede—a little wormlike animal with a few hundred tiny legs. Each leg

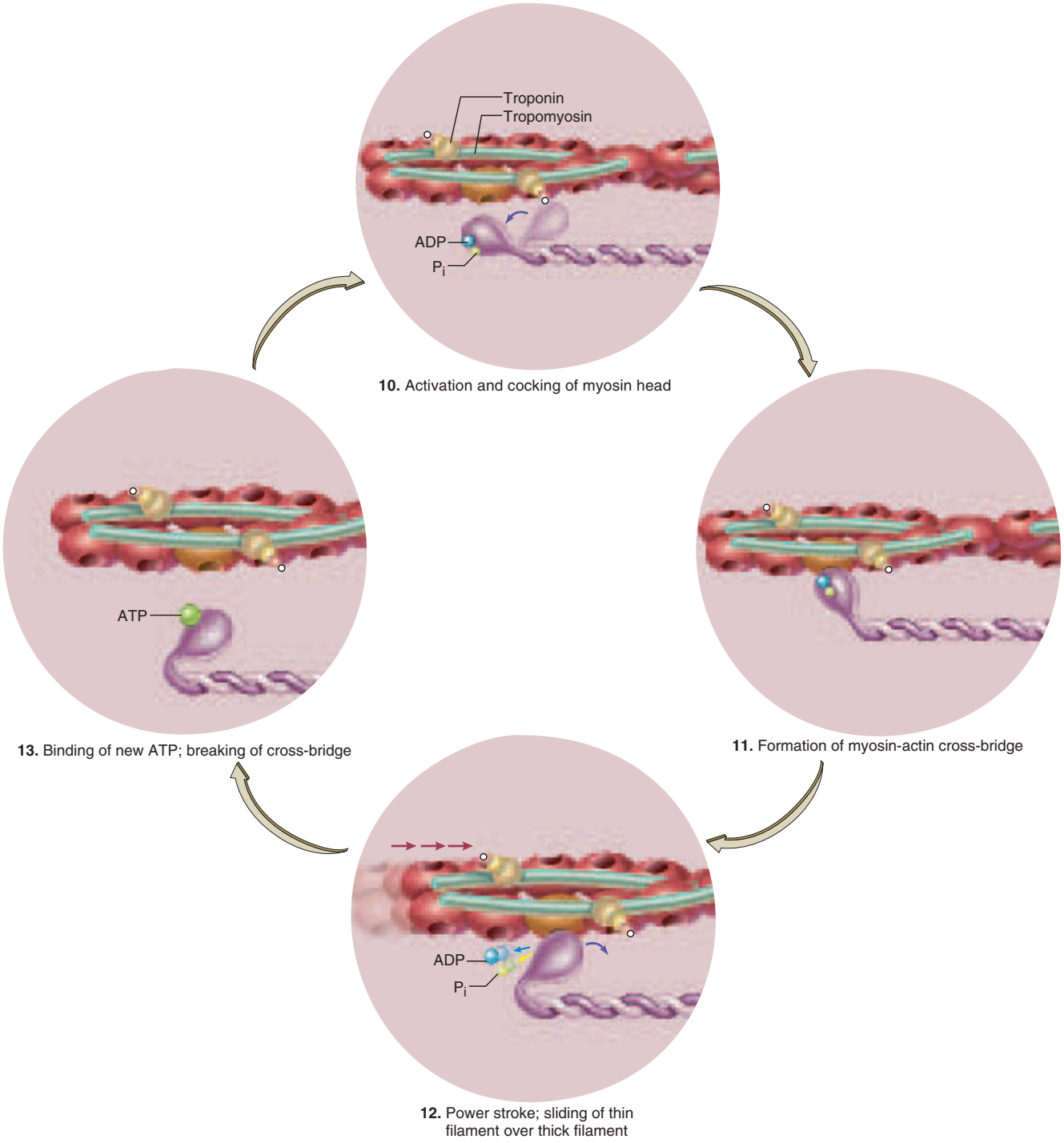


Figure 11.10 The Sliding Filament Mechanism of Contraction. This is a cycle of repetitive events that cause a thin filament to slide over a thick filament and generate tension in the muscle. The numbered steps in this figure begin where the previous figure left off.

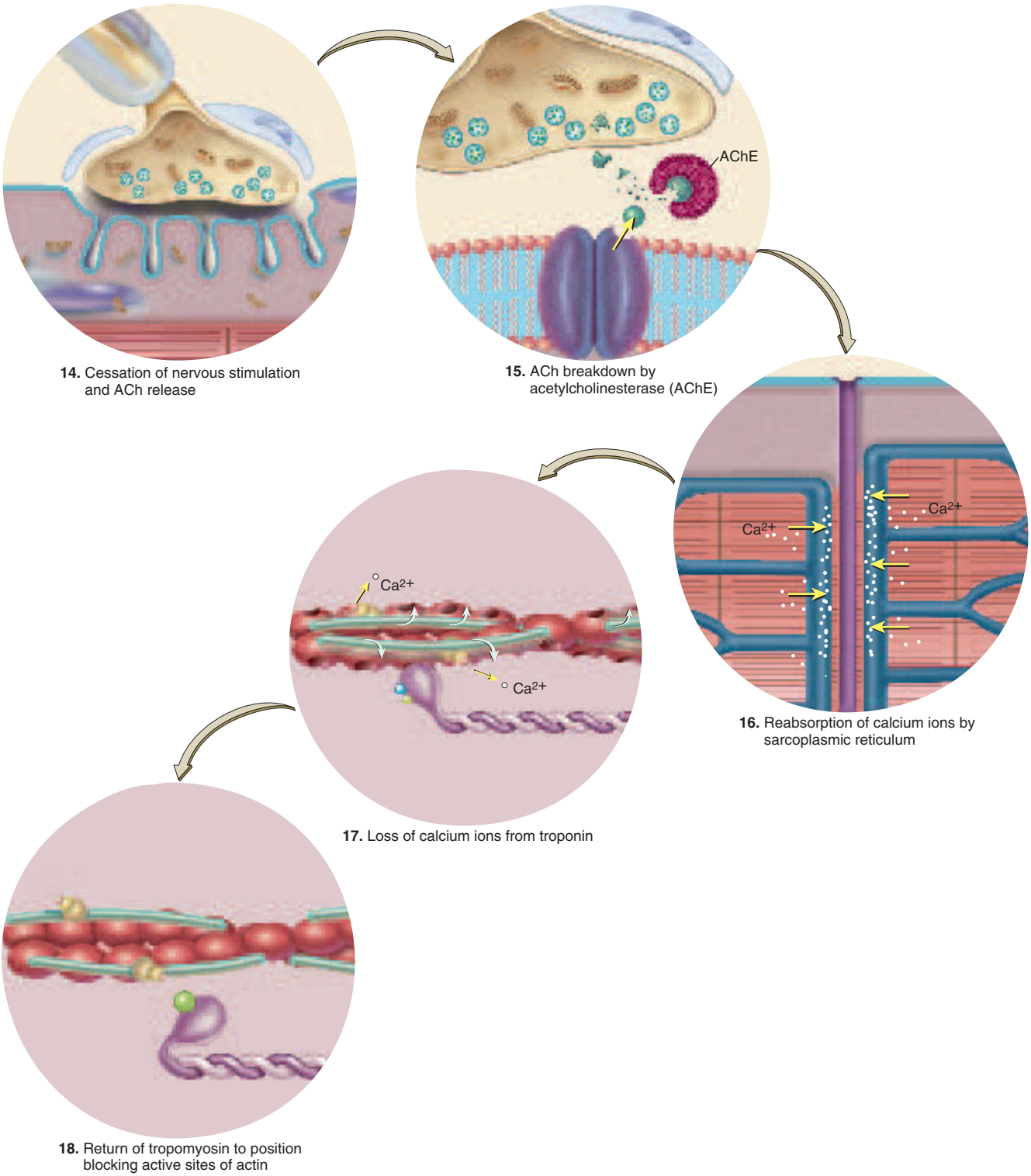


Figure 11.11 Relaxation of a Muscle Fiber. These events lead from the cessation of a nerve signal to the release of thin filaments by myosin. The numbered steps in this figure begin where the previous figure left off.

takes individual jerky steps, but all the legs working together produce smooth, steady movement—just as all the heads of a thick filament collectively produce a smooth, steady pull on the thin filament. Note that even though the muscle fiber contracts, the *myofilaments do not become shorter* any more than a rope becomes shorter as you pull in an anchor. The thin filaments slide over the thick ones, as the name of the theory implies.

A single cycle of power and recovery strokes by all the myosin heads in a muscle fiber would shorten the fiber by about 1%. A fiber, however, may shorten by as much as 40% of its resting length, so obviously the cycle of power and recovery must be repeated many times by each myosin head. Each head carries out about five strokes per second, and each stroke consumes one molecule of ATP.

Relaxation

When its work is done, a muscle fiber relaxes and returns to its resting length. This is achieved by the steps shown in figure 11.11.

14. Nerve signals stop arriving at the neuromuscular junction, so the synaptic knob stops releasing ACh.
15. As ACh dissociates (separates) from its receptor, acetylcholinesterase breaks it down into fragments that cannot stimulate the muscle. The synaptic knob reabsorbs these fragments for recycling. All of this happens continually while the muscle is being stimulated, too; but when nerve signals stop, no new ACh is released to replace that which is broken down. Therefore, stimulation of the muscle fiber by ACh ceases.
16. Active transport pumps in the sarcoplasmic reticulum (SR) begin to pump Ca^{2+} from the cytosol back into the cisternae. Here, the calcium binds to a protein called **calsequestrin** (CAL-see-QUES-trin) and is stored until the fiber is stimulated again. Since active transport requires ATP, you can see that *ATP is needed for muscle relaxation as well as for muscle contraction* (see insight 11.2).
17. As calcium ions dissociate from troponin, they are pumped into the SR and are not replaced.
18. Tropomyosin moves back into the position where it blocks the active sites of the actin filament. Myosin can no longer bind to actin, and the muscle fiber ceases to produce or maintain tension.

A muscle returns to its resting length with the aid of two forces: (1) like a recoiling rubber band, the series-elastic components stretch it; and (2) since muscles often occur in antagonistic pairs, the contraction of an antagonist lengthens the relaxed muscle. Contraction of the triceps brachii, for example, extends the elbow and lengthens the biceps brachii.

Insight 11.2 Clinical Application

Rigor Mortis

Rigor mortis[7] is the hardening of the muscles and stiffening of the body that begins 3 to 4 hours after death. It occurs partly because the deteriorating sarcoplasmic reticulum releases calcium ions into the cytosol, and the deteriorating sarcolemma admits more calcium ions from the extracellular fluid. The calcium ions activate myosin-actin cross bridging and muscle contraction. Furthermore, the muscle cannot relax without ATP, and ATP is no longer produced after death. Thus, the fibers remain contracted until the myofilaments begin to decay. Rigor mortis peaks about 12 hours after death and then diminishes over the next 48 to 60 hours.

[7] *rigor* = rigidity + *mortis* = of death

The Length-Tension Relationship and Muscle Tone

The amount of tension generated by a muscle, and therefore the force of its contraction, depends on how stretched or contracted it was before it was stimulated, among other

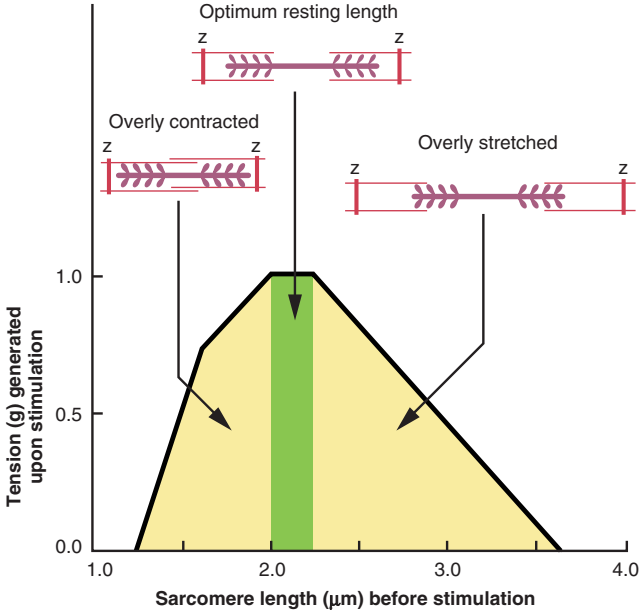


Figure 11.12 The Length-Tension Relationship. *Center:* In a resting muscle fiber, the sarcomeres are usually 2.0 to 2.25 μm long, the optimum length for producing maximum tension when the muscle is stimulated to contract. Note how this relates to the degree of overlap between the thick and thin filaments. *Left:* If the muscle is overly contracted, the thick filaments butt against the Z discs and the fiber cannot contract very much more when it is stimulated. *Right:* If the muscle is overly stretched, there is so little overlap between the thick and thin filaments that few cross-bridges can form between myosin and actin.

factors. This principle is called the **length-tension relationship.** The reasons for it can be seen in figure 11.12. If a fiber is overly contracted at rest, its thick filaments are rather close to the Z discs. The stimulated muscle may contract a little, but then the thick filaments butt up against the Z discs and can go no farther. The contraction is therefore a weak one. On the other hand, if a muscle fiber is too stretched before it is stimulated, there is relatively little overlap between its thick and thin filaments. When the muscle is stimulated, its myosin heads cannot "get a good grip" on the thin filaments, and again the contraction is weak. (As mentioned in chapter 10, this is one reason you should not bend at the waist to pick up a heavy object. Muscles of the back become overly stretched and cannot contract effectively to straighten your spine against a heavy resistance.)

Between these extremes, there is an optimum resting length at which a muscle produces the greatest force when it contracts. The central nervous system continually monitors and adjusts the length of a resting muscle, maintaining a state of partial contraction called **muscle tone.** This maintains optimum length and makes the muscles ideally ready for action. The elastic filaments of the sarcomere also help to maintain enough myofilament overlap to ensure an effective contraction when the muscle is called into action.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

12. What change does ACh cause in an ACh receptor? How does this electrically affect the muscle fiber?
13. How do troponin and tropomyosin regulate the interaction between myosin and actin?
14. Describe the roles played by ATP in the power and recovery strokes of myosin.
15. What steps are necessary for a contracted muscle to return to its resting length?

Behavior of Whole Muscles

Objectives

When you have completed this section, you should be able to

- describe the stages of a muscle twitch;
- describe treppe and explain how it relates to muscle warm-up;
- explain how muscle twitches add up to produce stronger muscle contractions;
- distinguish between isometric and isotonic contraction; and
- distinguish between concentric and eccentric contractions.

Now you know how an individual muscle cell shortens. Our next objective is to move up to the organ grade of construction and consider how this relates to the action of the muscle as a whole.

Threshold, Latent Period, and Twitch

Muscle contraction has often been studied and demonstrated using the gastrocnemius (calf) muscle of a frog, which can easily be isolated from the leg along with its connected sciatic nerve (see insight 11.3). This nerve-muscle preparation can be attached to stimulating electrodes and to a recording device that produces a *myogram,* a chart of the timing and strength of the muscle's contraction.

A sufficiently weak electrical stimulus to a muscle causes no contraction. By gradually increasing the voltage and stimulating the muscle again, we can determine the **threshold,** or minimum voltage necessary to generate an action potential in the muscle fiber and produce a contraction. The action potential triggers the release of a pulse of Ca^{2+} into the cytoplasm and activates the sliding filament mechanism. At threshold or higher, a stimulus thus causes a quick cycle of contraction and relaxation called a **twitch** (fig. 11.13).

There is a delay, or **latent period,** of about 2 milliseconds (msec) between the onset of the stimulus and the onset of the twitch. This is the time required for excitation, excitation-contraction coupling, and tensing of the series-elastic components of the muscle. The force generated during this time is called *internal tension.* It is not visible on the myogram because it causes no shortening of the muscle.

Once the series-elastic components are taut, the muscle begins to produce *external tension* and move a resisting object, or load. This is called the **contraction phase** of the twitch. In the frog gastrocnemius preparation, the load is the sensor of the recording apparatus; in the body, it is usually a bone. By analogy, imagine lifting a weight from a table with a rubber band. At first, internal tension would

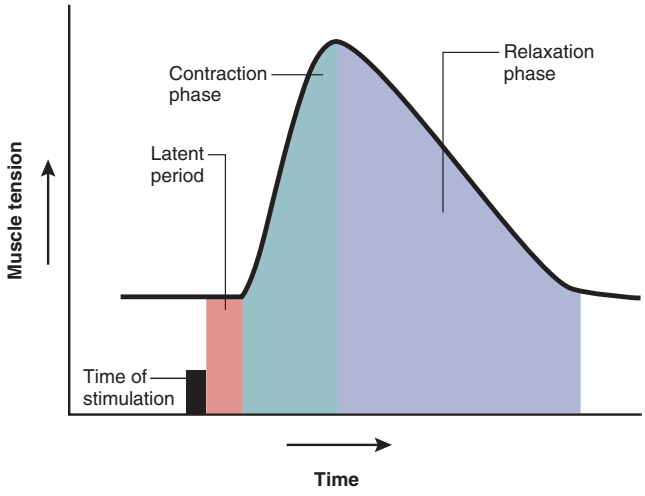


Figure 11.13 **A Muscle Twitch.**
What role does ATP play during the relaxation phase?

stretch the rubber band. Then as the rubber band became taut, external tension would lift the weight.

The contraction phase is short-lived, because the sacroplasmic reticulum quickly pumps Ca^{2+} back into itself before the muscle develops maximal force. As the Ca^{2+} level in the cytoplasm falls, myosin releases the thin filaments and muscle tension declines. This is seen in the myogram as the **relaxation phase.** The entire twitch lasts from about 7 to 100 msec.

Insight 11.3 Medical History

Galvani, Volta, and Animal Electricity

The invention of modern dry cells can be traced to studies of frog muscle by Italian anatomist Luigi Galvani (1737–98). He suspended isolated frog legs from a copper hook and noticed that they twitched when touched with an iron scalpel. He attributed this to "animal electricity" in the legs. The physicist Alessandro Volta (1745–1827) investigated Galvani's discovery further. He concluded that when two different metals (such as the copper hook and iron scalpel) are separated by an electrolyte solution (a frog's tissue fluids), a chemical reaction occurs that produces an electrical current. This current had stimulated the muscle in the legs of Galvani's frogs and caused the twitch. Based on this principle, Volta invented the first simple voltaic cell, the forerunner of today's dry cells.

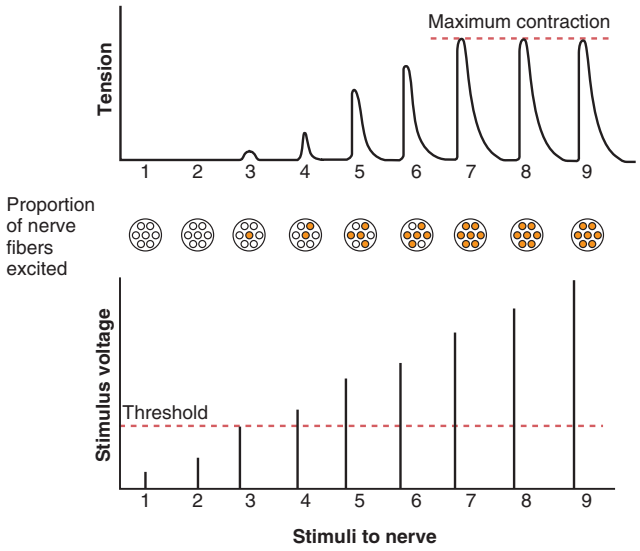


Figure 11.14 The Relationship Between Stimulus Intensity (voltage) and Muscle Tension. Weak stimuli (*1–2*) fail to stimulate any nerve fibers and therefore produce no muscle contraction. When stimuli reach or exceed threshold (*3–7*), they excite more and more nerve fibers and motor units and produce stronger and stronger contractions. This is multiple motor unit summation (recruitment). Once all of the nerve fibers are stimulated (*7–9*), further increases in stimulus strength produce no further increase in muscle tension.

Contraction Strength of Twitches

As long as the voltage of an artificial stimulus delivered directly to a muscle is at threshold or higher, a muscle gives a complete twitch. Increasing the voltage still more does not cause the twitches to become any stronger. There are other factors, however, that can produce stronger twitches. Indeed, an individual twitch is not strong enough to do any useful work. Muscles must be able to contract with variable strength—differently in lifting a glass of champagne than in lifting a heavy barbell, for example.

If we stimulate the nerve rather than the muscle, higher voltages produce stronger muscle contractions because they excite more nerve fibers and therefore more motor units. The more motor units that contract, the more strongly the muscle as a whole contracts (fig. 11.14). The process of bringing more motor units into play is called **recruitment,** or **multiple motor unit (MMU) summation.** It is seen not just in artificial stimulation but is part of the way the nervous system behaves normally to produce variable muscle contractions.

Another way to produce a stronger muscle contraction is to stimulate the muscle at a higher frequency. Even when voltage remains the same, high-frequency stimulation causes stronger contractions than low-frequency stimulation. In figure 11.15*a,* we see that when a muscle is stimulated at a low frequency (up to 10 stimuli/sec in this example), it produces an identical twitch for each stimulus and fully recovers between twitches.

Between 10 and 20 stimuli per second, the muscle still recovers fully between twitches, but each twitch develops more tension than the one before. This pattern of increasing tension with repetitive stimulation is called **treppe**[8] (TREP-eh), or the *staircase phenomenon,* after the appearance of the myogram (fig. 11.15*b*). One cause of treppe is that when stimuli arrive so rapidly, the sarcoplasmic reticulum does not have time between stimuli to completely reabsorb all the calcium that it released. Thus, the calcium concentration in the cytosol rises higher and higher with each stimulus and causes subsequent twitches to be stronger. Another factor is that the heat released by each twitch causes muscle enzymes such as myosin ATPase to work more efficiently and produce stronger twitches as the muscle warms up. One purpose of warm-up exercises before athletic competition is to induce treppe, so that the muscle contracts more effectively when the competition begins.

At a still higher stimulus frequency (20–40 stimuli/sec in fig. 11.15*c*), each new stimulus arrives before the previous twitch is over. Each new twitch "rides piggyback" on the previous one and generates higher tension.

[8] *treppe* = staircase

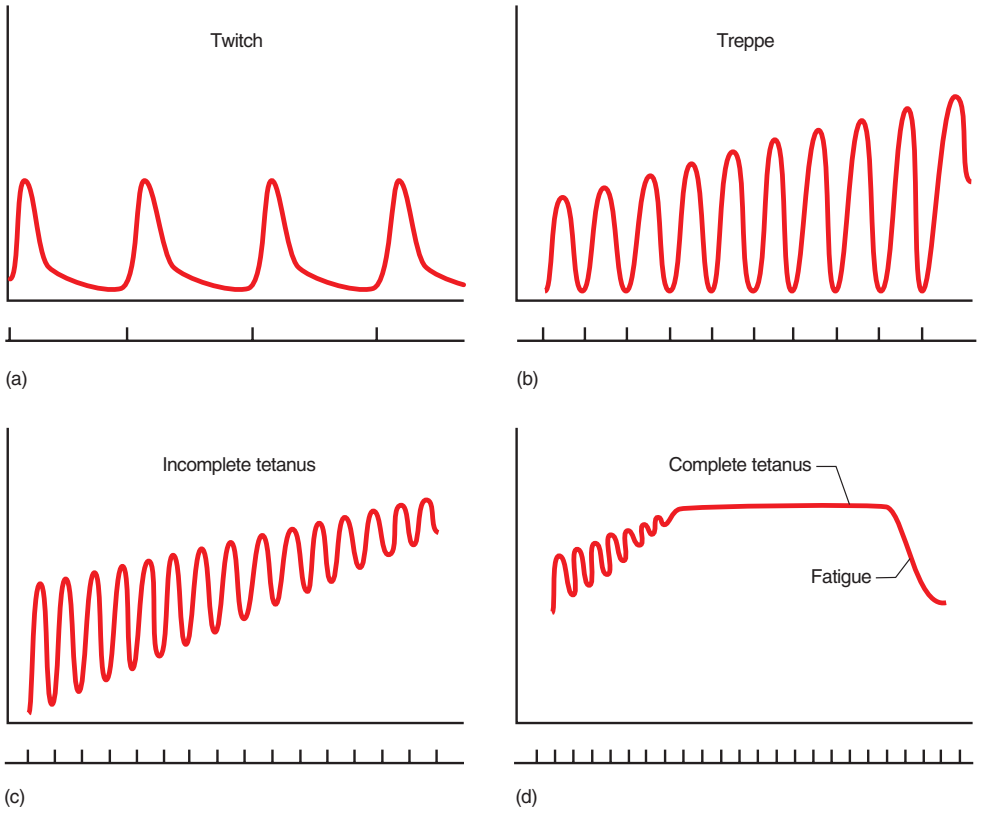


Figure 11.15 The Relationship Between Stimulus Frequency and Muscle Tension. (*a*) Twitch: At low frequency, the muscle relaxes completely between stimuli and shows twitches of uniform strength. (*b*) Treppe: At a moderate frequency of stimulation, the muscle relaxes fully between contractions, but successive twitches are stronger. (*c*) Wave summation and incomplete tetanus: At still higher stimulus frequency, the muscle does not have time to relax completely between twitches, and the force of each twitch builds on the previous one. (*d*) Complete tetanus: At high stimulus frequency, the muscle does not have time to relax at all between stimuli and exhibits a state of continual contraction with about four times as much tension as a single twitch. Tension declines as the muscle fatigues.

This phenomenon goes by two names: **temporal**[9] **summation,** because it results from two stimuli arriving close together, or **wave summation,** because it results from one wave of contraction added to another. Wave is added upon wave, so each twitch reaches a higher level of tension than the one before, and the muscle relaxes only partially between stimuli. This effect produces a state of sustained fluttering contraction called **incomplete tetanus.**

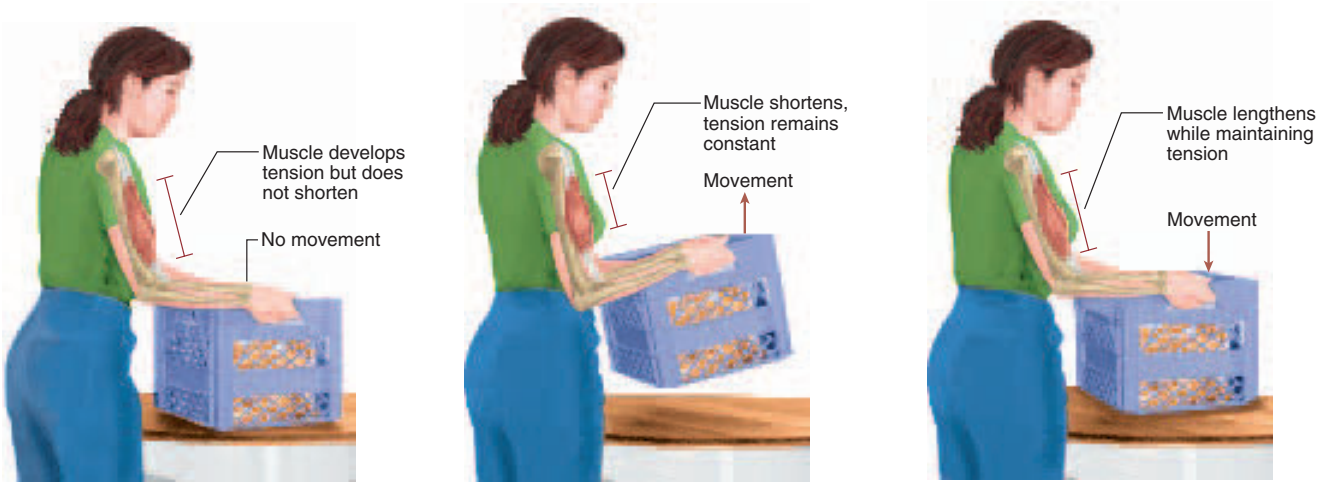
At a still higher frequency, such as 40 to 50 stimuli per second, the muscle has no time to relax at all between stimuli, and the twitches fuse into a smooth, prolonged contraction called **complete tetanus.** A muscle in complete tetanus produces about four times as much tension as a single twitch (fig. 11.15*d*). This type of tetanus should not be confused with the disease of the same name caused by the tetanus toxin, explained in insight 11.1.

[9] *tempor* = time

Complete tetanus is a phenomenon seen in artificial stimulation of a muscle, however, and rarely if ever occurs in the body. Even during the most intense muscle contractions, the frequency of stimulation by a motor neuron rarely exceeds 25/sec, which is far from sufficient to produce complete tetanus. The reason for the smoothness of muscle contractions is that motor units function asynchronously; when one motor unit relaxes, another contracts and "takes over" so that the muscle does not lose tension.

Isometric and Isotonic Contraction

In muscle physiology, "contraction" does not always mean the shortening of a muscle—it may mean only that the muscle is producing internal tension while an external resistance causes it to stay the same length or even to become longer. Thus, physiologists speak of different kinds of muscle contraction as *isometric* versus *isotonic* and *concentric* versus *eccentric.*



(a) Isometric contraction (b) Isotonic, concentric contraction (c) Isotonic, eccentric contraction

Figure 11.16 Isometric and Isotonic Contraction. (*a*) Isometric contraction, in which a muscle develops tension but does not shorten. This occurs at the beginning of any muscle contraction but is prolonged in actions such as lifting heavy weights. (*b*) Isotonic concentric contraction, in which the muscle shortens while maintaining a constant degree of tension. In this phase, the muscle moves a load. (*c*) Isotonic eccentric contraction, in which the muscle maintains tension while it lengthens, allowing a muscle to relax without going suddenly limp.
Name a muscle that undergoes eccentric contraction as you sit down in a chair.

Suppose you lift a heavy box of books from a table. When you first contract the muscles of your arms, you can feel the tension building in them even though the box is not yet moving. At this point, your muscles are contracting at a cellular level, but their tension is being absorbed by the series-elastic components and is resisted by the weight of the load; the muscle as a whole is not producing any external movement. This phase is called **isometric**[10] **contraction**—contraction without a change in length (fig. 11.16*a*). **Isotonic**[11] **contraction**—contraction with a change in length but no change in tension—begins when internal tension builds to the point that it overcomes the resistance. The muscle now shortens, moves the load, and maintains essentially the same tension from then on (fig. 11.16*b*). Isometric and isotonic contraction are both phases of normal muscular action (fig. 11.17).

There are two forms of isotonic contraction—concentric and eccentric. In **concentric contraction,** a muscle shortens as it maintains tension—for example, when the biceps brachii contracts and flexes the elbow. In an **eccentric contraction,** a muscle lengthens as it maintains tension. If you set that box of books down again (fig. 11.16*c*), your biceps brachii lengthens as you extend your elbow, but it maintains tension to act as a brake and keep you from simply dropping the box. A weight lifter

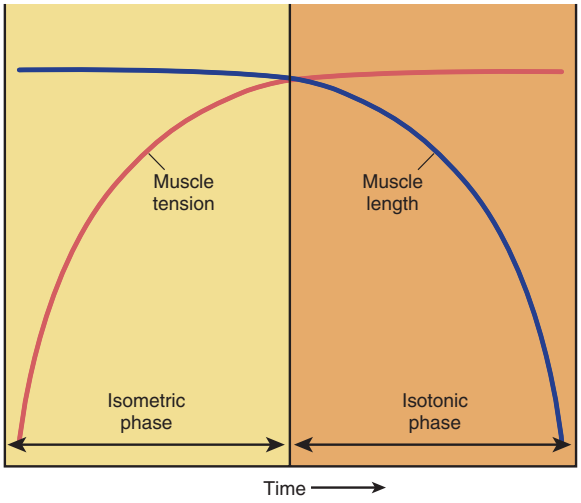


Figure 11.17 Isometric and Isotonic Phases of Contraction. At the beginning of a contraction (isometric phase), muscle tension rises but the length remains constant (the muscle does not shorten). When tension overcomes the resistance of the load, the tension levels off and the muscle begins to shorten and move the load (isotonic phase).
How would you extend this graph in order to show eccentric contraction?

[10] *iso* = same, uniform + *metr* = length
[11] *iso* = same, uniform + *ton* = tension

uses concentric contraction when lifting a barbell and eccentric contraction when lowering it to the floor.

In summary, during isometric contraction, a muscle develops tension without changing length, and in isotonic contraction, it changes length while maintaining constant tension. In concentric contraction, a muscle maintains tension as it shortens, and in eccentric contraction, it maintains tension while it is lengthening.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

16. Explain how warm-up is related to treppe and why it improves athletic performance.
17. Explain the role of tetanus in normal muscle action.
18. Describe an everyday activity *not* involving the arms in which your muscles would switch from isometric to isotonic contraction.
19. Describe an everyday activity *not* involving the arms that would involve concentric contraction and one that would involve eccentric contraction.

Muscle Metabolism

Objectives

When you have completed this section, you should be able to

- explain how skeletal muscle meets its energy demands during rest and exercise;
- explain the basis of muscle fatigue and soreness;
- define *oxygen debt* and explain why extra oxygen is needed even after an exercise has ended;
- distinguish between two physiological types of muscle fibers, and explain the functional roles of these two types;
- discuss the factors that affect muscular strength; and
- discuss the effects of resistance and endurance exercises on muscle.

ATP Sources

All muscle contraction depends on ATP; no other energy source can serve in its place. The supply of ATP depends, in turn, on the availability of oxygen and organic energy sources such as glucose and fatty acids. To understand how muscle manages its ATP budget, you must be familiar with the two main pathways of ATP synthesis—*anaerobic fermentation* and *aerobic respiration* (see fig. 2.31, p. 86). Each of these has advantages and disadvantages. Anaerobic fermentation enables a cell to produce ATP in the absence of oxygen, but the ATP yield is very limited and the process produces a toxic end product, lactic acid, which is a major factor in muscle fatigue. By contrast, aerobic respiration produces far more ATP and less toxic end products (carbon dioxide and water), but it requires a continual supply of oxygen. Although aerobic respiration is best known as a pathway for glucose oxidation, it is also used to extract energy from other organic compounds. In a resting muscle, most ATP is generated by the aerobic respiration of fatty acids.

During the course of exercise, different mechanisms of ATP synthesis are used depending on the exercise duration. We will view these mechanisms from the standpoint of immediate, short-term, and long-term energy, but it must be stressed that muscle does not make sudden shifts from one mechanism to another like an automobile transmission shifting gears. Rather, these mechanisms blend and overlap as the exercise continues (fig. 11.18).

Immediate Energy

In a short, intense exercise such as a 100 m dash, the respiratory and cardiovascular systems cannot deliver oxygen to the muscles quickly enough for aerobic respiration to meet the increased ATP demand. The myoglobin in a muscle fiber supplies oxygen for a limited amount of aerobic respiration, but in brief exercises a muscle meets most of its ATP demand by borrowing phosphate (P_i) groups from other molecules and transferring them to ADP. Two enzyme systems control these phosphate transfers (fig. 11.19):

1. **Myokinase** (MY-oh-KY-nase) transfers P_i groups from one ADP to another, converting the latter to ATP.
2. **Creatine kinase** (CREE-uh-tin KY-nase) obtains P_i groups from an energy-storage molecule, **creatine phosphate (CP),** and donates them to ADP to make ATP. This is a fast-acting system that helps to maintain the ATP level while other ATP-generating mechanisms are being activated.

ATP and CP, collectively called the **phosphagen system,** provide nearly all the energy used for short bursts of intense activity. Muscle contains about 5 millimoles of ATP and 15 millimoles of CP per kilogram of tissue, which is enough to power about 1 minute of brisk walking or 6 seconds of sprinting or fast swimming. The phosphagen system is especially important in activities requiring brief but maximal effort, such as football, baseball, and weight lifting.

Short-Term Energy

As the phosphagen system is exhausted, the muscles shift to anaerobic fermentation to "buy time" until cardiopulmonary function can catch up with the muscle's oxygen demand. During this period, the muscles obtain glucose from the blood and their own stored glycogen. The pathway from glycogen to lactic acid, called the **glycogen–lactic acid**

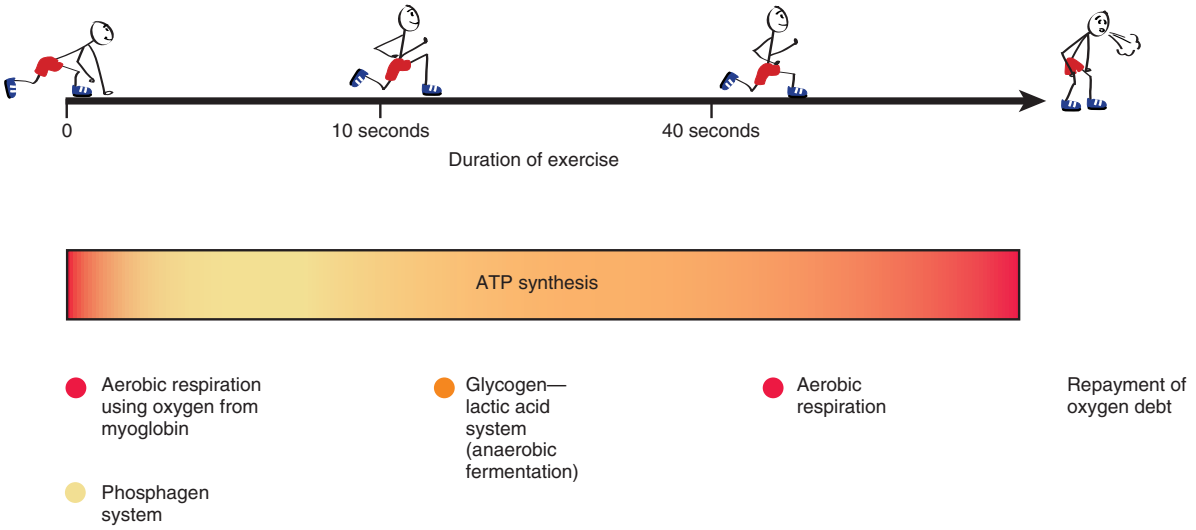


Figure 11.18 **Phases of ATP Production During Exercise.**

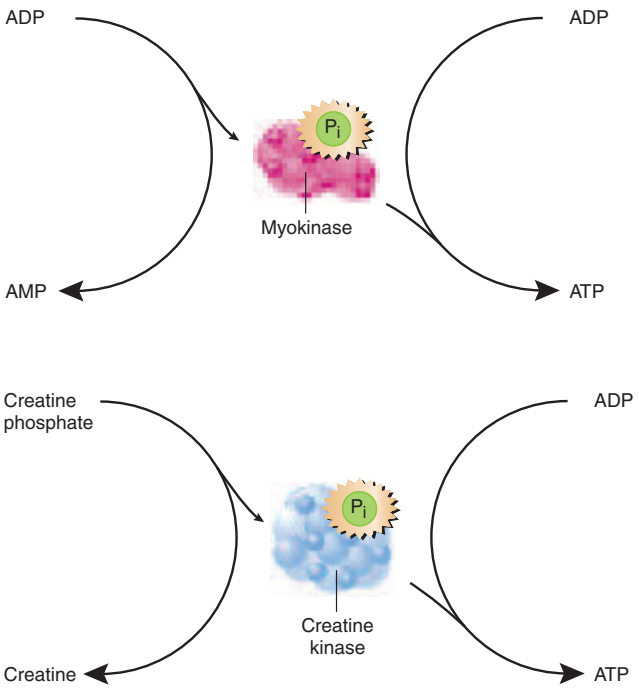


Figure 11.19 **The Phosphagen System.** Two enzymes, myokinase and creatine kinase, generate ATP in the absence of oxygen. Myokinase borrows phosphate groups from ADP, and creatine kinase borrows them from creatine phosphate, to convert an ADP to ATP.

system, produces enough ATP for 30 to 40 seconds of maximum activity. To play basketball or to run completely around a baseball diamond, for example, depends heavily on this energy-transfer system.

Long-Term Energy

After 40 seconds or so, the respiratory and cardiovascular systems "catch up" and deliver oxygen to the muscles fast enough for aerobic respiration to meet most of the ATP demand. One's rate of oxygen consumption rises for 3 to 4 minutes and then levels off at a *steady state* in which aerobic ATP production keeps pace with the demand. In exercises lasting more than 10 minutes, more than 90% of the ATP is produced aerobically.

Little lactic acid accumulates under steady state conditions, but this does not mean that aerobic exercise can continue indefinitely or that it is limited only by a person's willpower. The depletion of glycogen and blood glucose, together with the loss of fluid and electrolytes through sweating, set limits to endurance and performance even when lactic acid does not.

Fatigue and Endurance

Muscle **fatigue** is the progressive weakness and loss of contractility that results from prolonged use of the muscles. For example, if you hold this book at arm's length for a minute, you will feel your muscles growing weaker and

eventually you will be unable to hold it up. Repeatedly squeezing a rubber ball, pushing a video game button, or trying to take lecture notes from a fast-talking professor produces fatigue in the hand and finger muscles. Fatigue has multiple causes:

- ATP synthesis declines as glycogen is consumed.
- The ATP shortage slows down the sodium-potassium pumps, which are needed to maintain the resting membrane potential and excitability of the muscle fibers.
- Lactic acid lowers the pH of the sarcoplasm, which inhibits the enzymes involved in contraction, ATP synthesis, and other aspects of muscle function.
- Each action potential releases potassium ions from the sarcoplasm to the extracellular fluid. The accumulation of extracellular K^+ lowers the membrane potential and excitability of the muscle fiber.
- Motor nerve fibers use up their acetylcholine, which leaves them less capable of stimulating muscle fibers. This is called *junctional fatigue.*
- The central nervous system, where all motor commands originate, fatigues by processes not yet understood.

Think About It

Suppose you repeatedly stimulated the sciatic nerve in a frog nerve-muscle preparation until the muscle stopped contracting. What simple test could you do to determine whether this was due to junctional fatigue or to one of the other fatigue mechanisms?

A person's ability to maintain high-intensity exercise for more than 4 to 5 minutes is determined in large part by his or her **maximum oxygen uptake ($\dot{V}O_2$max)**—the point at which the rate of oxygen consumption reaches a plateau and does not increase further with an added workload. $\dot{V}O_2$max is proportional to body size; it peaks at around age 20; it is usually greater in males than in females; and it can be twice as great in a trained endurance athlete as in an untrained person (see the later discussion on effects of conditioning).

Physical endurance also depends on the supply of organic nutrients—fatty acids, amino acids, and especially glucose. Many endurance athletes use a dietary strategy called *carbohydrate loading* to "pack" as much as 5 g of glycogen into every 100 g of muscle. This can significantly increase endurance, but an extra 2.7 g of water is also stored with each added gram of glycogen. Some athletes feel that the resulting "heaviness" and other side effects outweigh the benefits of carbohydrate loading.

Oxygen Debt

You have probably noticed that you breathe heavily not only during a strenuous exercise but also for several minutes afterwards. This is because your body accrues an oxygen debt that must be "repaid." **Oxygen debt** is the difference between the resting rate of oxygen consumption and the elevated rate following an exercise; it is also known as *excess postexercise oxygen consumption (EPOC).* The total amount of extra oxygen consumed after a strenuous exercise is typically about 11 L. It is used for the following purposes:

- *Replacing the body's oxygen reserves* that were depleted in the first minute of exercise. These include 0.3 L of oxygen bound to muscle myoglobin, 1.0 L bound to blood hemoglobin, 0.25 L dissolved in the blood plasma and other extracellular fluids, and 0.1 L in the air in the lungs.
- *Replenishing the phosphagen system.* This involves synthesizing ATP and using some of it to donate phosphate groups back to creatine until the resting levels of ATP and CP are restored.
- *Oxidizing lactic acid.* About 80% of the lactic acid produced by muscle enters the bloodstream and is reconverted to pyruvic acid in the kidneys, the cardiac muscle, and especially the liver. Some of this pyruvic acid enters the aerobic (mitochondrial) pathway to make ATP, but the liver converts most of it back to glucose. Glucose is then available to replenish the glycogen stores of the muscle.
- *Serving the elevated metabolic rate.* As long as the body temperature remains elevated by exercise, the total metabolic rate remains high, and this requires extra oxygen.

Physiological Classes of Muscle Fibers

Not all muscle fibers are metabolically alike or adapted to perform the same task. Some respond slowly but are relatively resistant to fatigue, while others respond more quickly but also fatigue quickly (table 11.3). Each primary type of fiber goes by several names:

- **Slow oxidative (SO), slow-twitch, red,** or **type I fibers.** These fibers have relatively abundant mitochondria, myoglobin, and blood capillaries, and therefore a relatively deep red color. They are well adapted to aerobic respiration, which does not generate lactic acid. Thus, these fibers do not fatigue easily. However, in response to a single stimulus, they exhibit a relatively long twitch, lasting about 100 milliseconds (msec). The soleus muscle of the calf and the postural

Table 11.3 Classification of Skeletal Muscle Fibers

	Fiber Type	
Properties	**Slow Oxidative**	**Fast Glycolytic**
Relative diameter	Smaller	Larger
ATP synthesis	Aerobic	Anaerobic
Fatigue resistance	Good	Poor
ATP hydrolysis	Slow	Fast
Glycolysis	Moderate	Fast
Myoglobin content	Abundant	Low
Glycogen content	Low	Abundant
Mitochondria	Abundant and large	Fewer and smaller
Capillaries	Abundant	Fewer
Color	Red	White, pale
Representative Muscles in Which Fiber Type Is Predominant		
	Soleus	Gastrocnemius
	Erector spinae	Biceps brachii
	Quadratus lumborum	Muscles of eye movement

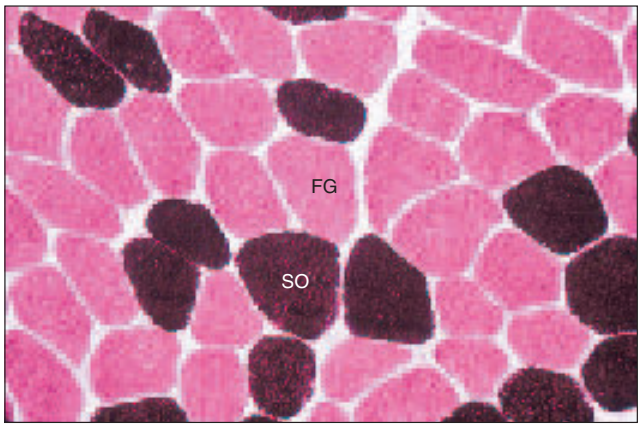


Figure 11.20 Types of Muscle Fibers. Muscle stained to distinguish fast glycolytic (FG) from slow oxidative (SO) fibers. Cross section.

Table 11.4 Proportion of Slow Oxidative (SO) and Fast Glycolytic (FG) Fibers in the Quadriceps Femoris Muscle of Male Athletes

Sample Population	SO	FG
Marathon runners	82%	18%
Swimmers	74	26
Average males	45	55
Sprinters and jumpers	37	63

muscles of the back are composed mainly of these slow oxidative, high-endurance fibers.

- **Fast glycolytic (FG), fast-twitch, white,** or **type II fibers.** These fibers are well adapted for quick responses but not for fatigue resistance. They are rich in enzymes of the phosphagen and glycogen–lactic acid systems. Their sarcoplasmic reticulum releases and reabsorbs Ca^{2+} quickly, which partially accounts for their quick, forceful contractions. They are poorer than SO fibers in mitochondria, myoglobin, and blood capillaries, so they are relatively pale (hence the expression *white* fibers). These fibers produce twitches as short as 7.5 msec, but because of the lactic acid they generate, they fatigue more easily than SO fibers. Thus, they are especially important in sports such as basketball that require stop-and-go activity and frequent changes of pace. The gastrocnemius muscle of the calf, biceps brachii of the arm, and the muscles of eye movement consist mainly of FG fibers.

Some authorities recognize two subtypes of FG fibers called types IIA and IIB. Type IIB is the common type just described, while IIA, or **intermediate fibers,** combine fast-twitch responses with aerobic fatigue-resistant metabolism. Type IIA fibers, however, are relatively rare except in some endurance-trained athletes. The three fiber types can be differentiated histologically by using stains for certain mitochondrial enzymes and other cellular components (fig. 11.20). All muscle fibers of one motor unit belong to the same physiological type.

Nearly all muscles are composed of both SO and FG fibers, but the proportions of these fiber types differ from one muscle to another. Muscles composed mainly of SO fibers are called *red muscles* and those composed mainly of FG fibers are called *white muscles.* People with different types and levels of physical activity differ in the proportion of one fiber type to another even in the same muscle, such as the *quadriceps femoris* of the anterior thigh (table 11.4). It is thought that people are born with a genetic predisposition for a certain ratio of fiber types. Those who go into competitive sports discover the sports at which they can excel and gravitate toward those for which heredity has best equipped them. One person might be a "born sprinter" and another a "born marathoner."

We noted earlier that sometimes two or more muscles act across the same joint and superficially seem to have the same function. We have already seen some reasons why such muscles are not as redundant as they seem. Another reason is that they may differ in the proportion of SO to FG fibers. For example, the gastrocnemius and soleus muscles of the calf both insert on the calcaneus through the same tendon, the calcaneal tendon, so they exert the same pull on the heel. The gastrocnemius, however, is a white, predominantly FG muscle adapted for quick, powerful movements such as jumping, whereas the soleus is a red, predominantly SO muscle that does most of the work in endurance exercises such as jogging and skiing.

Muscular Strength and Conditioning

We have far more muscular strength than we normally use. The gluteus maximus can generate 1,200 kg of tension, and all the muscles of the body can produce a total tension of 22,000 kg (nearly 25 tons). Indeed, the muscles can generate more tension than the bones and tendons can withstand—a fact that accounts for many injuries to the patellar and calcaneal tendons. Muscular strength depends on a variety of anatomical and physiological factors:

- **Muscle size.** The strength of a muscle depends primarily on its size; this is why weight lifting increases the size and strength of a muscle simultaneously. A muscle can exert a tension of about 3 to 4 kg/cm^2 (50 lb/in.^{2}) of cross-sectional area.
- **Fascicle arrangement.** Pennate muscles such as the quadriceps femoris are stronger than parallel muscles such as the sartorius, which in turn are stronger than circular muscles such as the orbicularis oculi.
- **Size of active motor units.** Large motor units produce stronger contractions than small ones.
- **Multiple motor unit summation.** When a stronger muscle contraction is desired, the nervous system activates more motor units. This process is the *recruitment,* or *multiple motor unit (MMU) summation,* described earlier. It can produce extraordinary feats of strength under desperate conditions—rescuing a loved one pinned under an automobile, for example. Getting "psyched up" for athletic competition is also partly a matter of MMU summation.
- **Temporal summation.** Nerve impulses usually arrive at a muscle in a series of closely spaced action potentials. Because of the *temporal summation* described earlier, the greater the frequency of stimulation, the more strongly a muscle contracts.
- **The length-tension relationship.** As noted earlier, a muscle resting at optimum length is prepared to contract more forcefully than a muscle that is excessively contracted or stretched.
- **Fatigue.** Muscles contract more weakly when they are fatigued.

Resistance exercise, such as weight lifting, is the contraction of muscles against a load that resists movement. A few minutes of resistance exercise at a time, a few times each week, is enough to stimulate muscle growth. Growth results primarily from cellular enlargement, not cellular division. The muscle fibers synthesize more myofilaments and the myofibrils grow thicker. Myofibrils split longitudinally when they reach a certain size, so a well-conditioned muscle has more myofibrils than a poorly conditioned one. Muscle fibers themselves are incapable of mitosis, but there is some evidence that as they enlarge, they too may split longitudinally. A small part of muscle growth may therefore result from an increase in the number of fibers, but most results from the enlargement of fibers that have existed since childhood.

Think About It

Is muscle growth mainly the result of hypertrophy or hyperplasia?

Endurance (aerobic) exercise, such as jogging and swimming, improves the fatigue resistance of the muscles. Slow-twitch fibers, especially, produce more mitochondria and glycogen and acquire a greater density of blood capillaries as a result of conditioning. Endurance exercise also improves skeletal strength, increases the red blood cell count and the oxygen transport capacity of the blood, and enhances the function of the cardiovascular, respiratory, and nervous systems. Endurance training does not significantly increase muscular strength, and resistance training does not improve endurance. Optimal performance and skeletomuscular health requires **cross-training,** which incorporates elements of both types. If muscles are not kept sufficiently active, they become *deconditioned*—weaker and more easily fatigued.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

20. From which two molecules can ADP borrow a phosphate group to become ATP? What is the enzyme that catalyzes each transfer?
21. In a long period of intense exercise, why does muscle generate ATP anaerobically at first and then switch to aerobic respiration?
22. List four causes of muscle fatigue.
23. List three causes of oxygen debt.
24. What properties of fast glycolytic and slow oxidative fibers adapt them for different physiological purposes?

Cardiac and Smooth Muscle

Objectives

When you have completed this section, you should be able to

- describe the structural and physiological differences between cardiac muscle and skeletal muscle;
- explain why these differences are important to cardiac function;
- describe the structural and physiological differences between smooth muscle and skeletal muscle; and
- relate the unique properties of smooth muscle to its locations and functions.

In this section, we compare cardiac muscle and smooth muscle to skeletal muscle. As you will find, cardiac and smooth muscle have special structural and physiological properties related to their distinctive functions. They also have certain properties in common with each other. The muscle cells of both cardiac and smooth muscle are called **myocytes.** By comparison to the long multinucleate fibers of skeletal muscle, these are relatively short cells with only one nucleus. Cardiac and smooth muscle are *involuntary* muscle tissues, not usually subject to our conscious control.

Cardiac Muscle

Cardiac muscle constitutes most of the heart. Its form and function are discussed extensively in chapter 19 so that you will be able to relate these to the actions of the heart. Here, we only briefly compare it to skeletal and smooth muscle (table 11.5).

Cardiac muscle is striated like skeletal muscle, but its myocytes *(cardiocytes)* are shorter and thicker, they branch like a Y, and each myocyte is linked to several others at its ends (see fig. 19.11). The linkages, called **intercalated** (in-TUR-kuh-LAY-ted) **discs,** appear as thick dark lines in stained tissue sections. An intercalated disc has electrical *gap junctions* that allow each myocyte to directly stimulate its neighbors, and mechanical junctions

Table 11.5 Comparison of Skeletal, Cardiac, and Smooth Muscle

Feature	Skeletal Muscle	Cardiac Muscle	Smooth Muscle
Location	Associated with skeletal system	Heart	Walls of viscera and blood vessels, iris of eye, piloerector of hair follicles
Cell shape	Long cylindrical fibers	Short branched cells	Fusiform cells
Cell length	100 μm–30 cm	50–100 μm	50–200 μm
Cell width	10–100 μm	10–20 μm	2–10 μm
Striations	Present	Present	Absent
Nuclei	Multiple nuclei, adjacent to sarcolemma	Usually one nucleus, near middle of cell	One nucleus, near middle of cell
Connective tissues	Endomysium, perimysium, epimysium	Endomysium only	Endomysium only
Sarcoplasmic reticulum	Abundant	Present	Scanty
T tubules	Present, narrow	Present, wide	Absent
Gap junctions	Absent	Present in intercalated discs	Present in single-unit smooth muscle
Autorhythmicity	Absent	Present	Present in single-unit smooth muscle
Thin filament attachment	Z discs	Z discs	Dense bodies
Regulatory proteins	Tropomyosin, troponin	Tropomyosin, troponin	Calmodulin, light-chain myokinase
Ca^{2+} source	Sarcoplasmic reticulum	Sarcoplasmic reticulum and extracellular fluid	Mainly extracellular fluid
Ca^{2+} receptor	Troponin of thin filament	Troponin of thin filament	Calmodulin of thick filament
Innervation and control	Somatic motor fibers (voluntary)	Autonomic fibers (involuntary)	Autonomic fibers (involuntary)
Nervous stimulation required?	Yes	No	No
Effect of nervous stimulation	Excitatory only	Excitatory or inhibitory	Excitatory or inhibitory
Mode of tissue repair	Limited regeneration, mostly fibrosis	Limited regeneration, mostly fibrosis	Relatively good capacity for regeneration

that keep the myocytes from pulling apart when the heart contracts. The sarcoplasmic reticulum is less developed than in skeletal muscle, but the T tubules are larger and admit supplemental Ca^{2+} from the extracellular fluid. Damaged cardiac muscle is repaired by fibrosis. Cardiac muscle has no satellite cells, and even though mitosis has recently been detected in cardiac myocytes following heart attacks, it is not yet certain that it produces a significant amount of regenerated functional muscle.

Unlike skeletal muscle, cardiac muscle can contract without the need of nervous stimulation. It contains a built-in **pacemaker** that rhythmically sets off a wave of electrical excitation. This wave travels through the cardiac muscle and triggers the contraction of the heart chambers. Cardiac muscle is said to be **autorhythmic**[12] because of this ability to contract rhythmically and independently. The heart does, however, receive fibers from the *autonomic nervous system* that can either increase or decrease the heart rate and contraction strength. Cardiac muscle does not exhibit quick twitches like skeletal muscle. Rather, it maintains tension for about 200 to 250 msec, enabling the heart to expel blood.

Cardiac muscle uses aerobic respiration almost exclusively. It is very rich in myoglobin and glycogen, and it has especially large mitochondria that fill about 25% of the cell, compared to smaller mitochondria occupying about 2% of a skeletal muscle fiber. Cardiac muscle is very adaptable with respect to the fuel used, but very vulnerable to interruptions in oxygen supply. Because it makes little use of anaerobic fermentation, cardiac muscle is very resistant to fatigue.

Smooth Muscle

Smooth muscle is composed of myocytes with a fusiform shape, about 30 to 200 μm long, 5 to 10 μm wide at the middle, and tapering to a point at each end. There is only one nucleus, located near the middle of the cell. Although thick and thin filaments are both present, they are not aligned with each other and produce no visible striations or sarcomeres; this is the reason for the name *smooth* muscle. Z discs are absent; instead, the thin filaments are attached by way of the cytoskeleton to **dense bodies,** little masses of protein scattered throughout the sarcoplasm and on the inner face of the sarcolemma.

The sarcoplasmic reticulum is scanty, and there are no T tubules. The calcium needed to activate smooth muscle contraction comes mainly from the extracellular fluid (ECF) by way of calcium channels in the sarcolemma. During relaxation, calcium is pumped back out of the cell. Some smooth muscle has no nerve supply, but when nerve fibers are present, they are autonomic (like those of cardiac muscle) and not somatic motor fibers.

Unlike skeletal and cardiac muscle, smooth muscle is capable of mitosis and hyperplasia. Thus, an organ such as the pregnant uterus can grow by adding more myocytes, and injured smooth muscle regenerates well.

Types of Smooth Muscle

There are two functional categories of smooth muscle called *multiunit* and *single-unit* types (fig. 11.21). **Multiunit smooth muscle** occurs in some of the largest arteries and pulmonary air passages, in the piloerector muscles of the hair follicles, and in the iris of the eye. Its innervation, although autonomic, is otherwise similar to that of skeletal muscle—the terminal branches of a nerve fiber synapse with individual myocytes and form a motor unit. Each motor unit contracts independently of the others, hence the name of this muscle type.

Single-unit smooth muscle is more widespread. It occurs in most blood vessels and in the digestive, respiratory, urinary, and reproductive tracts—thus, it is also called **visceral muscle.** In many of the hollow viscera, it forms two or more layers—typically an inner *circular layer,* in which the myocytes encircle the organ, and an outer *longitudinal layer,* in which the myocytes run lengthwise along the

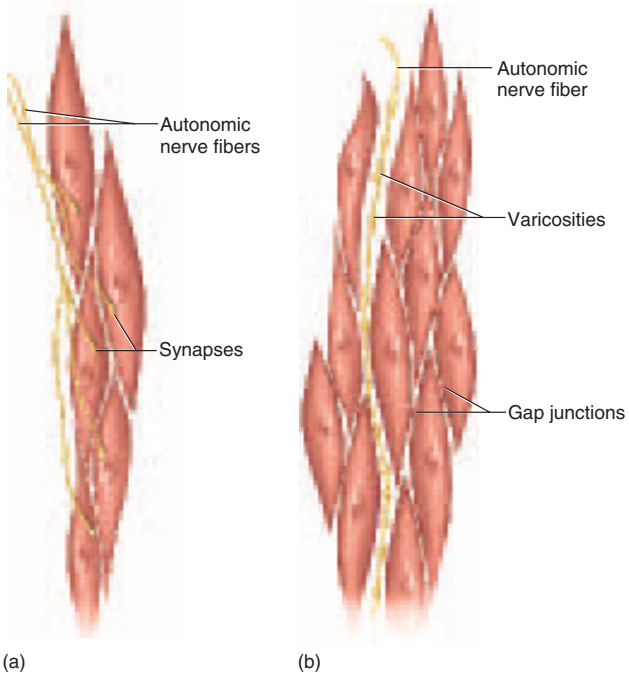


Figure 11.21 Smooth Muscle Innervation. (*a*) Multiunit smooth muscle, in which each muscle cell receives its own nerve supply. (*b*) Single-unit smooth muscle, in which a nerve fiber passes through the tissue without synapsing with any specific muscle cell.

[12] *auto* = self

organ (fig. 11.22). The name *single-unit* refers to the fact that the myocytes of this type of muscle are electrically coupled to each other by gap junctions. Thus, they directly stimulate each other and a large number of cells contract as a unit, almost as if they were a single cell.

Stimulation of Smooth Muscle

Like cardiac muscle, smooth muscle is involuntary and capable of contracting without nervous stimulation. Some smooth muscle contracts in response to chemical stimuli such as hormones, carbon dioxide, low pH, and oxygen deficiency and in response to stretch (as in a full stomach or bladder). Some single-unit smooth muscle, especially in the stomach and intestines, has pacemaker cells that spontaneously depolarize and set off waves of contraction throughout an entire layer of muscle. Such smooth muscle is autorhythmic, like cardiac muscle, although with a much slower rhythm.

But like cardiac muscle, smooth muscle is innervated by autonomic nerve fibers that can trigger or modify its contractions. Autonomic nerve fibers stimulate smooth muscle with either acetylcholine or norepinephrine. The nerve fibers have contrasting effects on smooth muscle in different locations. They relax the smooth muscle of arteries while contracting the smooth muscle in the bronchioles of the lungs, for example.

In single-unit smooth muscle, each autonomic nerve fiber has up to 20,000 beadlike swellings called **varicosities** along its length (figs. 11.21 and 11.23). Each varicosity contains synaptic vesicles and a few mitochondria. Instead of closely approaching any one myocyte, the nerve fiber passes amid several myocytes and stimulates all of them at once when it releases its neurotransmitter. The muscle cells do not have motor end plates or any other specialized area of sarcolemma to bind the neurotransmitter; rather, they have receptor sites scattered throughout the surface. Such nerve-muscle relationships are called **diffuse junctions** because there is no one-to-one relationship between a nerve fiber and a myocyte.

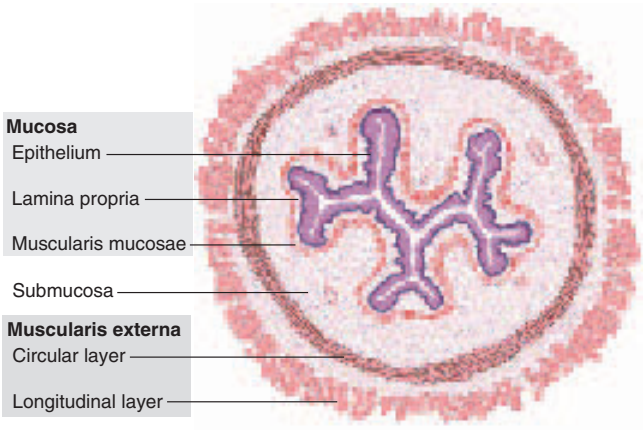


Figure 11.22 Layers of Visceral (single-unit) Smooth Muscle in a Cross Section of the Esophagus. Many hollow organs have alternating circular and longitudinal layers of smooth muscle.

Contraction and Relaxation

Smooth muscle resembles the other muscle types in that contraction is triggered by calcium ions (Ca^{2+}), energized by ATP, and achieved by the sliding of thin filaments over the

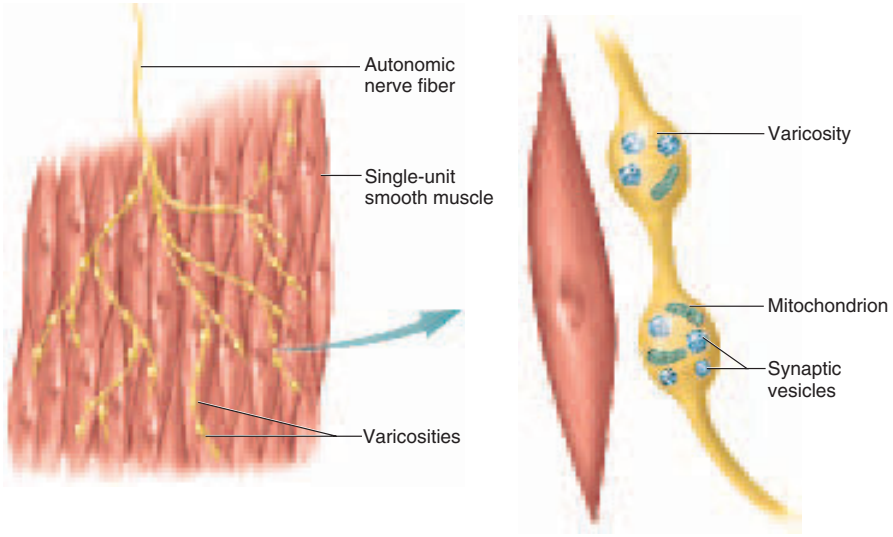


Figure 11.23 Varicosities of an Autonomic Nerve Fiber in Single-Unit Smooth Muscle.

thick filaments. The mechanism of excitation-contraction coupling, however, is very different. Little of the Ca^{2+} comes from the sarcoplasmic reticulum; most comes from the extracellular fluid and enters the cell through calcium channels in the sarcolemma. Some of these channels are voltage-gated and open in response to changes in membrane voltage; some are ligand-gated and open in response to hormones and neurotransmitters; and some are mechanically gated and open in response to stretching of the cell.

Think About It

How is smooth muscle contraction affected by the drugs called calcium channel blockers? (see p. 101)

Smooth muscle has no troponin. Calcium binds instead to a similar protein called **calmodulin**[13] (cal-MOD-you-lin), associated with the thick filaments. Calmodulin then activates an enzyme called **myosin light-chain kinase,** which transfers a phosphate group from ATP to the head of the myosin. This activates the myosin ATPase and enables it to bind to actin, but in order to execute a power stroke, the myosin must bind and hydrolyze yet another ATP. It then produces power and recovery strokes like those of skeletal muscle.

As thick filaments pull on the thin ones, the thin filaments pull on intermediate filaments, which in turn pull on the dense bodies of the plasma membrane. This shortens the entire cell. When a smooth muscle cell contracts, it twists in a spiral fashion, somewhat like wringing out a wet towel except that the "towel" wrings itself (fig. 11.24).

In skeletal muscle, there is typically a 2 msec latent period between stimulation and the onset of contraction. In smooth muscle, by contrast, the latent period is 50 to 100 msec long. Tension peaks about 500 msec (0.5 sec) after the stimulus and then declines over a period of 1 to 2 seconds. The effect of all this is that compared to skeletal muscle, smooth muscle is very slow to contract and relax. It is slow to contract because its myosin ATPase is a slow enzyme. It is slow to relax because the pumps that remove Ca^{2+} from the cell are also slow. As the Ca^{2+} level falls, myosin is dephosphorylated and is no longer able to hydrolyze ATP and execute power strokes. However, it does not necessarily detach from actin immediately. Its myosin has a *latch-bridge mechanism* that enables it to remain attached to actin for a prolonged time without consuming more ATP.

Smooth muscle often exhibits tetanus and is very resistant to fatigue. It makes most of its ATP aerobically, but its ATP requirement is small and it has relatively few mitochondria. Skeletal muscle requires 10 to 300 times as much ATP as smooth muscle to maintain the same amount of tension. The fatigue-resistance and latch-bridge mechanism of smooth muscle are important in enabling it to maintain a state of continual **smooth muscle tone (tonic contraction).** This tonic contraction keeps the arteries in a state of partial constriction called *vasomotor tone.* A loss of muscle tone in the arteries can cause a dangerous drop in blood pressure. Smooth muscle tone also keeps the intestines partially contracted. The intestines are much longer in a cadaver than they are in a living person because of the loss of muscle tone at death.

[13]acronym for *cal*cium *modul*ating prote*in*

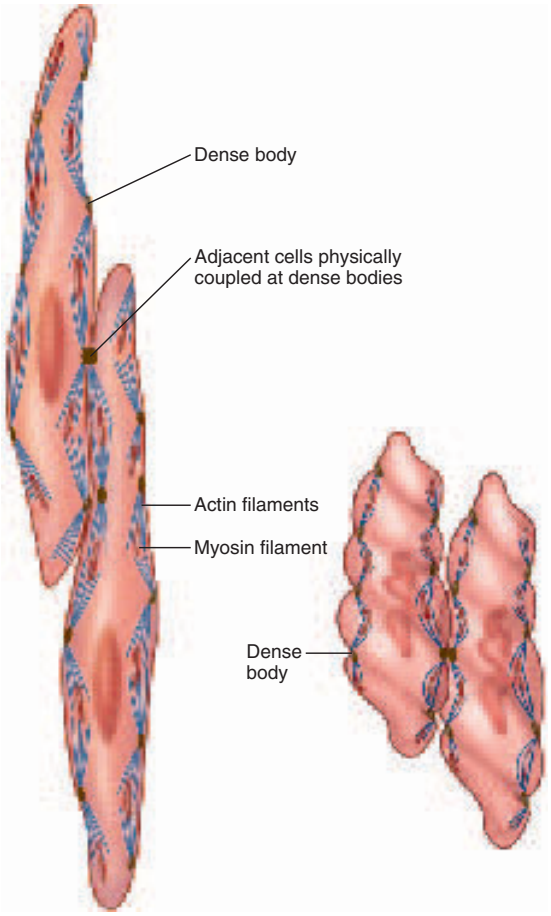


Figure 11.24 Smooth Muscle Contraction. (*a*) Relaxed cells. Actin myofilaments are anchored to dense bodies in the sarcoplasm and on the plasma membrane, rather than to Z discs. (*b*) Contracted cells. Note the twisting effect.

Response to Stretch

Stretch alone sometimes causes smooth muscle to contract by opening mechanically gated calcium channels in the sarcolemma. Distension of the esophagus with food or the colon with feces, for example, evokes a wave of contraction called **peristalsis** (PERR-ih-STAL-sis) that propels the contents along the organ.

Smooth muscle exhibits a reaction called the **stress-relaxation** (or **receptive relaxation**) **response.** When stretched, it briefly contracts and resists, but then relaxes. The significance of this response is apparent in the urinary bladder, whose wall consists of three layers of smooth muscle. If the stretched bladder contracted and did not soon relax, it would expel urine almost as soon as it began to fill, thus failing to store the urine until an opportune time.

Remember that skeletal muscle cannot contract very forcefully if it is overstretched. Smooth muscle is not subject to the limitations of this length-tension relationship. It must be able to contract forcefully even when greatly stretched, so that hollow organs such as the stomach and bladder can fill and then expel their contents efficiently. Skeletal muscle must be within 30% of optimum length in order to contract strongly when stimulated. Smooth muscle, by contrast, can be anywhere from half to twice its resting length and still contract powerfully. There are three reasons for this: (1) there are no Z discs, so thick filaments cannot butt against them and stop the contraction; (2) since the thick and thin filaments are not arranged in orderly sarcomeres, stretching of the muscle does not cause a situation where there is too little overlap for cross-bridges to form; and (3) the thick filaments of smooth muscle have myosin heads along their entire length (there is no bare zone), so cross-bridges can form anywhere, not just at the ends. Smooth muscle also exhibits **plasticity**—the ability to adjust its tension to the degree of stretch. Thus, a hollow organ such as the bladder can be greatly stretched yet not become flabby when it is empty.

The muscular system suffers fewer diseases than any other organ system, but several of its more common dysfunctions are listed in table 11.6. The effects of aging on the muscular system are described on pages 1109–1110.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

25. Explain why intercalated discs are important to cardiac muscle function.
26. Explain why it is important for cardiac muscle to have a longer action potential and longer refractory period than skeletal muscle.
27. How do single-unit and multiunit smooth muscle differ in innervation and contractile behavior?
28. How does smooth muscle differ from skeletal muscle with respect to its source of calcium and its calcium receptor?
29. Explain why the stress-relaxation response is an important factor in smooth muscle function.

Table 11.6 Some Disorders of the Muscular System

Delayed onset muscle soreness	Pain, stiffness, and tenderness felt from several hours to a day after strenuous exercise. Associated with microtrauma to the muscles, with disrupted Z discs, myofibrils, and plasma membranes; and with elevated levels of myoglobin, creatine kinase, and lactate dehydrogenase in the blood.
Cramps	Painful muscle spasms triggered by heavy exercise, extreme cold, dehydration, electrolyte loss, low blood glucose, or lack of blood flow.
Contracture	Abnormal muscle shortening not caused by nervous stimulation. Can result from failure of the calcium pump to remove Ca^{2+} from the sarcoplasm or from contraction of scar tissue, as in burn patients.
Fibromyalgia	Diffuse, chronic muscular pain and tenderness, often associated with sleep disturbances and fatigue; often misdiagnosed as chronic fatigue syndrome. Can be caused by various infectious diseases, physical or emotional trauma, or medications. Most common in women 30 to 50 years old.
Crush syndrome	A shocklike state following the massive crushing of muscles; associated with high and potentially fatal fever, cardiac irregularities resulting from K^+ released from the muscle, and kidney failure resulting from blockage of the renal tubules with myoglobin released by the traumatized muscle. Myoglobinuria (myoglobin in the urine) is a common sign.
Disuse atrophy	Reduction in the size of muscle fibers as a result of nerve damage or muscular inactivity, for example in limbs in a cast and in patients confined to a bed or wheelchair. Muscle strength can be lost at a rate of 3% per day of bed rest.
Myositis	Muscle inflammation and weakness resulting from infection or autoimmune disease.

Disorders described elsewhere

Athletic injuries p. 386	Hernia p. 351	Pulled groin p. 386
Back injuries p. 349	Muscular dystrophy p. 437	Pulled hamstrings p. 386
Baseball finger p. 386	Myasthenia gravis p. 437	Rotator cuff injury p. 386
Carpal tunnel syndrome p. 365	Paralysis p. 414	Tennis elbow p. 386
Charley horse p. 386	Pitcher's arm p. 386	Tennis leg p. 386
Compartment syndrome p. 386		

Insight 11.4 Clinical Application

Muscular Dystrophy and Myasthenia Gravis

Muscular dystrophy[14] is a collective term for several hereditary diseases in which the skeletal muscles degenerate, lose strength, and are gradually replaced by adipose and fibrous tissue. This new connective tissue impedes blood circulation, which in turn accelerates muscle degeneration in a fatal spiral of positive feedback. The most common form of the disease is *Duchenne*[15] *muscular dystrophy (DMD),* caused by a sex-linked recessive allele. Like other sex-linked traits (see chapter 4), DMD is mainly a disease of males. It occurs in about 1 in 3,500 male live births, but is not usually diagnosed until the age of 2 to 10 years. Difficulties begin to appear early on, as a child begins to walk. The child falls frequently and has difficulty standing up again. The disease affects the hips first, then the legs, and progresses to the abdominal and spinal muscles. The muscles shorten as they atrophy, causing postural abnormalities such as scoliosis. DMD is incurable but is treated with exercise to slow the atrophy and with braces to reinforce the weakened hips and correct the posture. Patients are usually confined to a wheelchair by early adolescence and rarely live beyond the age of 20.

The DMD gene was identified in 1987, and genetic screening is now available to inform prospective parents of whether or not they are carriers. The normal allele of this gene makes *dystrophin,* a large protein that links to actin filaments at one end and to membrane glycoproteins on the other. In DMD, dystrophin is absent, the plasma membranes of the muscle fibers become torn, and the muscle fibers die.

A less severe form of muscular dystrophy is *facioscapulohumeral (Landouzy–Dejerine*[16]*) muscular dystrophy,* an autosomal dominant trait that begins in adolescence and affects both sexes. It involves the facial and shoulder muscles more than the pelvic muscles and disables some individuals while it barely affects others. A third form, *limb-girdle dystrophy,* is a combination of several diseases of intermediate severity that affect the shoulder, arm, and pelvic muscles.

Myasthenia gravis[17] (MY-ass-THEE-nee-uh GRAV-is) *(MG)* usually occurs in women between the ages of 20 and 40. It is an autoimmune disease in which antibodies attack the neuromuscular junctions and bind ACh receptors together in clusters. The muscle fiber then removes the clusters from the sarcolemma by endocytosis. As a result, the muscle fibers become less and less sensitive to ACh. The effects often appear first in the facial muscle (fig. 11.25) and commonly include drooping eyelids and double vision (due to weakness of the eye muscles). The initial symptoms are often followed by difficulty in swallowing, weakness of the limbs, and poor physical endurance. Some people with MG die quickly as a result of respiratory failure, but others have normal life spans. One method of assessing the progress of the disease is to use *bungarotoxin,* a protein from cobra venom that binds to ACh receptors. The amount that binds is proportional to the number of receptors that are still functional. The muscle of an MG patient sometimes binds less than one-third as much bungarotoxin as normal muscle does.

Myasthenia gravis is often treated with cholinesterase inhibitors. These drugs retard the breakdown of ACh in the neuromuscular junction and enable it to stimulate the muscle longer. Immunosuppressive agents such as Prednisone and Imuram may be used to suppress the production of the antibodies that destroy ACh receptors. Since certain immune cells are stimulated by hormones from the thymus, removal of the thymus *(thymectomy)* helps to dampen the overactive immune response that causes myasthenia gravis. Also, a technique called *plasmapheresis* may be used to remove harmful antibodies from the blood plasma.

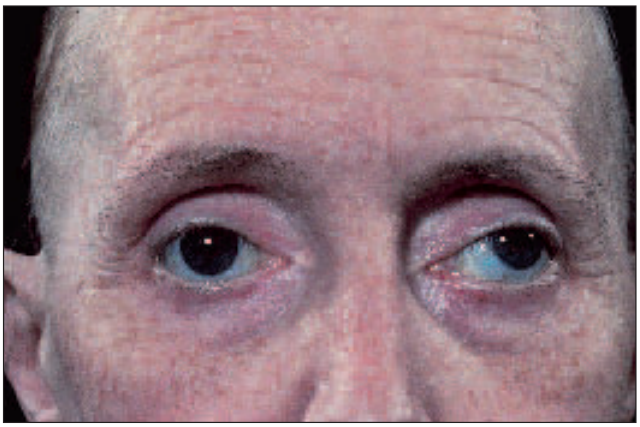


Figure 11.25 Myasthenia Gravis. This disorder especially affects the muscles of the head. It is characterized by drooping of the eyelids, weakness of the muscles of eye movement, and double vision resulting from the divergence *(strabismus)* of the eyes.

[14] *dys* = bad, abnormal + *trophy* = growth
[15] Guillaume B. A. Duchenne (1806–75), French physician
[16] Louis T. J. Landouzy (1845–1917) and Joseph J. Dejerine (1849–1917), French neurologists
[17] *my* = muscle + *asthen* = weakness + *grav* = severe

Chapter Review

Review of Key Concepts

Types and Characteristics of Muscular Tissue (p. 408)

1. Muscular tissue has the properties of responsiveness, conductivity, contractility, extensibility, and elasticity.
2. Skeletal muscle is voluntary striated muscle that is usually attached to one or more bones.
3. A skeletal muscle cell, or muscle fiber, is a threadlike cell typically 100 μm in diameter and 3 cm long.

Microscopic Anatomy of Skeletal Muscle (p. 409)

1. A muscle fiber forms by the fusion of many stem cells called *myoblasts*, and is thus multinucleate.
2. The *sarcolemma* (plasma membrane) exhibits tunnel-like infoldings called *transverse (T) tubules* that cross from one side of the cell to the other.
3. The *sarcoplasm* (cytoplasm) is occupied mainly by protein bundles called *myofibrils.* Mitochondria, glycogen, and myoglobin are packed between the myofibrils.
4. The fiber has an extensive *sarcoplasmic reticulum* (SR) that serves as a Ca^{2+} reservoir. On each side of a T tubule, the SR expands into a *terminal cisterna.*
5. A myofibril is a bundle of two kinds of protein *myofilaments* called thick and thin filaments.
6. *Thick filaments* are composed of bundles of *myosin* molecules, each of which has a filamentous tail and a globular head.
7. Thin filaments are composed mainly of a double strand of *actin,* with a myosin-binding *active site* on each of its globular subunits. In the groove between the two actin strands are two regulatory proteins, *tropomyosin* and *troponin.*
8. Elastic filaments composed of *titin* run through the core of a thick filament and attach to Z discs.
9. Skeletal and cardiac muscle exhibit alternating light and dark bands, or *striations,* that result from the pattern of overlap between thick and thin filaments. The principal striations are a dark *A band* with a light *H zone* in the middle, and a light *I band* with a dark line, the *Z disc,* in the middle.
10. The functional unit of a muscle fiber is the *sarcomere,* which is a segment from one Z disc to the next.

The Nerve-Muscle Relationship (p. 412)

1. Skeletal muscle contracts only when it is stimulated by a *somatic motor nerve fiber.*
2. One somatic motor fiber branches at the end and innervates from 3 to 1,000 muscle fibers. The nerve fiber and its muscle fibers are called a *motor unit.* Small motor units (few muscle fibers per nerve fiber) are found in muscles where fine control of movement is important, and large motor units in muscles where strength is more important than precision.
3. The point where a nerve fiber meets a muscle fiber is a type of synapse called the *neuromuscular junction.* It consists of the *synaptic knob* (a dilated tip of the nerve fiber) and a *motor end plate* (a folded depression in the sarcolemma). The gap between the knob and end plate is the *synaptic cleft.*
4. *Synaptic vesicles* in the knob release a neurotransmitter called *acetylcholine (ACh),* which diffuses across the cleft and binds to *ACh receptors* on the end plate.
5. An unstimulated nerve, muscle, or other cell has a difference in positive and negative charges on the two sides of its plasma membrane; it is *polarized.* The charge difference, called the *resting membrane potential,* is typically about −90 mV on a muscle fiber.
6. When a nerve or muscle fiber is stimulated, a quick, self-propagating voltage shift called an *action potential* occurs. Action potentials form nerve signals and activate muscle contraction.

Behavior of Skeletal Muscle Fibers (p. 416)

1. The first stage of muscle action is *excitation.* An arriving nerve signal triggers ACh release, ACh binds to receptors on the motor end plate and triggers a voltage change called an *end-plate potential (EPP),* and the EPP triggers action potentials in adjacent regions of the sarcolemma.
2. The second stage is *excitation-contraction coupling.* Action potentials spread along the sarcolemma and down the T tubules, and trigger Ca^{2+} release from the terminal cisternae of the SR. Ca^{2+} binds to troponin of the thin filaments, and tropomyosin shifts position to expose the active sites on the actin.
3. The third stage is *contraction.* A myosin head binds to an active site on actin, flexes, tugs the thin filament closer to the A band, then releases the actin and repeats the process. Each cycle of binding and release consumes one ATP.
4. The fourth and final stage is *relaxation.* When nerve signals cease, ACh release ceases. The enzyme acetylcholinesterase degrades the ACh already present, halting stimulation of the muscle fiber. The SR pumps Ca^{2+} back into it for storage. In the absence of Ca^{2+}, tropomyosin blocks the active sites of actin so myosin can no longer bind to them, and the muscle relaxes.
5. Overly contracted and overly stretched muscle fibers respond poorly to stimulation. A muscle responds best when it is slightly contracted before it is stimulated, so that there is optimal overlap between the resting thick and thin filaments. This is the *length-tension relationship. Muscle tone* maintains an optimal resting length and readiness to respond.

Behavior of Whole Muscles (p. 423)

1. A stimulus must be of at least *threshold* strength to make a muscle

contract. After a short *latent period,* the muscle responds to a single stimulus with a brief contraction called a *twitch.*
2. A single twitch does no useful work for the body. In *recruitment,* however, multiple motor units are activated at once to produce a stronger muscle contraction. In high-frequency stimulation, successive twitches become progressively stronger; this is called *treppe* when the muscle completely relaxes between twitches and *incomplete tetanus* when it relaxes only partially and each twitch "piggybacks" on the previous ones to achieve greater tension.
3. In *isometric contraction,* a muscle develops tension without changing length; in *isotonic contraction,* it changes length while maintaining constant tension. In *concentric contraction,* a muscle maintains tension as it shortens; in *eccentric contraction,* it maintains tension as it lengthens.

Muscle Metabolism (p. 427)

1. A muscle must have ATP in order to contract. It generates ATP by different mechanisms over the duration of a period of exercise.
2. At the outset, muscle uses oxygen from its myoglobin to generate ATP by aerobic respiration.
3. As the stored oxygen is depleted, muscle regenerates ATP from ADP by adding a phosphate (P_i) to it. It gets this P_i either from another ADP, using the enzyme myokinase to transfer the phosphate, or from creatine phosphate, using the enzyme creatine kinase to do so. This is the *phosphagen system* for regenerating ATP.
4. Further into an exercise, as the phosphagen system is depleted, a muscle shifts to anaerobic fermentation (the *glycogen–lactic acid system*).
5. Still later, the respiratory and circulatory systems may catch up with the demands of a muscle and deliver enough oxygen for aerobic respiration to meet the muscle's ATP demand.
6. Muscle fatigue results from several factors: ATP and ACh depletion, loss of membrane excitability, lactic acid accumulation, and central nervous system mechanisms.
7. The ability to maintain high-intensity exercise depends partly on one's *maximum oxygen uptake,* which varies with body size, age, sex, and physical condition.
8. Prolonged exercise produces an *oxygen debt* that is "repaid" by continued heavy breathing after the exercise is over. The extra O_2 breathed during this time goes mainly to restore oxygen reserves in the myoglobin and blood, replenish the phosphagen system, oxidize lactic acid, and meet the needs of a metabolic rate elevated by the high post-exercise body temperature.
9. *Slow oxidative* muscle fibers are adapted for aerobic respiration and relatively resistant to fatigue, but produce relatively slow responses. *Fast glycolytic* muscle fibers respond more quickly but fatigue sooner. *Intermediate fibers* are relatively rare but combine fast responses with fatigue resistance.
10. The strength of a muscle depends on its size, fascicle arrangement, size of its motor units, multiple motor unit summation, temporal summation of twitches, prestimulation length, and fatigue.
11. Resistance exercise stimulates muscle growth and increases strength; endurance exercise increases fatigue resistance.

Cardiac and Smooth Muscle (p. 432)

1. Cardiac muscle consists of relatively short, branched, striated cells joined physically and electrically by *intercalated discs.*
2. Cardiac muscle is *autorhythmic* and thus contracts even without innervation.
3. Cardiac muscle is rich in myoglobin, glycogen, and large mitochondria, uses aerobic respiration almost exclusively, and is very fatigue-resistant.
4. Smooth muscle consists of short, fusiform, nonstriated cells.
5. Smooth muscle has no T tubules and little sarcoplasmic reticulum; it gets Ca^{2+} from the extracellular fluid.
6. In multiunit smooth muscle, each cell is separately innervated by an autonomic nerve fiber and contracts independently. In single-unit smooth muscle, the muscle cells are connected by gap junctions and respond as a unit. Nerve fibers do not synapse with any specific muscle cells in the latter type.
7. In smooth muscle, Ca^{2+} binds to calmodulin rather than troponin. This activates a kinase, which phosphorylates myosin and triggers contraction.
8. Smooth muscle lacks Z discs. Its myofilaments indirectly pull on *dense bodies* and cause the cell to contract in a twisting fashion.
9. Smooth muscle has a latch-bridge mechanism that enables it to maintain tonic contraction with little ATP expenditure.
10. Smooth muscle is not subject to the length-tension relationship. Its unusual ability to stretch and maintain responsiveness allows such organs as the stomach and urinary bladder to expand greatly without losing contractility.

Selected Vocabulary

skeletal muscle 408
striation 408
voluntary 408
involuntary 408
myoglobin 409
sarcoplasmic reticulum 409
thick filament 409
myosin 409
thin filament 409
actin 409
neuromuscular junction 413
acetylcholine 414
acetylcholinesterase 414
muscle tone 423
twitch 423
recruitment 424
treppe 424
tetanus 425
fatigue 428
oxygen debt 429
cardiac muscle 432
autorhythmic 433
smooth muscle 433

Testing Your Recall

1. To make a muscle contract more strongly, the nervous system can activate more motor units. This process is called
   a. recruitment.
   b. summation.
   c. incomplete tetanus.
   d. twitch.
   e. treppe.
2. The _____ is a depression in the sarcolemma that receives a motor nerve ending.
   a. T tubule
   b. terminal cisterna
   c. sarcomere
   d. motor end plate
   e. synapse
3. Before a muscle fiber can contract, ATP must bind to
   a. a Z disc.
   b. the myosin head.
   c. tropomyosin.
   d. troponin.
   e. actin.
4. Before a muscle fiber can contract, Ca^{2+} must bind to
   a. calsequestrin.
   b. the myosin head.
   c. tropomyosin.
   d. troponin.
   e. actin.
5. Skeletal muscle fibers have _____, whereas smooth muscle cells do not.
   a. T tubules
   b. ACh receptors
   c. thick myofilaments
   d. thin myofilaments
   e. dense bodies
6. Smooth muscle cells have_____, whereas skeletal muscle fibers do not.
   a. sarcoplasmic reticulum
   b. tropomyosin
   c. calmodulin
   d. Z discs
   e. myosin ATPase
7. ACh receptors are found mainly in
   a. synaptic vesicles.
   b. terminal cisternae.
   c. thick filaments.
   d. thin filaments.
   e. junctional folds.
8. Single-unit smooth muscle cells can stimulate each other because they have
   a. a latch-bridge.
   b. diffuse junctions.
   c. gap junctions.
   d. tight junctions.
   e. calcium pumps.
9. Warm-up exercises take advantage of _____ to enable muscles to perform at peak strength.
   a. the stress-relaxation response
   b. the length-tension relationship
   c. excitatory junction potentials
   d. oxygen debt
   e. treppe
10. Slow oxidative fibers have all of the following *except*
    a. an abundance of myoglobin.
    b. an abundance of glycogen.
    c. high fatigue resistance.
    d. a red color.
    e. a high capacity to synthesize ATP aerobically.
11. The minimum stimulus intensity that will make a muscle contract is called _____.
12. A state of prolonged maximum contraction is called _____.
13. Parts of the sarcoplasmic reticulum called _____ lie on each side of a T tubule.
14. Thick myofilaments consist mainly of the protein _____.
15. The neurotransmitter that stimulates skeletal muscle is _____.
16. Muscle contains an oxygen-binding pigment called _____.
17. The _____ of skeletal muscle play the same role as dense bodies in smooth muscle.
18. In autonomic nerve fibers that stimulate single-unit smooth muscle, the neurotransmitter is contained in swellings called _____.
19. A state of continual partial muscle contraction is called _____.
20. _____ is an end product of anaerobic fermentation that causes muscle fatigue.

Answers in Appendix B

True or False

Determine which five of the following statements are false, and briefly explain why.

1. Each motor neuron supplies just one muscle fiber.
2. To initiate muscle contraction, calcium ions must bind to the myosin heads.
3. Slow oxidative fibers are relatively resistant to fatigue.
4. Thin filaments are found in both the A bands and I bands of striated muscle.
5. Thin filaments do not change length when a muscle contracts.
6. Smooth muscle lacks striations because it does not have thick and thin myofilaments.
7. A muscle must contract to the point of complete tetanus if it is to move a load.
8. If no ATP were available to a muscle fiber, the excitation stage of muscle action could not occur.
9. For the first 30 seconds of an intense exercise, muscle gets most of its energy from lactic acid.
10. Cardiac and some smooth muscle are autorhythmic, but skeletal muscle is not.

Answers in Appendix B

Testing Your Comprehension

1. Without ATP, relaxed muscle cannot contract and a contracted muscle cannot relax. Explain why.
2. Slight pH variations can cause enzymes to change conformation and can reduce enzyme activity. Explain how this relates to muscle fatigue.
3. Why would skeletal muscle be unsuitable for the wall of the urinary bladder? Explain how this illustrates the complementarity of form and function at a cellular and molecular level.
4. As skeletal muscle contracts, one or more bands of the sarcomere become narrower and disappear, and one or more of them remain the same width. Which bands will change—A, H, or I—and why?
5. Botulism occurs when a bacterium, *Clostridium botulinum,* releases a neurotoxin that prevents motor neurons from releasing ACh. In view of this, what early signs of botulism would you predict? Explain why a person with botulism could die of suffocation.

Answers at the Online Learning Center

Answers to Figure Legend Questions

11.4 The I band

11.13 ATP is needed to pump Ca^{2+} back into the sarcoplasmic reticulum by active transport, and to induce each myosin head to release actin so the sarcomere can relax.

11.16 The gluteus maximus and quadriceps femoris

11.17 The muscle tension line would drop gradually while the muscle length line would rise.

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