CHAPTER

4

Excitable Tissue: Nerve

OBJECTIVES

After studying this chapter, you should be able to:

- Name the various types of glia and their functions.
- Name the parts of a neuron and their functions.
- Describe the chemical nature of myelin, and summarize the differences in the ways in which unmyelinated and myelinated neurons conduct impulses.
- Describe orthograde and retrograde axonal transport.
- Describe the changes in ionic channels that underlie the action potential.
- List the various nerve fiber types found in the mammalian nervous system.
- Describe the function of neurotrophins.

INTRODUCTION

The human central nervous system (CNS) contains about 10^{11} (100 billion) **neurons.** It also contains 10–50 times this number of **glial cells.** The CNS is a complex organ; it has been calculated that 40% of the human genes participate, at least to a degree, in its formation. The neurons, the basic building blocks of the nervous system, have evolved from primitive neuroeffector cells that respond to various stimuli by contracting. In more complex animals, contraction has become the specialized function of muscle cells, whereas integration and transmission of nerve impulses have become the specialized functions of neurons. Neurons and glial cells along with brain capillaries form a functional unit that is required for normal brain function, including synaptic activity, extracellular fluid homeostasis, energy metabolism, and neural protection. Disturbances in the interaction of these elements are the pathophysiological basis for many neurological disorders (eg, cerebral ischemia, seizures, neurodegenerative diseases, and cerebral edema). This chapter describes the cellular components of the CNS and the excitability of neurons, which involves the genesis of electrical signals that enable neurons to integrate and transmit impulses (eg, action potentials, receptor potentials, and synaptic potentials).

CELLULAR ELEMENTS IN THE CNS

GLIAL CELLS

For many years following their discovery, glial cells (or glia) were viewed as CNS connective tissue. In fact, the word *glia* is Greek for *glue.* However, today theses cells are recognized for their role in communication within the CNS in partnership with neurons. Unlike neurons, glial cells continue to undergo cell division in adulthood and their ability to proliferate is particularly noticeable after brain injury (eg, stroke).

There are two major types of glial cells in the vertebrate nervous system: **microglia** and **macroglia.** Microglia are scavenger cells that resemble tissue macrophages and remove debris resulting from injury, infection, and disease (eg, multiple sclerosis, AIDS-related dementia, Parkinson disease, and Alzheimer disease). Microglia arise from macrophages outside of the nervous system and are physiologically and embryologically unrelated to other neural cell types.

There are three types of macroglia: oligodendrocytes, Schwann cells, and astrocytes (Figure 4–1). **Oligodendrocytes** and **Schwann cells** are involved in myelin formation around axons in the CNS and peripheral nervous system, respectively. **Astrocytes,** which are found throughout the brain, are of two subtypes. **Fibrous astrocytes,** which contain many intermediate filaments, are found primarily in white matter.

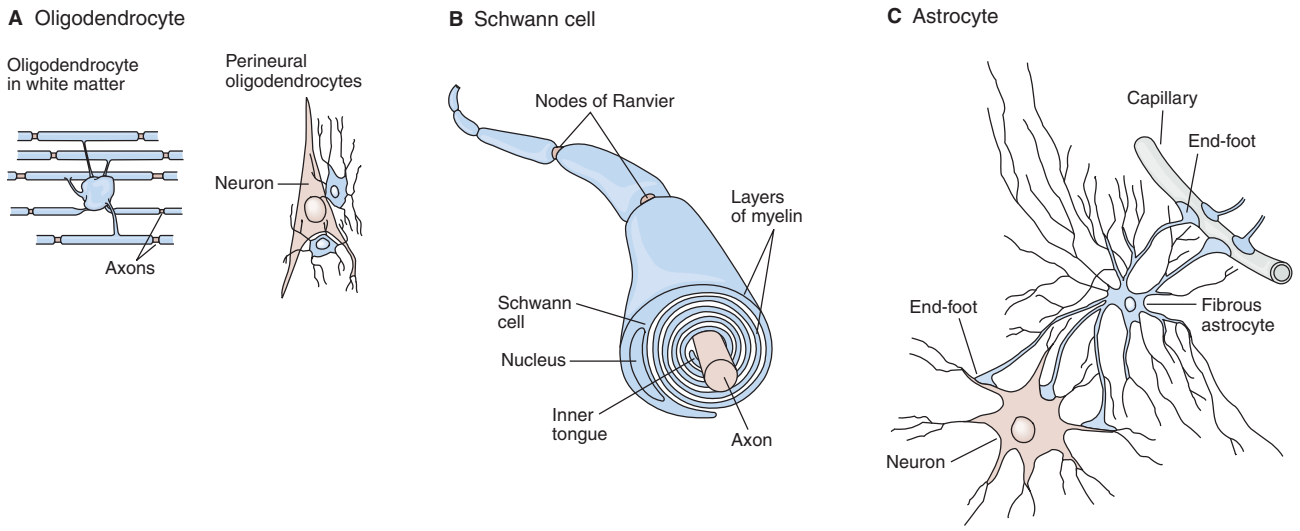

FIGURE 4–1 The principal types of macroglia in the nervous system. A) Oligodendrocytes are small with relatively few processes. Those in the white matter provide myelin, and those in the gray matter support neurons. **B)** Schwann cells provide myelin to the peripheral nervous system. Each cell forms a segment of myelin sheath about 1 mm long; the sheath assumes its form as the inner tongue of the Schwann cell turns around the axon several times, wrapping in concentric layers. Intervals between segments of myelin are the nodes of Ranvier. **C)** Astrocytes are the most common glia in the CNS and are characterized by their starlike shape. They contact both capillaries and neurons and are thought to have a nutritive function. They are also involved in forming the blood–brain barrier. (From Kandel ER, Schwartz JH, Jessell TM (editors): *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.)

Protoplasmic astrocytes are found in gray matter and have a granular cytoplasm. Both types send processes to blood vessels, where they induce capillaries to form the tight junctions making up the **blood–brain barrier.** They also send processes that envelop synapses and the surface of nerve cells. Protoplasmic astrocytes have a membrane potential that varies with the external K^+ concentration but do not generate propagated potentials. They produce substances that are tropic to neurons, and they help maintain the appropriate concentration of ions and neurotransmitters by taking up K^+ and the neurotransmitters glutamate and γ-aminobutyrate (GABA).

NEURONS

Neurons in the mammalian CNS come in many different shapes and sizes. Most have the same parts as the typical spinal motor neuron illustrated in Figure 4–2. The cell body **(soma)** contains the nucleus and is the metabolic center of the neuron. Neurons have several processes called **dendrites** that extend outward from the cell body and arborize extensively. Particularly in the cerebral and cerebellar cortex, the dendrites have small knobby projections called **dendritic spines.** A typical neuron also has a long fibrous **axon** that originates from a somewhat thickened area of the cell body, the **axon hillock.** The first portion

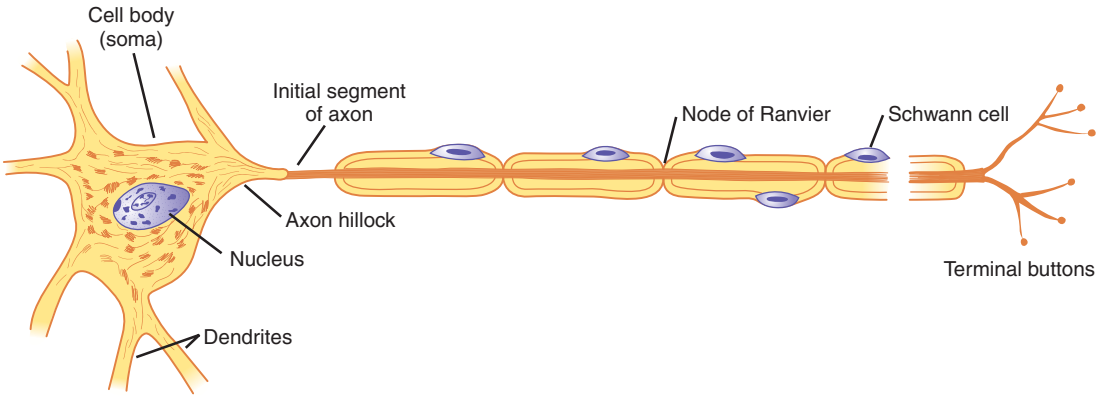

FIGURE 4–2 Motor neuron with a myelinated axon. A motor neuron is comprised of a cell body (soma) with a nucleus, several processes called dendrites, and a long fibrous axon that originates from the axon hillock. The first portion of the axon is called the initial segment. A myelin sheath forms from Schwann cells and surrounds the axon except at its ending and at the nodes of Ranvier. Terminal buttons (boutons) are located at the terminal endings.

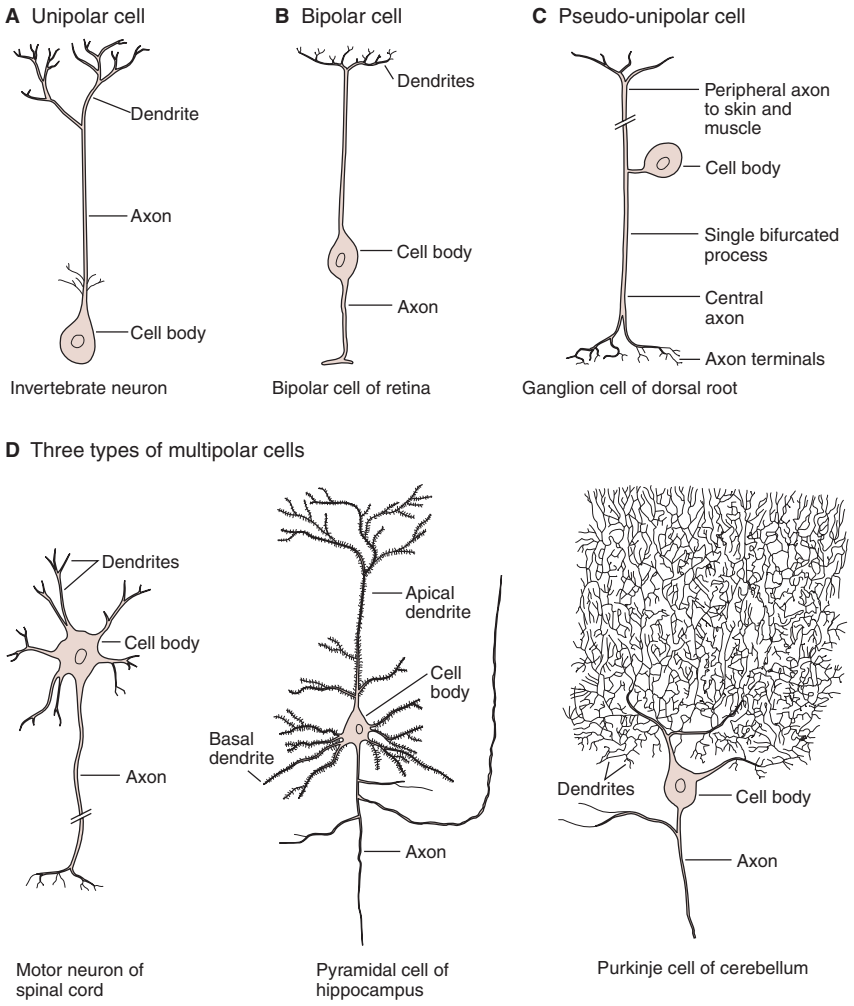

FIGURE 4–3 Some of the types of neurons in the mammalian nervous system. A) Unipolar neurons have one process, with different segments serving as receptive surfaces and releasing terminals. **B)** Bipolar neurons have two specialized processes: a dendrite that carries information to the cell and an axon that transmits information from the cell. **C)** Some sensory neurons are in a subclass of bipolar cells called pseudo-unipolar cells. As the cell develops, a single process splits into two, both of which function as axons—one going to skin or muscle and another to the spinal cord. **D)** Multipolar cells have one axon and many dendrites. Examples include motor neurons, hippocampal pyramidal cells with dendrites in the apex and base, and cerebellar Purkinje cells with an extensive dendritic tree in a single plane. (From Kandel ER, Schwartz JH, Jessell TM (editors): *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.)

of the axon is called the **initial segment.** The axon divides into **presynaptic terminals,** each ending in a number of **synaptic knobs** which are also called **terminal buttons** or **boutons.** They contain granules or vesicles in which the synaptic transmitters secreted by the nerves are stored. Based on the number of processes that emanate from their cell body, neurons can be classified as **unipolar, bipolar,** and **multipolar** (Figure 4–3).

The conventional terminology used for the parts of a neuron works well enough for spinal motor neurons and interneurons, but there are problems in terms of "dendrites" and "axons" when it is applied to other types of neurons found in the nervous system. From a functional point of view, neurons generally have four important zones: (1) a receptor, or dendritic zone, where multiple local potential changes generated by synaptic connections are integrated; (2) a site where propagated action potentials are generated (the initial segment in spinal motor neurons, the initial node of Ranvier in cutaneous sensory neurons); (3) an axonal process that transmits propagated impulses to the nerve endings; and (4) the nerve endings, where action potentials cause the release of synaptic transmitters. The cell body is often located at the dendritic zone end of the axon, but it can be within the axon (eg, auditory neurons) or attached to the side of the axon (eg, cutaneous neurons). Its location makes no difference as far as the receptor function of the dendritic zone and the transmission function of the axon are concerned.

The axons of many neurons are myelinated, that is, they acquire a sheath of **myelin,** a protein–lipid complex that is wrapped around the axon (Figure 4–1B). In the peripheral nervous system, myelin forms when a Schwann cell wraps its membrane around an axon up to 100 times. The myelin is then

CLINICAL BOX 4–1

Demyelinating Diseases

Normal conduction of action potentials relies on the insulating properties of **myelin.** Thus, defects in myelin can have major adverse neurological consequences. One example is **multiple sclerosis (MS),** an autoimmune disease that affects over 3 million people worldwide, usually striking between the ages of 20 and 50 and affecting women about twice as often as men. The cause of MS appears to include both genetic and environmental factors. It is most common among Caucasians living in countries with temperate climates including Europe, southern Canada, northern United States, and southeastern Australia. Environmental triggers include early exposure to viruses such as Epstein-Barr virus and those that cause measles, herpes, chicken pox, or influenza. In MS, antibodies and white blood cells in the immune system attack myelin, causing inflammation and injury to the sheath and eventually the nerves that it surrounds. Loss of myelin leads to leakage of K^+ through voltage-gated channels, hyperpolarization, and failure to conduct action potentials. Initial presentation commonly includes reports of **paraparesis** (weakness in lower extremities) that may be accompanied by mild spasticity and hyperreflexia; **paresthesia;** numbness; urinary incontinence; and heat intolerance. Clinical assessment often reports **optic neuritis,** characterized by blurred vision, a change in color perception, visual field defect (**central scotoma**), and pain with eye movements; **dysarthria;** and **dysphagia.** Symptoms are often exacerbated by increased body temperature or ambient temperature. Progression of the disease is quite variable. In the most common form called **relapsing-remitting MS,** transient episodes appear suddenly, last a few weeks or months, and then gradually disappear. Subsequent episodes can appear years later, and eventually full recovery does not occur. Many of these individuals later develop a steadily worsening course with only minor periods of remission (**secondary-progressive MS**). Others have a progressive form of the disease in which there are no periods of remission (**primary-progressive MS**). Diagnosing MS is very difficult and generally is delayed until multiple episodes occur with deficits separated in time and space. **Nerve conduction tests** can detect slowed conduction in motor and sensory pathways. Cerebral spinal fluid analysis can detect the presence of **oligoclonal** bands indicative of an abnormal immune reaction against myelin. The most definitive assessment is **magnetic resonance imaging (MRI)** to visualize multiple scarred (sclerotic) areas or plaques in the brain. These plaques often appear in the periventricular regions of the cerebral hemispheres.

THERAPEUTIC HIGHLIGHTS

Although there is no cure for MS, **corticosteroids** (eg, **prednisone**) are the most common treatment used to reduce the inflammation that is accentuated during a relapse. Some drug treatments are designed to modify the course of the disease. For example, daily injections of **β-interferons** suppress the immune response to reduce the severity and slow the progression of the disease. **Glatiramer acetate** may block the immune system's attack on the myelin. **Natalizumab** interferes with the ability of potentially damaging immune cells to move from the bloodstream to the CNS. A recent clinical trial using B cell–depleting therapy with **rituximab,** an anti-CD20 monoclonal antibody, showed that the progression of the disease was slowed in patients under the age of 51 who were diagnosed with the primary-progressive form of MS. Another recent clinical trial has shown that oral administration of **fingolimod** slowed the progression of the relapsing-remitting form of MS. This immunosuppressive drug acts by sequestering lymphocytes in the lymph nodes, thereby limiting their access to the CNS.

compacted when the extracellular portions of a membrane protein called protein zero (P_0) lock to the extracellular portions of P_0 in the apposing membrane. Various mutations in the gene for P_0 cause peripheral neuropathies; 29 different mutations have been described that cause symptoms ranging from mild to severe. The myelin sheath envelops the axon except at its ending and at the **nodes of Ranvier,** periodic 1-µm constrictions that are about 1 mm apart (Figure 4–2). The insulating function of myelin is discussed later in this chapter. Not all neurons are myelinated; some are **unmyelinated,** that is, simply surrounded by Schwann cells without the wrapping of the Schwann cell membrane that produces myelin around the axon.

In the CNS of mammals, most neurons are myelinated, but the cells that form the myelin are oligodendrocytes rather than Schwann cells (Figure 4–1). Unlike the Schwann cell, which forms the myelin between two nodes of Ranvier on a single neuron, oligodendrocytes emit multiple processes that form myelin on many neighboring axons. In multiple sclerosis, a crippling autoimmune disease, patchy destruction of myelin occurs in the CNS (see Clinical Box 4–1). The loss of myelin is associated with delayed or blocked conduction in the demyelinated axons.

AXONAL TRANSPORT

Neurons are secretory cells, but they differ from other secretory cells in that the secretory zone is generally at the end of the axon, far removed from the cell body. The apparatus for protein synthesis is located for the most part in the cell body, with transport of proteins and polypeptides to the axonal ending by

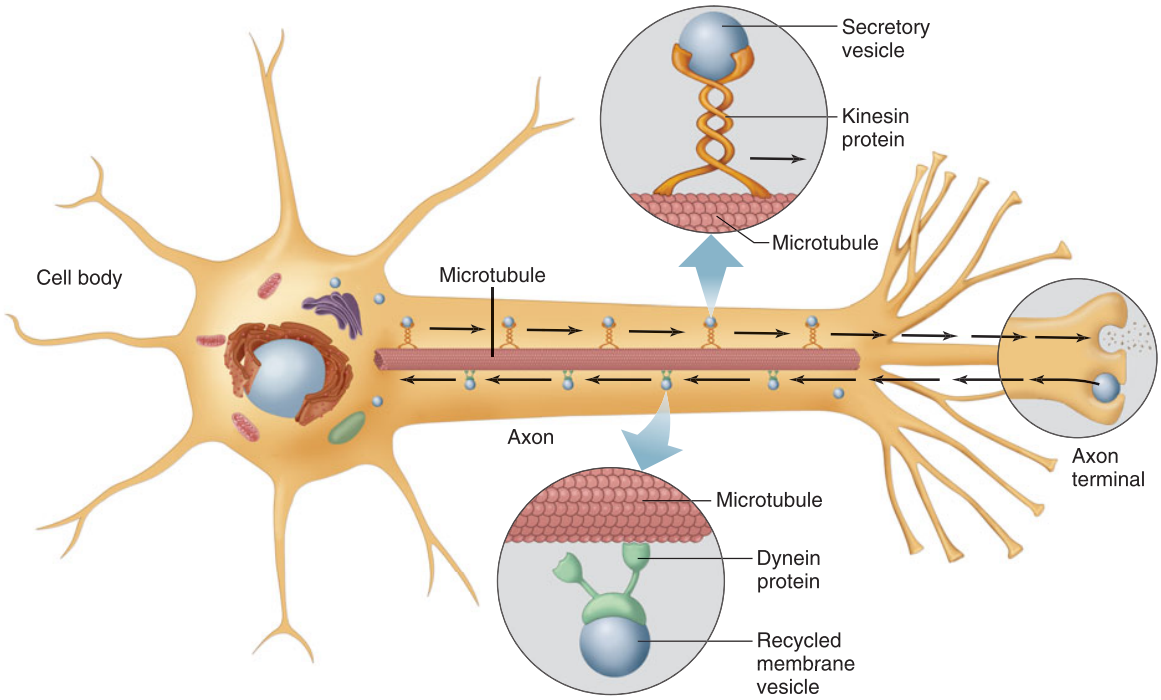

FIGURE 4–4 Axonal transport along microtubules by dynein and kinesin. Fast (400 mm/day) and slow (0.5–10 mm/day) axonal orthograde transport occurs along microtubules that run along the length of the axon from the cell body to the terminal. Retrograde transport (200 mm/day) occurs from the terminal to the cell body. (From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

axoplasmic flow. Thus, the cell body maintains the functional and anatomic integrity of the axon; if the axon is cut, the part distal to the cut degenerates **(wallerian degeneration).**

Orthograde transport occurs along microtubules that run along the length of the axon and requires two molecular motors, dynein and kinesin (Figure 4–4). Orthograde transport moves from the cell body toward the axon terminals. It has both fast and slow components; **fast axonal transport** occurs at about 400 mm/day, and **slow axonal transport** occurs at 0.5 to 10 mm/day. **Retrograde transport,** which is in the opposite direction (from the nerve ending to the cell body), occurs along microtubules at about 200 mm/day. Synaptic vesicles recycle in the membrane, but some used vesicles are carried back to the cell body and deposited in lysosomes. Some materials taken up at the ending by endocytosis, including **nerve growth factor (NGF)** and some viruses, are also transported back to the cell body. A potentially important exception to these principles seems to occur in some dendrites. In them, single strands of mRNA transported from the cell body make contact with appropriate ribosomes, and protein synthesis appears to create local protein domains.

EXCITATION & CONDUCTION

A hallmark of nerve cells is their excitable membrane. Nerve cells respond to electrical, chemical, or mechanical stimuli. Two types of physicochemical disturbances are produced: local, nonpropagated potentials called, depending on their location, **synaptic, generator,** or **electrotonic potentials;** and propagated potentials, the **action potentials** (or **nerve impulses**). Action potentials are the primary electrical responses of neurons and other excitable tissues, and they are the main form of communication within the nervous system. They are due to changes in the conduction of ions across the cell membrane. The electrical events in neurons are rapid, being measured in **milliseconds (ms);** and the potential changes are small, being measured in **millivolts (mV).**

The impulse is normally transmitted **(conducted)** along the axon to its termination. Nerves are not "telephone wires" that transmit impulses passively; conduction of nerve impulses, although rapid, is much slower than that of electricity. Nerve tissue is in fact a relatively poor passive conductor, and it would take a potential of many volts to produce a signal of a fraction of a volt at the other end of a meter-long axon in the absence of active processes in the nerve. Instead, conduction is an active, self-propagating process, and the impulse moves along the nerve at a constant amplitude and velocity. The process is often compared to what happens when a match is applied to one end of a trail of gunpowder; by igniting the powder particles immediately in front of it, the flame moves steadily down the trail to its end as it is extinguished in its wake.

RESTING MEMBRANE POTENTIAL

When two electrodes are connected through a suitable amplifier and placed on the surface of a single axon, no potential difference is observed. However, if one electrode is inserted

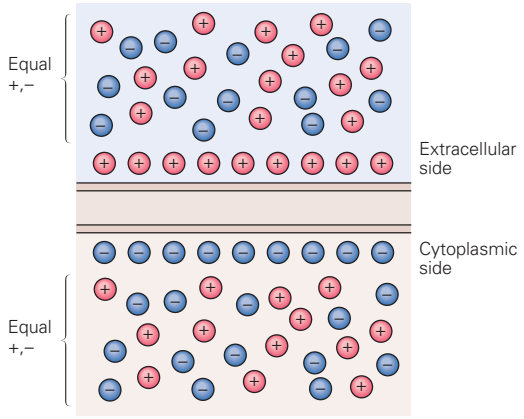

FIGURE 4–5 A membrane potential results from separation of positive and negative charges across the cell membrane. The excess of positive charges (red circles) outside the cell and negative charges (blue circles) inside the cell at rest represents a small fraction of the total number of ions present. (From Kandel ER, Schwartz JH, Jessell TM (editors): *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.).

into the interior of the cell, a constant **potential difference** is observed, with the inside negative relative to the outside of the cell at rest. A membrane potential results from separation of positive and negative charges across the cell membrane (Figure 4–5).

In order for a potential difference to be present across a membrane lipid bilayer, two conditions must be met. First, there must be an unequal distribution of ions of one or more species across the membrane (ie, a concentration gradient). Second, the membrane must be permeable to one or more of these ion species. The permeability is provided by the existence of channels or pores in the bilayer; these channels are usually permeable to a single species of ions. The resting membrane potential represents an equilibrium situation at which the driving force for the membrane-permeant ions down their concentration gradients across the membrane is equal and opposite to the driving force for these ions down their electrical gradients.

In neurons, the concentration of K^+ is much higher inside than outside the cell, while the reverse is the case for Na^+. This concentration difference is established by Na, K ATPase. The outward K^+ concentration gradient results in passive movement of K^+ out of the cell when K^+-selective channels are open. Similarly, the inward Na^+ concentration gradient results in passive movement of Na^+ into the cell when Na^+-selective channels are open.

In neurons, the **resting membrane potential** is usually about –70 mV, which is close to the equilibrium potential for K^+ (step 1 in Figure 4–6). Because there are more open K^+ channels than Na^+ channels at rest, the membrane permeability to K^+ is greater. Consequently, the intracellular and extracellular K^+ concentrations are the prime determinants of the resting membrane potential, which is therefore close to the equilibrium potential for K^+. Steady ion leaks cannot continue forever without eventually dissipating the ion gradients. This is prevented by the Na, K ATPase, which actively moves Na^+ and K^+ against their electrochemical gradients.

IONIC FLUXES DURING THE ACTION POTENTIAL

The cell membranes of nerves, like those of other cells, contain many different types of ion channels. Some of these are voltage-gated and others are ligand-gated. It is the behavior of these channels, and particularly Na^+ and K^+ channels, which explains the electrical events in neurons.

The changes in membrane conductance of Na^+ and K^+ that occur during the action potentials are shown by steps 1 through 7 in Figure 4–6. The conductance of an ion is the reciprocal of its electrical resistance in the membrane and is a measure of the membrane permeability to that ion. In response to a depolarizing stimulus, some of the voltage-gated Na^+ channels open and Na^+ enters the cell and the membrane is brought to its **threshold potential** (step 2) and the voltage-gated Na^+ channels overwhelm the K^+ and other channels. The entry of Na^+ causes the opening of more voltage-gated Na^+ channels and further depolarization, setting up a **positive feedback loop.** The rapid upstroke in the membrane potential ensues (step 3). The membrane potential moves toward the equilibrium potential for Na^+ (+60 mV) but does not reach it during the action potential (step 4), primarily because the increase in Na^+ conductance is short-lived. The Na^+ channels rapidly enter a closed state called the **inactivated state** and remain in this state for a few milliseconds before returning to the resting state, when they again can be activated. In addition, the direction of the electrical gradient for Na^+ is reversed during the **overshoot** because the membrane potential is reversed, and this limits Na^+ influx; also the voltage-gated K^+ channels open. These factors contribute to **repolarization.** The opening of voltage-gated K^+ channels is slower and more prolonged than the opening of the Na^+ channels, and consequently, much of the increase in K^+ conductance comes after the increase in Na^+ conductance (step 5). The net movement of positive charge out of the cell due to K^+ efflux at this time helps complete the process of repolarization. The slow return of the K^+ channels to the closed state also explains the **after-hyperpolarization** (step 6), followed by a return to the resting membrane potential (step 7). Thus, voltage-gated K^+ channels bring the action potential to an end and cause closure of their gates through a **negative feedback process.** Figure 4–7 shows the sequential feedback control in voltage-gated K^+ and Na^+ channels during the action potential.

Decreasing the external Na^+ concentration reduces the size of the action potential but has little effect on the resting membrane potential. The lack of much effect on the resting membrane potential would be predicted, since the permeability of the membrane to Na^+ at rest is relatively low. In contrast, since the resting membrane potential is close to the equilibrium potential for K^+, changes in the changes in the external concentration of this ion can have major effects on the resting membrane potential. If the extracellular level of K^+ is

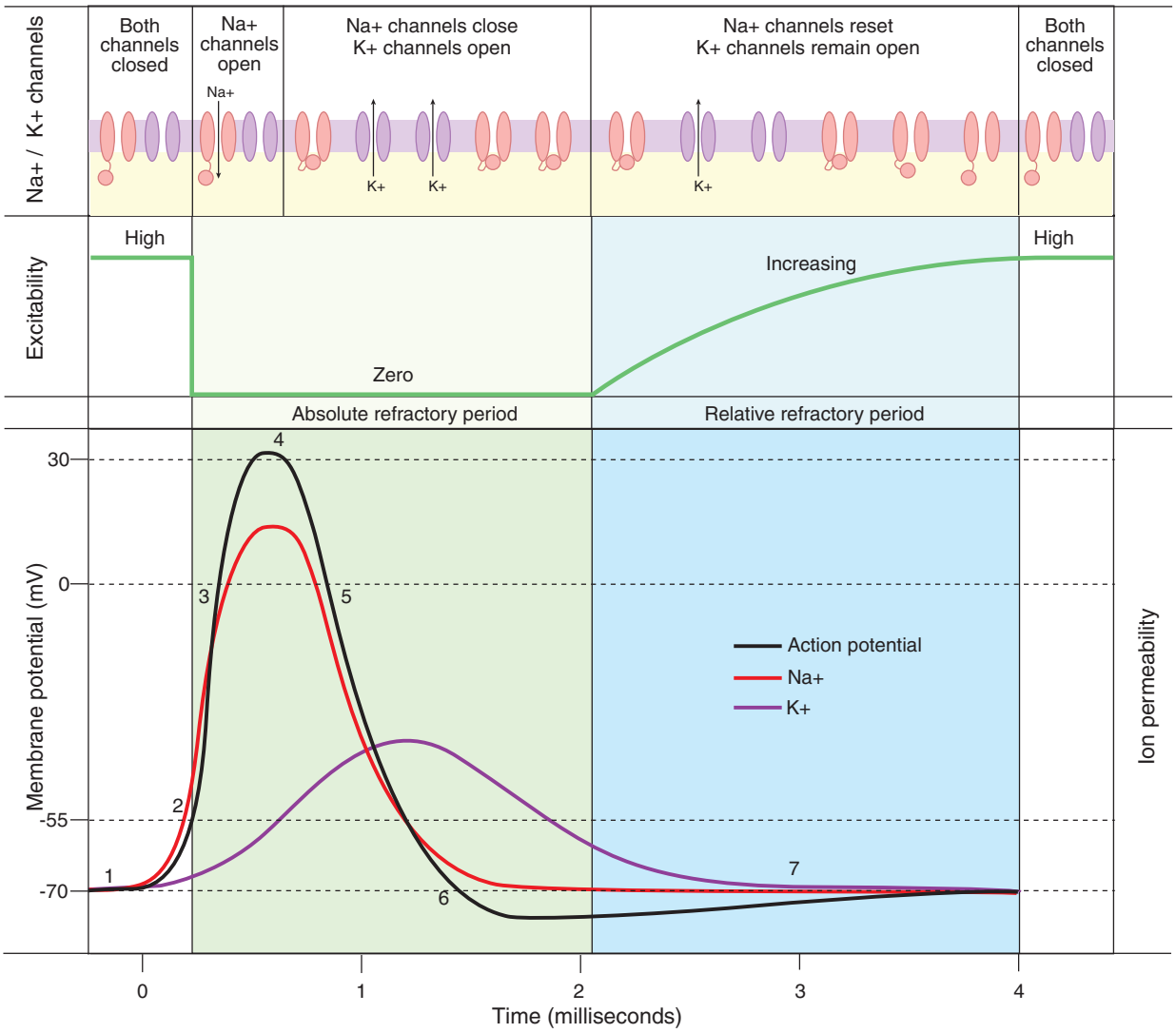

FIGURE 4–6 Changes in membrane potential and relative membrane permeability to Na^+ and K^+ during an action potential. Steps 1 through 7 are detailed in the text. These changes in threshold for activation (excitability) are correlated with the phases of the action potential. (Modified from Silverthorn DU: *Human Physiology: An Integrated Approach,* 5th ed. Pearson, 2010.)

increased **(hyperkalemia),** the resting potential moves closer to the threshold for eliciting an action potential, thus the neuron becomes more excitable. If the extracellular level of K^+ is decreased **(hypokalemia),** the membrane potential is reduced and the neuron is hyperpolarized.

Although Na^+ enters the nerve cell and K^+ leaves it during the action potential, very few ions actually move across the membrane. It has been estimated that only 1 in 100,000 K^+ ions cross the membrane to change the membrane potential from +30 mV (peak of the action potential) to –70 mV (resting potential). Significant differences in ion concentrations can be measured only after prolonged, repeated stimulation.

Other ions, notably Ca^{2+}, can affect the membrane potential through both channel movement and membrane interactions. A decrease in extracellular Ca^{2+} concentration increases the excitability of nerve and muscle cells by decreasing the amount of depolarization necessary to initiate the changes in the Na^+ and K^+ conductance that produce the action potential. Conversely, an increase in extracellular Ca^{2+} concentration can stabilize the membrane by decreasing excitability.

ALL-OR-NONE ACTION POTENTIALS

It is possible to determine the minimal intensity of stimulating current **(threshold intensity)** that, acting for a given duration, will just produce an action potential. The threshold intensity varies with the duration; with weak stimuli it is long, and with strong stimuli it is short. The relation between the strength and the duration of a threshold stimulus is called the **strength–duration curve.** Slowly rising currents fail to fire the nerve because the nerve adapts to the applied stimulus, a process called **adaptation.**

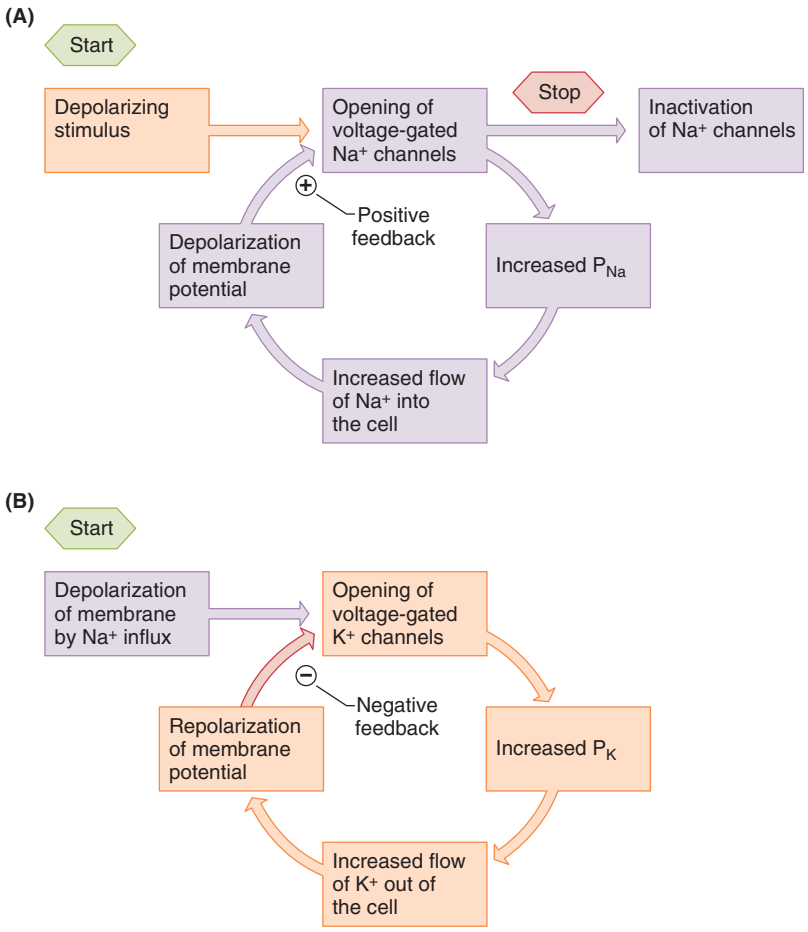

FIGURE 4–7 Feedback control in voltage-gated ion channels in the membrane. A) Na^+ channels exert positive feedback. **B)** K^+ channels exert negative feedback. P_{Na}, P_K is permeability to Na^+ and K^+, respectively. (From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Once threshold intensity is reached, a full-fledged action potential is produced. Further increases in the intensity of a stimulus produce no increment or other change in the action potential as long as the other experimental conditions remain constant. The action potential fails to occur if the stimulus is subthreshold in magnitude, and it occurs with constant amplitude and form regardless of the strength of the stimulus if the stimulus is at or above threshold intensity. The action potential is therefore **all-or-none** in character.

ELECTROTONIC POTENTIALS, LOCAL RESPONSE, & FIRING LEVEL

Although subthreshold stimuli do not produce an action potential, they do have an effect on the membrane potential. This can be demonstrated by placing recording electrodes within a few millimeters of a stimulating electrode and applying subthreshold stimuli of fixed duration. Application of such currents leads to a localized depolarizing potential change that rises sharply and decays exponentially with time. The magnitude of this response drops off rapidly as the distance between the stimulating and recording electrodes is increased. Conversely, an anodal current produces a hyperpolarizing potential change of similar duration. These potential changes are called **electrotonic potentials.** As the strength of the current is increased, the response is greater due to the increasing addition of a **local response** of the membrane (Figure 4–8). Finally, at 7–15 mV of depolarization (potential of –55 mV), the **firing level** (threshold potential) is reached and an action potential occurs.

CHANGES IN EXCITABILITY DURING ELECTROTONIC POTENTIALS & THE ACTION POTENTIAL

During the action potential, as well as during electrotonic potentials and the local response, the threshold of the neuron to stimulation changes (Figure 4–6). Hyperpolarizing responses elevate the threshold, and depolarizing potentials

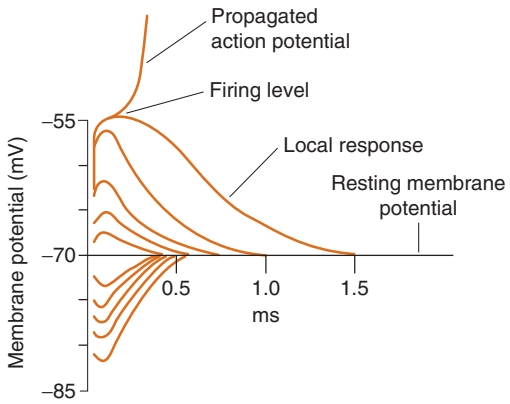

FIGURE 4–8 Electrotonic potentials and local response. The changes in the membrane potential of a neuron following application of stimuli of 0.2, 0.4, 0.6, 0.8, and 1.0 times threshold intensity are shown superimposed on the same time scale. The responses below the horizontal line are those recorded near the anode, and the responses above the line are those recorded near the cathode. The stimulus of threshold intensity was repeated twice. Once it caused a propagated action potential (top line), and once it did not.

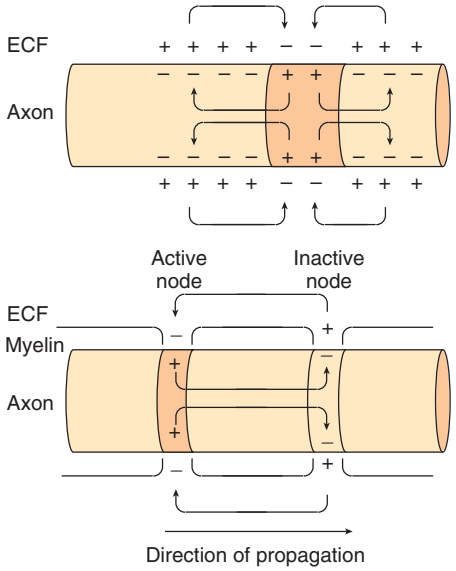

FIGURE 4–9 Local current flow (movement of positive charges) around an impulse in an axon. Top: Unmyelinated axon. **Bottom:** Myelinated axon. Positive charges from the membrane ahead of and behind the action potential flow into the area of negativity represented by the action potential ("current sink"). In myelinated axons, depolarization appears to "jump" from one node of Ranvier to the next (saltatory conduction).

lower it as they move the membrane potential closer to the firing level. During the local response, the threshold is lowered, but during the rising and much of the falling phases of the spike potential, the neuron is refractory to stimulation. This **refractory period** is divided into an **absolute refractory period,** corresponding to the period from the time the firing level is reached until repolarization is about one-third complete, and a **relative refractory period,** lasting from this point to the start of after-depolarization. During the absolute refractory period, no stimulus, no matter how strong, will excite the nerve, but during the relative refractory period, stronger than normal stimuli can cause excitation. These changes in threshold are correlated with the phases of the action potential in Figure 4–6.

CONDUCTION OF THE ACTION POTENTIAL

The nerve cell membrane is polarized at rest, with positive charges lined up along the outside of the membrane and negative charges along the inside. During the action potential, this polarity is abolished and for a brief period is actually reversed (Figure 4–9). Positive charges from the membrane ahead of and behind the action potential flow into the area of negativity represented by the action potential ("current sink"). By drawing off positive charges, this flow decreases the polarity of the membrane ahead of the action potential. Such electrotonic depolarization initiates a local response, and when the firing level is reached, a propagated response occurs that in turn electrotonically depolarizes the membrane in front of it.

The spatial distribution of ion channels along the axon plays a key role in the initiation and regulation of the action potential. Voltage-gated Na^+ channels are highly concentrated in the nodes of Ranvier and the initial segment in myelinated neurons. The number of Na^+ channels per square micrometer of membrane in myelinated mammalian neurons has been estimated to be 50–75 in the cell body, 350–500 in the initial segment, less than 25 on the surface of the myelin, 2000–12,000 at the nodes of Ranvier, and 20–75 at the axon terminals. Along the axons of unmyelinated neurons, the number is about 110. In many myelinated neurons, the Na^+ channels are flanked by K^+ channels that are involved in repolarization.

Conduction in myelinated axons depends on a similar pattern of circular current flow as described above. However, myelin is an effective insulator, and current flow through it is negligible. Instead, depolarization in myelinated axons travels from one node of Ranvier to the next, with the current sink at the active node serving to electrotonically depolarize the node ahead of the action potential to the firing level (Figure 4–9). This "jumping" of depolarization from node to node is called **saltatory conduction.** It is a rapid process that allows myelinated axons to conduct up to 50 times faster than the fastest unmyelinated fibers.

ORTHODROMIC & ANTIDROMIC CONDUCTION

An axon can conduct in either direction. When an action potential is initiated in the middle of the axon, two impulses traveling in opposite directions are set up by electrotonic

TABLE 4–1 Types of mammalian nerve fibers.

Fiber Type	Function	Fiber Diameter (μm)	Conduction Velocity (m/s)	Spike Duration (ms)	Absolute Refractory Period (ms)
Aα	Proprioception; somatic motor	12–20	70–120		
Aβ	Touch, pressure	5–12	30–70	0.4–0.5	0.4–1
Aγ	Motor to muscle spindles	3–6	15–30		
Aδ	Pain, temperature	2–5	12–30		
B	Preganglionic autonomic	<3	3–15	1.2	1.2
C, Dorsal root	Pain, temperature	0.4–1.2	0.5–2	2	2
C, Sympathetic	Postganglionic sympathetic	0.3–1.3	0.7–2.3	2	2

depolarization on either side of the initial current sink. In the natural situation, impulses pass in one direction only, ie, from synaptic junctions or receptors along axons to their termination. Such conduction is called **orthodromic.** Conduction in the opposite direction is called **antidromic.** Because synapses, unlike axons, permit conduction in one direction only, an antidromic impulse will fail to pass the first synapse they encounter and die out at that point.

PROPERTIES OF MIXED NERVES

Peripheral nerves in mammals are made up of many axons bound together in a fibrous envelope called the **epineurium.** Potential changes recorded extracellularly from such nerves therefore represent an algebraic summation of the all-or-none action potentials of many axons. The thresholds of the individual axons in the nerve and their distance from the stimulating electrodes vary. With subthreshold stimuli, none of the axons are stimulated and no response occurs. When the stimuli are of threshold intensity, axons with low thresholds fire and a small potential change is observed. As the intensity of the stimulating current is increased, the axons with higher thresholds are also discharged. The electrical response increases proportionately until the stimulus is strong enough to excite all of the axons in the nerve. The stimulus that produces excitation of all the axons is the **maximal stimulus,** and application of greater, supramaximal stimuli produces no further increase in the size of the observed potential.

After a stimulus is applied to a nerve, there is a **latent period** before the start of the action potential. This interval corresponds to the time it takes the impulse to travel along the axon from the site of stimulation to the recording electrodes. Its duration is proportionate to the distance between the stimulating and recording electrodes and inversely proportionate to the speed of conduction. If the duration of the latent period and the distance between the stimulating and recording electrodes are known, **axonal conduction velocity** can be calculated.

NERVE FIBER TYPES & FUNCTION

Erlanger and Gasser divided mammalian nerve fibers into A, B, and C groups, further subdividing the A group into α, β, γ, and δ fibers. In Table 4–1, the various fiber types are listed with their diameters, electrical characteristics, and functions. By comparing the neurologic deficits produced by careful dorsal root section and other nerve-cutting experiments with the histologic changes in the nerves, the functions and histologic characteristics of each of the families of axons responsible for the various peaks of the compound action potential have been established. In general, the greater the diameter of a given nerve fiber, the greater is its speed of conduction. The large axons are concerned primarily with proprioceptive sensation, somatic motor function, conscious touch, and pressure, while the smaller axons subserve pain and temperature sensations and autonomic function.

Further research has shown that not all the classically described lettered components are homogeneous, and a numerical system (Ia, Ib, II, III, and IV) has been used by some physiologists to classify sensory fibers. Unfortunately, this has led to confusion. A comparison of the number system and the letter system is shown in Table 4–2.

TABLE 4–2 Numerical classification of sensory nerve fibers.

Number	Origin	Fiber Type
Ia	Muscle spindle, annulo-spiral ending	Aα
Ib	Golgi tendon organ	Aα
II	Muscle spindle, flower-spray ending; touch, pressure	Aβ
III	Pain and cold receptors; some touch receptors	Aδ
IV	Pain, temperature, and other receptors	Dorsal root C

TABLE 4–3 Relative susceptibility of mammalian A, B, and C nerve fibers to conduction block produced by various agents.

Susceptibility To:	Most Susceptible	Intermediate	Least Susceptible
Hypoxia	B	A	C
Pressure	A	B	C
Local anesthetics	C	B	A

TABLE 4–4 Neurotrophins.

Neurotrophin	Receptor
Nerve growth factor (NGF)	Trk A
Brain-derived neurotrophic factor (BDNF)	Trk B
Neurotrophin 3 (NT-3)	Trk C, less on Trk A and Trk B
Neurotrophin 4/5 (NT-4/5)	Trk B

In addition to variations in speed of conduction and fiber diameter, the various classes of fibers in peripheral nerves differ in their sensitivity to hypoxia and anesthetics (Table 4–3). This fact has clinical as well as physiologic significance. Local anesthetics depress transmission in the group C fibers before they affect group A touch fibers (see Clinical Box 4–2). Conversely, pressure on a nerve can cause loss of conduction in large-diameter motor, touch, and pressure fibers while pain sensation remains relatively intact. Patterns of this type are sometimes seen in individuals who sleep with their arms under their heads for long periods, causing compression of the nerves in the arms. Because of the association of deep sleep with alcoholic intoxication, the syndrome is most common on weekends and has acquired the interesting name Saturday night or Sunday morning paralysis.

NEUROTROPHINS

A number of proteins necessary for survival and growth of neurons have been isolated and studied. Some of these **neurotrophins** are products of the muscles or other structures that the neurons innervate, but many in the CNS are produced by astrocytes. These proteins bind to receptors at the endings of a neuron. They are internalized and then transported by retrograde transport to the neuronal cell body, where they foster the production of proteins associated with neuronal development, growth, and survival. Other neurotrophins are produced in neurons and transported in an anterograde fashion to the nerve ending, where they maintain the integrity of the postsynaptic neuron.

RECEPTORS

Four established neurotrophins and their three high-affinity **tyrosine kinase associated (Trk) receptors** are listed in Table 4–4. Each of these Trk receptors dimerizes, and this initiates autophosphorylation in the cytoplasmic tyrosine kinase domains of the receptors. An additional low-affinity NGF receptor that is a 75-kDa protein is called **$p75^{NTR}$.** This receptor binds all four of the listed neurotrophins with equal affinity. There is some evidence that it can form a heterodimer with Trk A monomer and that the dimer has increased affinity and specificity

CLINICAL BOX 4–2

Local Anesthesia

Local or regional anesthesia is used to block the conduction of action potentials in sensory and motor nerve fibers. This usually occurs as a result of blockade of voltage-gated Na^+ channels on the nerve cell membrane. This causes a gradual increase in the threshold for electrical excitability of the nerve, a reduction in the rate of rise of the action potential, and a slowing of axonal conduction velocity. There are two major categories of local anesthetics: **ester-linked** (eg, **cocaine, procaine, tetracaine**) or **amide-linked** (eg, **lidocaine, bupivacaine**). In addition to either the ester or amide, all local anesthetics contain an aromatic and an amine group. The structure of the aromatic group determines the drug's hydrophobic characteristics, and the amine group determines its latency to onset of action and its potency. Application of these drugs into the vicinity of a central **(eg, epidural, spinal anesthesia)** or peripheral nerve can lead to rapid, temporary, and near complete interruption of neural traffic to allow a surgical or other potentially noxious procedure to be done without eliciting pain. Cocaine (from the coca shrub, *Erythroxylan coca*) was the first chemical to be identified as having local anesthetic properties and remains the only naturally occurring local anesthetic. In 1860, Albert Niemann isolated the chemical, tasted it, and reported a numbing effect on his tongue. The first clinical use of cocaine as a local anesthetic was in 1886 when Carl Koller used it as a topical ophthalmic anesthetic. Its addictive and toxic properties prompted the development of other local anesthetics. In 1905, procaine was synthesized as the first suitable substitute for cocaine. Nociceptive fibers (unmyelinated C fibers) are the most sensitive to the blocking effect of local anesthetics. This is followed by sequential loss of sensitivity to temperature, touch, and deep pressure. Motor nerve fibers are the most resistant to the actions of local anesthetics.

CLINICAL BOX 4–3

Axonal Regeneration

Peripheral nerve damage is often reversible. Although the axon will degenerate distal to the damage, connective elements of the so-called **distal stump** often survive. **Axonal sprouting** occurs from the proximal stump, growing toward the nerve ending. This results from **growth-promoting factors** secreted by **Schwann cells** that attract axons toward the distal stump. Adhesion molecules of the immunoglobulin superfamily (eg, NgCAM/L1) promote axon growth along cell membranes and extracellular matrices. Inhibitory molecules in the perineurium assure that the regenerating axons grow in a correct trajectory. Denervated distal stumps are able to upregulate production of **neurotrophins** that promote growth. Once the regenerated axon reaches its target, a new functional connection (eg, neuromuscular junction) is formed. Regeneration allows for considerable, although not full, recovery. For example, fine motor control may be permanently impaired because some motor neurons are guided to an inappropriate motor fiber. Nonetheless, recovery of peripheral nerves from damage far surpasses that of central nerve pathways. The proximal stump of a damaged axon in the CNS will form short sprouts, but distant stump recovery is rare, and the damaged axons are unlikely to form new synapses. This is in part because CNS neurons do not have the growth-promoting chemicals needed for regeneration. In fact, CNS myelin is a potent inhibitor of axonal growth. In addition, following CNS injury several events—**astrocytic proliferation, activation of microglia, scar formation, inflammation,** and **invasion of immune cells**—provide an inappropriate environment for regeneration. Thus, treatment of brain and spinal cord injuries frequently focuses on rehabilitation rather than reversing the nerve damage. New research is aiming to identify ways to initiate and maintain axonal growth, to direct regenerating axons to reconnect with their target neurons, and to reconstitute original neuronal circuitry.

THERAPEUTIC HIGHLIGHTS

There is evidence showing that the use of **nonsteroidal anti-inflammatory drugs** (NSAIDs) like ibuprofen can overcome the factors that inhibit axonal growth following injury. This effect is thought to be mediated by the ability of NSAIDs to inhibit RhoA, a small GTPase protein that normally prevents repair of neural pathways and axons. Growth cone collapse in response to myelin-associated inhibitors after nerve injury is prevented by drugs such as **pertussis toxin,** which interfere with signal transduction via trimeric G protein. Experimental drugs that inhibit the **phosphoinositide 3-kinase (PI3) pathway** or the **inositol triphosphate (IP_3) receptor** have also been shown to promote regeneration after nerve injury.

for NGF. However, it now appears that $p75^{NTR}$ receptors can form homodimers that in the absence of Trk receptors cause apoptosis, an effect opposite to the usual growth-promoting and nurturing effects of neurotrophins. Research is ongoing to characterize the distinct roles of $p75^{NTR}$ and Trk receptors and factors that influence their expression in neurons.

FUNCTION OF NEUROTROPHINS

The first neurotrophin to be characterized was NGF, a protein growth factor that is necessary for the growth and maintenance of sympathetic neurons and some sensory neurons. It is present in a broad spectrum of animal species, including humans, and is found in many different tissues. In male mice, there is a particularly high concentration in the submandibular salivary glands, and the level is reduced by castration to that seen in females. The factor is made up of two α, two β, and two γ subunits. The β subunits, each of which has a molecular mass of 13,200 Da, have all the nerve growth-promoting activity, the α subunits have trypsin-like activity, and the γ subunits are serine proteases. The function of the proteases is unknown. The structure of the β subunit of NGF resembles that of insulin.

NGF is picked up by neurons and is transported in retrograde fashion from the endings of the neurons to their cell bodies. It is also present in the brain and appears to be responsible for the growth and maintenance of cholinergic neurons in the basal forebrain and the striatum. Injection of antiserum against NGF in newborn animals leads to almost total destruction of the sympathetic ganglia; it thus produces an **immunosympathectomy.** There is evidence that the maintenance of neurons by NGF is due to a reduction in apoptosis.

Brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), NT-4/5, and NGF each maintain a different pattern of neurons, although there is some overlap. Disruption of NT-3 by gene knockout causes a marked loss of cutaneous mechanoreceptors, even in heterozygotes. BDNF acts rapidly and can actually depolarize neurons. BDNF-deficient mice lose peripheral sensory neurons and have severe degenerative changes in their vestibular ganglia and blunted long-term potentiation.

OTHER FACTORS AFFECTING NEURONAL GROWTH

The regulation of neuronal growth is a complex process. Schwann cells and astrocytes produce **ciliary neurotrophic factor (CNTF).** This factor promotes the survival of damaged and embryonic spinal cord neurons and may prove to be of value in treating human diseases in which motor neurons degenerate. **Glial cell line-derived neurotrophic factor (GDNF)**

maintains midbrain dopaminergic neurons in vitro. However, GDNF knockouts have dopaminergic neurons that appear normal, but they have no kidneys and fail to develop an enteric nervous system. Another factor that enhances the growth of neurons is **leukemia inhibitory factor (LIF).** In addition, neurons as well as other cells respond to **insulin-like growth factor I (IGF-I)** and the various forms of **transforming growth factor (TGF), fibroblast growth factor (FGF),** and **platelet-derived growth factor (PDGF).**

Clinical Box 4–3 compares the ability to regenerate neurons after central and peripheral nerve injury.

CHAPTER SUMMARY

- There are two main types of glia: microglia and macroglia. Microglia are scavenger cells. Macroglia include oligodendrocytes, Schwann cells, and astrocytes. The first two are involved in myelin formation; astrocytes produce substances that are tropic to neurons, and they help maintain the appropriate concentration of ions and neurotransmitters.
- Neurons are composed of a cell body (soma) that is the metabolic center of the neuron, dendrites that extend outward from the cell body and arborize extensively, and a long fibrous axon that originates from a somewhat thickened area of the cell body, the axon hillock.
- The axons of many neurons acquire a sheath of myelin, a protein–lipid complex that is wrapped around the axon. Myelin is an effective insulator, and depolarization in myelinated axons travels from one node of Ranvier to the next, with the current sink at the active node serving to electrotonically depolarize to the firing level the node ahead of the action potential.
- Orthograde transport occurs along microtubules that run the length of the axon and requires two molecular motors: dynein and kinesin. It moves from the cell body toward the axon terminals and has both fast (400 mm/day) and slow (0.5–10 mm/day) components. Retrograde transport, which is in the opposite direction (from the nerve ending to the cell body), occurs along microtubules at about 200 mm/day.
- In response to a depolarizing stimulus, voltage-gated Na^+ channels become active, and when the threshold potential is reached, an action potential results. The membrane potential moves toward the equilibrium potential for Na^+. The Na^+ channels rapidly enter a closed state (inactivated state) before returning to the resting state. The direction of the electrical gradient for Na^+ is reversed during the overshoot because the membrane potential is reversed, and this limits Na^+ influx. Voltage-gated K^+ channels open and the net movement of positive charge out of the cell helps complete the process of repolarization. The slow return of the K^+ channels to the closed state explains after-hyperpolarization, followed by a return to the resting membrane potential.
- Nerve fibers are divided into different categories (A, B, and C) based on axonal diameter, conduction velocity, and function. A numerical classification (Ia, Ib, II, III, and IV) is also used for sensory afferent fibers.
- Neurotrophins such as NGF are carried by retrograde transport to the neuronal cell body, where they foster the production of proteins associated with neuronal development, growth, and survival.

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. Which of the following statements about glia is true?
   A. Microglia arise from macrophages outside of the nervous system and are physiologically and embryologically similar to other neural cell types.
   B. Glia do not undergo proliferation.
   C. Protoplasmic astrocytes produce substances that are tropic to neurons to help maintain the appropriate concentration of ions and neurotransmitters by taking up K^+ and the neurotransmitters glutamate and GABA.
   D. Oligodendrocytes and Schwann cells are involved in myelin formation around axons in the peripheral and central nervous systems, respectively.
   E. Macroglia are scavenger cells that resemble tissue macrophages and remove debris resulting from injury, infection, and disease.
2. A 13-year-old girl was being seen by her physician because of experiencing frequent episodes of red, painful, warm extremities. She was diagnosed with primary erythromelalgia, which may be due to a peripheral nerve sodium channelopathy. Which part of a neuron has the highest concentration of Na^+ channels per square micrometer of cell membrane?
   A. dendrites
   B. cell body near dendrites
   C. initial segment
   D. axonal membrane under myelin
   E. none of Ranvier
3. A 45-year-old female office worker had been experiencing tingling in her index and middle fingers and thumb of her right hand. Recently, her wrist and hand had become weak. Her physician ordered a nerve conduction test to evaluate her for carpal tunnel syndrome. Which one of the following nerves has the slowest conduction velocity?
   A. Aα fibers
   B. Aβ fibers
   C. Aγ fibers
   D. B fibers
   E. C fibers
4. Which of the following is *not* correctly paired?
   A. Synaptic transmission: Antidromic conduction
   B. Molecular motors: Dynein and kinesin
   C. Fast axonal transport: ~400 mm/day
   D. Slow axonal transport: 0.5–10 mm/day
   E. Nerve growth factor: Retrograde transport
5. A 32-year-old female received an injection of a local anesthetic for a tooth extraction. Within 2 h, she noted palpitations, diaphoresis, and dizziness. Which of the following ionic changes is correctly matched with a component of the action potential?
   A. Opening of voltage-gated K^+ channels: After-hyperpolarization
   B. A decrease in extracellular Ca^{2+}: Repolarization
   C. Opening of voltage-gated Na^+ channels: Depolarization
   D. Rapid closure of voltage-gated Na^+ channels: Resting membrane potential
   E. Rapid closure of voltage-gated K^+ channels: Relative refractory period

6. A man falls into a deep sleep with one arm under his head. This arm is paralyzed when he awakens, but it tingles, and pain sensation in it is still intact. The reason for the loss of motor function without loss of pain sensation is that in the nerves to his arm,
   A. A fibers are more susceptible to hypoxia than B fibers.
   B. A fibers are more sensitive to pressure than C fibers.
   C. C fibers are more sensitive to pressure than A fibers.
   D. Motor nerves are more affected by sleep than sensory nerves.
   E. Sensory nerves are nearer the bone than motor nerves and hence are less affected by pressure.
7. Which of the following statements about nerve growth factor is *not* true?
   A. It is made up of three polypeptide subunits.
   B. It is responsible for the growth and maintenance of adrenergic neurons in the basal forebrain and the striatum.
   C. It is necessary for the growth and development of the sympathetic nervous system.
   D. It is picked up by nerves from the organs they innervate.
   E. It can express both $p75^{NTR}$ and Trk A receptors.
8. A 20-year old female student awakens one morning with severe pain and blurry vision in her left eye; the symptoms abate over several days. About 6 months later, on a morning after playing volleyball with friends, she notices weakness but not pain in her right leg; the symptoms intensify while taking a hot shower. Which of the following is most likely to be the case?
   A. The two episodes described are not likely to be related.
   B. She may have primary-progressive multiple sclerosis.
   C. She may have relapsing-remitting multiple sclerosis.
   D. She may have a lumbar disk rupture.
   E. She may have Guillain–Barre syndrome.

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CHAPTER 5

Excitable Tissue: Muscle

OBJECTIVES

After studying this chapter, you should be able to:

- Differentiate the major classes of muscle in the body.
- Describe the molecular and electrical makeup of muscle cell excitation–contraction coupling.
- Define elements of the sarcomere that underlie striated muscle contraction.
- Differentiate the role(s) for Ca^{2+} in skeletal, cardiac, and smooth muscle contraction.
- Appreciate muscle cell diversity and function.

INTRODUCTION

Muscle cells, like neurons, can be excited chemically, electrically, and mechanically to produce an action potential that is transmitted along their cell membranes. Unlike neurons, they respond to stimuli by activating a contractile mechanism. The contractile protein myosin and the cytoskeletal protein actin are abundant in muscle, where they are the primary structural components that bring about contraction.

Muscle is generally divided into three types: **skeletal, cardiac,** and **smooth,** although smooth muscle is not a homogeneous single category. Skeletal muscle makes up the great mass of the somatic musculature. It has well-developed cross-striations, does not normally contract in the absence of nervous stimulation, lacks anatomic and functional connections between individual muscle fibers, and is generally under voluntary control. Cardiac muscle also has cross-striations, but it is functionally syncytial and, although it can be modulated via the autonomic nervous system, it can contract rhythmically in the absence of external innervation owing to the presence in the myocardium of pacemaker cells that discharge spontaneously (see Chapter 29). Smooth muscle lacks cross-striations and can be further subdivided into two broad types: unitary (or visceral) smooth muscle and multiunit smooth muscle. The type found in most hollow viscera is functionally syncytial and contains pacemakers that discharge irregularly. The multiunit type found in the eye and in some other locations is not spontaneously active and resembles skeletal muscle in graded contractile ability.

SKELETAL MUSCLE MORPHOLOGY

ORGANIZATION

Skeletal muscle is made up of individual muscle fibers that are the "building blocks" of the muscular system in the same sense that the neurons are the building blocks of the nervous system. Most skeletal muscles begin and end in tendons, and the muscle fibers are arranged in parallel between the tendinous ends, so that the force of contraction of the units is additive. Each muscle fiber is a single cell that is multinucleated, long, cylindrical, and surrounded by a cell membrane, the **sarcolemma** (Figure 5–1). There are no syncytial bridges between cells. The muscle fibers are made up of myofibrils, which are divisible into individual filaments. These myofilaments contain several proteins that together make up the contractile machinery of the skeletal muscle.

The contractile mechanism in skeletal muscle largely depends on the proteins **myosin-II, actin, tropomyosin,** and **troponin.** Troponin is made up of three subunits: **troponin I, troponin T,** and **troponin C.** Other important proteins in muscle are involved in maintaining the proteins that participate in contraction in appropriate structural relation to one another and to the extracellular matrix.

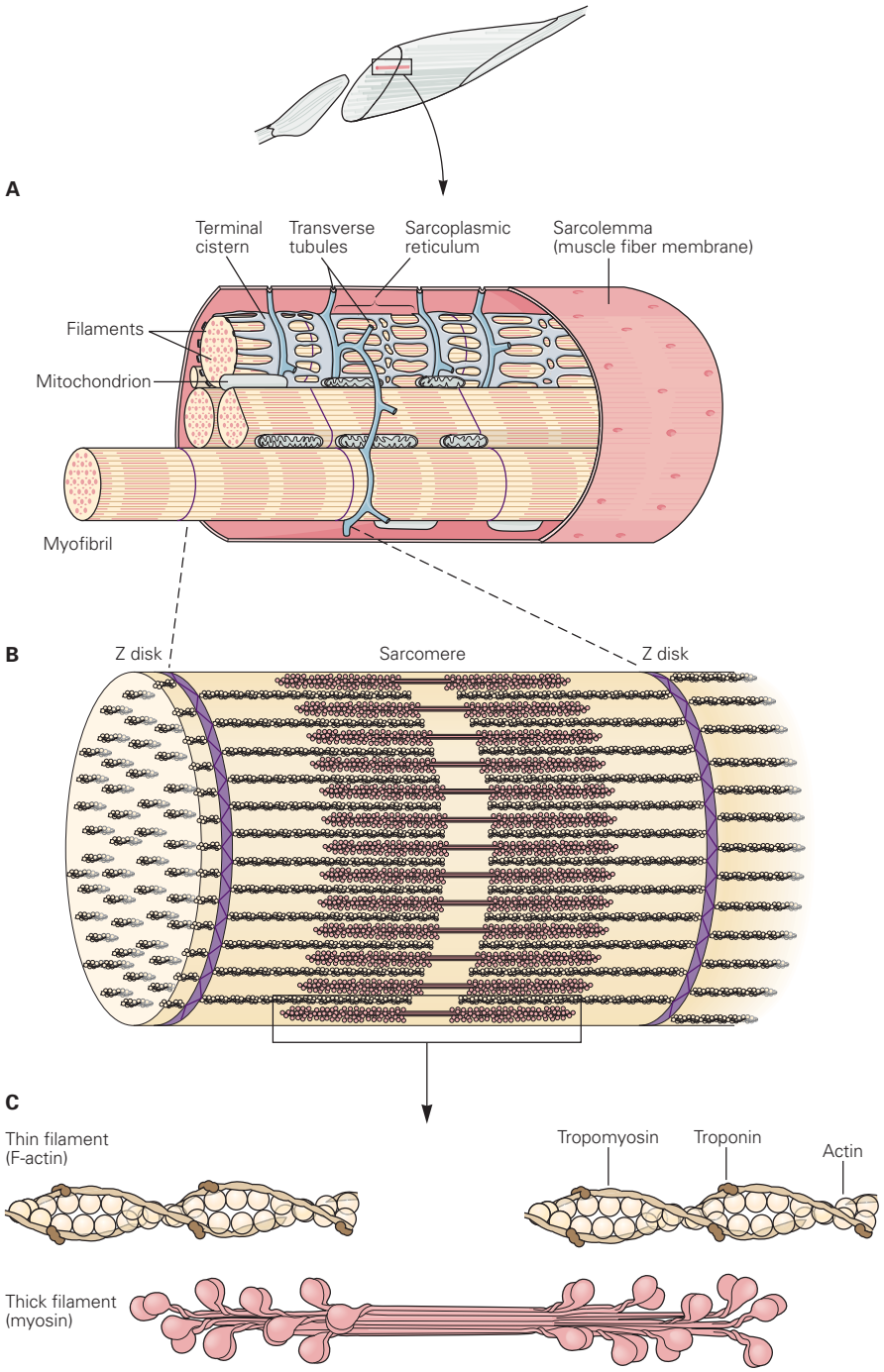


FIGURE 5–1 Mammalian skeletal muscle. A single muscle fiber surrounded by its sarcolemma has been cut away to show individual myofibrils. The cut surface of the myofibrils shows the arrays of thick and thin filaments. The sarcoplasmic reticulum with its transverse (T) tubules and terminal cisterns surrounds each myofibril. The T tubules invaginate from the sarcolemma and contact the myofibrils twice in every sarcomere. Mitochondria are found between the myofibrils and a basal lamina surrounds the sarcolemma.

STRIATIONS

Differences in the refractive indexes of the various parts of the muscle fiber are responsible for the characteristic cross-striations seen in skeletal muscle when viewed under the microscope. The parts of the cross-striations are frequently identified by letters (Figure 5–2). The light I band is divided by the dark Z line, and the dark A band has the lighter H band in its center. A transverse M line is seen in the middle of the H band, and this line plus the narrow light areas on either side of

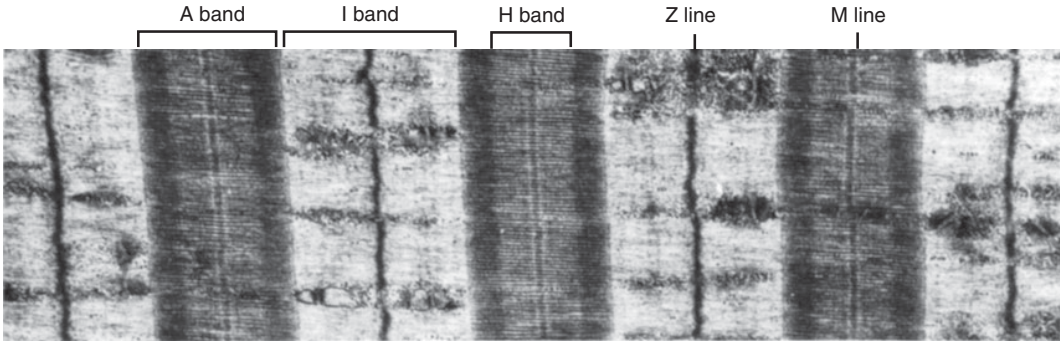


FIGURE 5–2 Electronmicrograph of human gastrocnemius muscle. The various bands and lines are identified at the top (× 13,500). (Courtesy of Walker SM, Schrodt GR.)

it are sometimes called the pseudo-H zone. The area between two adjacent Z lines is called a **sarcomere.** The orderly arrangement of actin, myosin, and related proteins that produces this pattern is shown in Figure 5–3. The thick filaments, which are about twice the diameter of the thin filaments, are made up of myosin; the thin filaments are made up of actin, tropomyosin, and troponin. The thick filaments are lined up to form the A bands, whereas the array of thin filaments extends out of the A band and into the less dense staining I bands. The lighter H bands in the center of the A bands are the regions where, when the muscle is relaxed, the thin filaments do not overlap the thick filaments. The Z lines allow for anchoring of the thin filaments. If a transverse section through the A band is examined under the electron microscope, each thick filament is seen to be surrounded by six thin filaments in a regular hexagonal pattern.

The form of myosin found in muscle is myosin-II, with two globular heads and a long tail. The heads of the myosin molecules form cross-bridges with actin. Myosin contains heavy chains and light chains, and its heads are made up of the light chains and the amino terminal portions of the heavy chains. These heads contain an actin-binding site and a catalytic site that hydrolyzes ATP. The myosin molecules are arranged symmetrically on either side of the center of the sarcomere, and it is this arrangement that

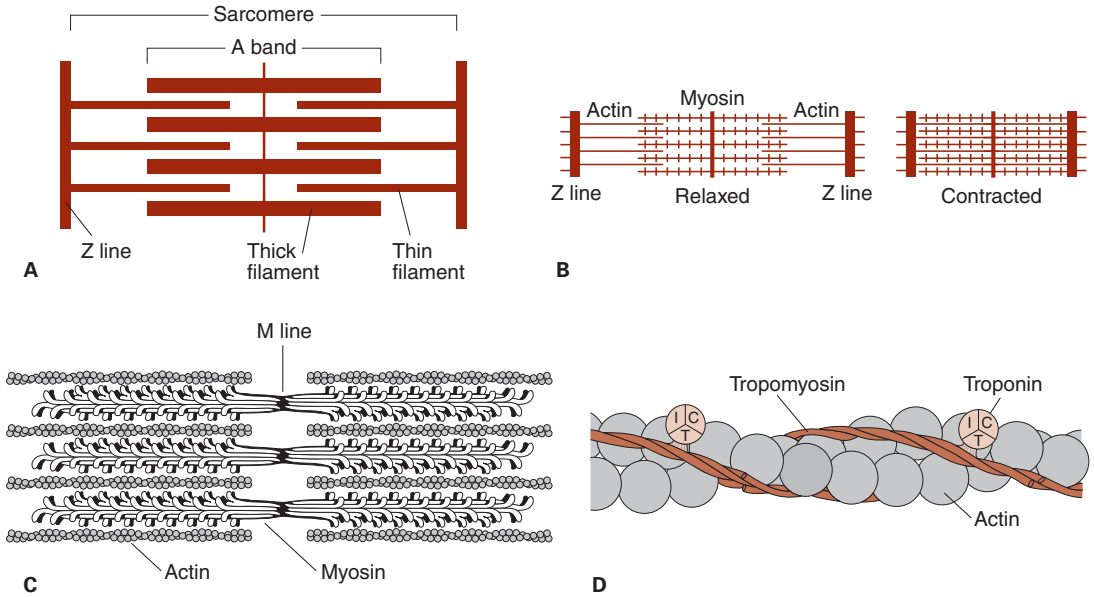


FIGURE 5–3 A) Arrangement of thin (actin) and thick (myosin) filaments in skeletal muscle (compare to Figure 5–2). B) Sliding of actin on myosin during contraction so that Z lines move closer together. **C)** Detail of relation of myosin to actin in an individual sarcomere, the functional unit of the muscle. **D)** Diagrammatic representation of the arrangement of actin, tropomyosin, and troponin of the thin filaments in relation to a myosin thick filament. The globular heads of myosin interact with the thin filaments to create the contraction. Note that myosin thick filaments reverse polarity at the M line in the middle of the sarcomere, allowing for contraction. (C and D are modified with permision from Kandel ER, Schwartz JH, Jessell TM [editors]: *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.)

creates the light areas in the pseudo-H zone. The M line is the site of the reversal of polarity of the myosin molecules in each of the thick filaments. At these points, there are slender cross-connections that hold the thick filaments in proper array. Each thick filament contains several hundred myosin molecules.

The thin filaments are polymers made up of two chains of actin that form a long double helix. Tropomyosin molecules are long filaments located in the groove between the two chains in the actin (Figure 5–3). Each thin filament contains 300–400 actin molecules and 40–60 tropomyosin molecules. Troponin molecules are small globular units located at intervals along the tropomyosin molecules. Each of the three troponin subunits has a unique function: Troponin T binds the troponin components to tropomyosin; troponin I inhibits the interaction of myosin with actin; and troponin C contains the binding sites for the Ca^{2+} that helps to initiate contraction.

Some additional structural proteins that are important in skeletal muscle function include **actinin, titin,** and **desmin.** Actinin binds actin to the Z lines. Titin, the largest known protein (with a molecular mass near 3,000,000 Da), connects the Z lines to the M lines and provides scaffolding for the sarcomere. It contains two kinds of folded domains that provide muscle with its elasticity. At first when the muscle is stretched there is relatively little resistance as the domains unfold, but with further stretch there is a rapid increase in resistance that protects the structure of the sarcomere. Desmin adds structure to the Z lines in part by binding the Z lines to the plasma membrane. Some muscle disorders associated these structural components are described in **Clinical Box 5–1**. It should be noted that although these proteins are important in muscle structure/function, by no means do they represent an exhaustive list.

SARCOTUBULAR SYSTEM

The muscle fibrils are surrounded by structures made up of membranes that appear in electronmicrographs as vesicles and tubules. These structures form the **sarcotubular system,** which is made up of a **T system** and a **sarcoplasmic reticulum.** The

CLINICAL BOX 5–1

Structural and Metabolic Disorders in Muscle Disease

The term **muscular dystrophy** is applied to diseases that cause progressive weakness of skeletal muscle. About 50 such diseases have been described, some of which include cardiac as well as skeletal muscle. They range from mild to severe and some are eventually fatal. They have multiple causes, but mutations in the genes for the various components of the dystrophin–glycoprotein complex are a prominent cause. The dystrophin gene is one of the largest in the body, and mutations can occur at many different sites in it. **Duchenne muscular dystrophy** is a serious form of dystrophy in which the dystrophin protein is absent from muscle. It is X-linked and usually fatal by the age of 30. In a milder form of the disease, **Becker muscular dystrophy,** dystrophin is present but altered or reduced in amount. Limb-girdle muscular dystrophies of various types are associated with mutations of the genes coding for the sarcoglycans or other components of the dystrophin–glycoprotein complex.

Due to its enormous size and structural role in the sarcomere, **titin** is a prominent target for mutations that give rise to muscle disease. Mutations that encode for shorter titin structure have been associated with dilated cardiomyopathy, while other mutations have been associated with hypertrophic cardiomyopathy. The skeletal muscle-associated tibialis muscular dystrophy is a genetic muscle disease of titin that is predicted to destabilize the folded state of the protein. Interestingly, many of the titin mutations identified thus far are in regions of titin that are expressed in all striated muscles, yet, not all muscles are affected in the same way. Such muscle type–specific phenotypes underscore the need to study titin's multiple functions in different muscles, under both normal and pathological conditions.

Desmin-related myopathies are a very rare heterogeneous group of muscle disorders that typically result in cellular aggregates of desmin. Common symptoms of these diseases are failing and wasting in the distal muscles of the lower limbs that can later be identified in other body areas. Studies in desmin knockout mice have revealed defects in skeletal, smooth, and cardiac muscle, notably in the diaphragm and heart.

Metabolic Myopathies

Mutations in genes that code for enzymes involved in the metabolism of carbohydrates, fats, and proteins to CO_2 and H_2O in muscle and the production of ATP can cause **metabolic myopathies** (eg, McArdle syndrome). Metabolic myopathies all have in common exercise intolerance and the possibility of muscle breakdown due to accumulation of toxic metabolites.

THERAPEUTIC HIGHLIGHTS

Although acute muscle pain and soreness can be treated with anti-inflammatory drugs and rest, the genetic dysfunctions described above are not as easily addressed. The overall goals are to slow muscle function/structure loss and, when possible relieve symptoms associated with the disease. Extensive monitoring, physical therapy and appropriate drugs including corticosteroids can aid to slow disease progression. Assistive devices and surgery are not uncommon as the diseases progress.

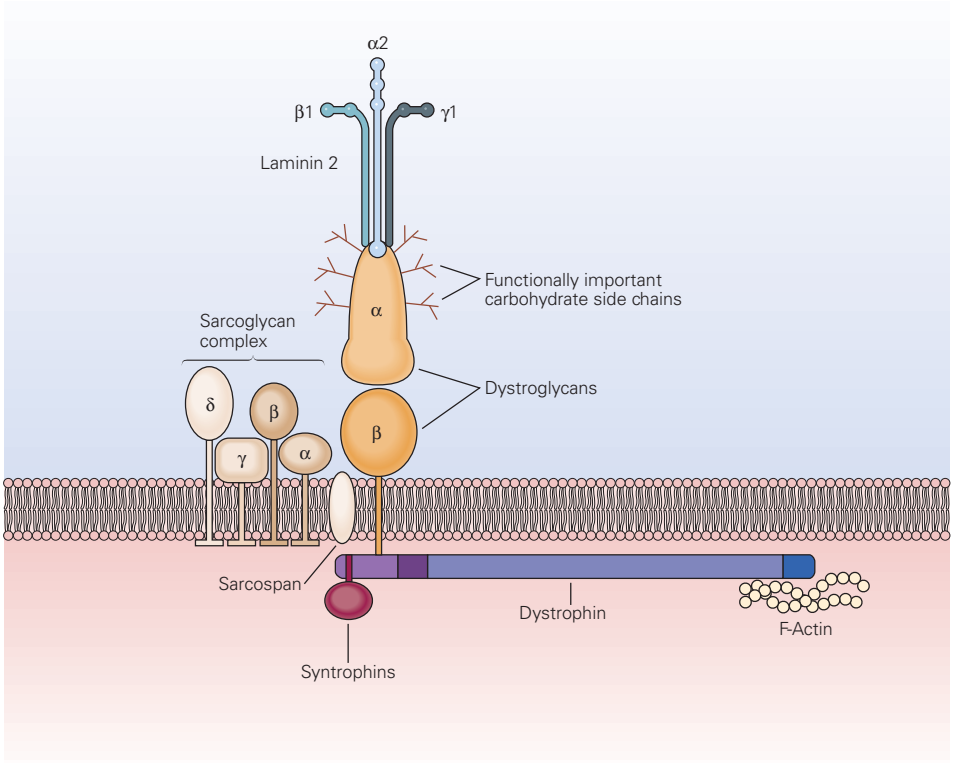


FIGURE 5–4 The dystrophin–glycoprotein complex. Dystrophin connects F-actin to the two members of the dystroglycan (DG) complex, α and β-dystroglycan, and these in turn connect to the merosin subunit of laminin 211 in the extracellular matrix. The sarcoglycan complex of four glycoproteins, α-, β-, γ-, and γ-sarcoglycan, sarcospan, and syntropins are all associated with the dystroglycan complex. There are muscle disorders associated with loss, abnormalities, or both of the sarcoglycans and merosin. (This diagram was adapted from diagrams by Justin Fallon and Kevin Campbell.)

T system of transverse tubules, which is continuous with the sarcolemma of the muscle fiber, forms a grid perforated by the individual muscle fibrils (Figure 5–1). The space between the two layers of the T system is an extension of the extracellular space. The sarcoplasmic reticulum, which forms an irregular curtain around each of the fibrils, has enlarged **terminal cisterns** in close contact with the T system at the junctions between the A and I bands. At these points of contact, the arrangement of the central T system with a cistern of the sarcoplasmic reticulum on either side has led to the use of the term **triads** to describe the system. The T system, which is continuous with the sarcolemma, provides a path for the rapid transmission of the action potential from the cell membrane to all the fibrils in the muscle. The sarcoplasmic reticulum is an important store of Ca^{2+} and also participates in muscle metabolism.

DYSTROPHIN–GLYCOPROTEIN COMPLEX

The large **dystrophin** protein (molecular mass 427,000 Da) forms a rod that connects the thin actin filaments to the transmembrane protein **β-dystroglycan** in the sarcolemma by smaller proteins in the cytoplasm, **syntrophins.** β-dystroglycan is connected to **merosin** (merosin refers to laminins that contain the α2 subunit in their trimeric makeup) in the extracellular matrix by **α-dystroglycan** (Figure 5–4). The dystroglycans are in turn associated with a complex of four transmembrane glycoproteins: α-, β-, γ-, and δ-**sarcoglycan.** This **dystrophin–glycoprotein complex** adds strength to the muscle by providing a scaffolding for the fibrils and connecting them to the extracellular environment. Disruption of these important structural features can result in several different muscular dystrophies (see Clinical Box 5–1).

ELECTRICAL PHENOMENA & IONIC FLUXES

ELECTRICAL CHARACTERISTICS OF SKELETAL MUSCLE

The electrical events in skeletal muscle and the ionic fluxes that underlie them share distinct similarities to those in nerve, with quantitative differences in timing and magnitude.

TABLE 5–1 Steady-state distribution of ions in the intracellular and extracellular compartments of mammalian skeletal muscle, and the equilibrium potentials for these ions.

Ion[a]	Concentration (mmol/L)		Equilibrium Potential (mV)
	Intracellular Fluid	Extracellular Fluid	
Na^+	12	145	+65
K^+	155	4	–95
H^+	13×10^{-5}	3.8×10^{-5}	–32
Cl^-	3.8	120	–90
HCO_3^-	8	27	–32
A^-	155	0	…
Membrane potential = –90 mV			

[a]A^- represents organic anions. The value for intracellular Cl^- is calculated from the membrane potential, using the Nernst equation.

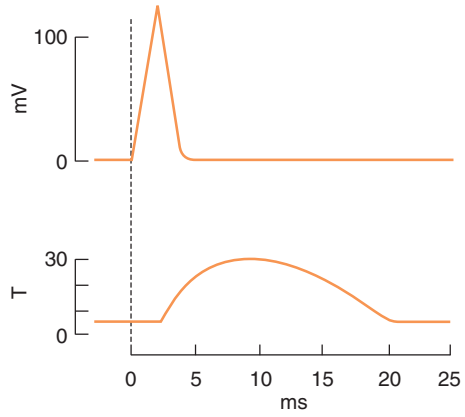


FIGURE 5–5 The electrical and mechanical responses of a mammalian skeletal muscle fiber to a single maximal stimulus. The electrical response (mV potential change) and the mechanical response (T, tension in arbitrary units) are plotted on the same abscissa (time). The mechanical response is relatively long-lived compared to the electrical response that initiates contraction.

The resting membrane potential of skeletal muscle is about –90 mV. The action potential lasts 2–4 ms and is conducted along the muscle fiber at about 5 m/s. The absolute refractory period is 1–3 ms long, and the after-polarizations, with their related changes in threshold to electrical stimulation, are relatively prolonged. The initiation of impulses at the myoneural junction is discussed in the next chapter.

ION DISTRIBUTION & FLUXES

The distribution of ions across the muscle fiber membrane is similar to that across the nerve cell membrane. Approximate values for the various ions and their equilibrium potentials are shown in Table 5–1. As in nerves, depolarization is largely a manifestation of Na^+ influx, and repolarization is largely a manifestation of K^+ efflux.

CONTRACTILE RESPONSES

It is important to distinguish between the electrical and mechanical events in skeletal muscle. Although one response does not normally occur without the other, their physiologic bases and characteristics are different. Muscle fiber membrane depolarization normally starts at the motor end plate, the specialized structure under the motor nerve ending. The action potential is transmitted along the muscle fiber and initiates the contractile response.

THE MUSCLE TWITCH

A single action potential causes a brief contraction followed by relaxation. This response is called a **muscle twitch.** In Figure 5–5, the action potential and the twitch are plotted on the same time scale. The twitch starts about 2 ms after the start of depolarization of the membrane, before repolarization is complete. The duration of the twitch varies with the type of muscle being tested. "Fast" muscle fibers, primarily those concerned with fine, rapid, precise movement, have twitch durations as short as 7.5 ms. "Slow" muscle fibers, principally those involved in strong, gross, sustained movements, have twitch durations up to 100 ms.

MOLECULAR BASIS OF CONTRACTION

The process by which the contraction of muscle is brought about is a sliding of the thin filaments over the thick filaments. Note that this shortening is not due to changes in the actual lengths of the thick and thin filaments, rather, by their increased overlap within the muscle cell. The width of the A bands is constant, whereas the Z lines move closer together when the muscle contracts and farther apart when it relaxes (Figure 5–3).

The sliding during muscle contraction occurs when the myosin heads bind firmly to actin, bend at the junction of the head with the neck, and then detach. This "power stroke" depends on the simultaneous hydrolysis of ATP. Myosin-II molecules are dimers that have two heads, but only one attaches to actin at any given time. The probable sequence of events of the power stroke is outlined in Figure 5–6. In resting muscle, troponin I is bound to actin and tropomyosin and covers the sites where myosin heads interact with actin. Also at rest, the myosin head contains tightly bound ADP. Following an action potential, cytosolic Ca^{2+} is increased and free Ca^{2+} binds to troponin C. This binding results in a weakening of the troponin I interaction with actin and exposes the actin binding site for myosin to allow for formation of myosin/actin cross-bridges.

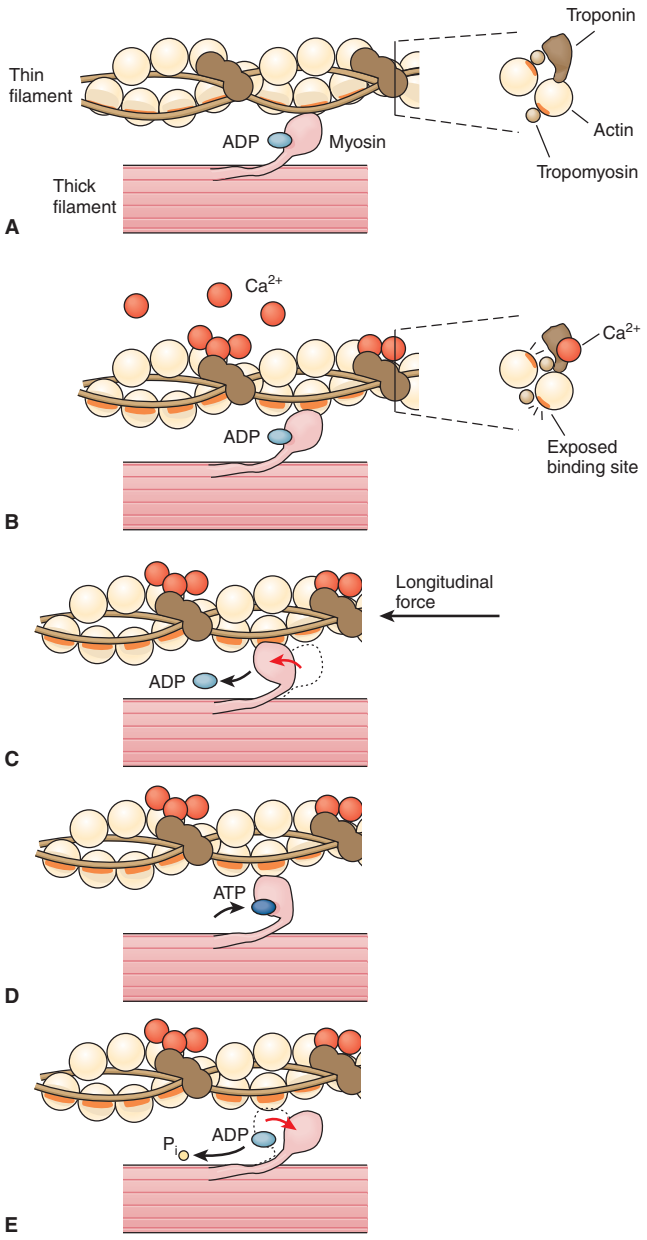


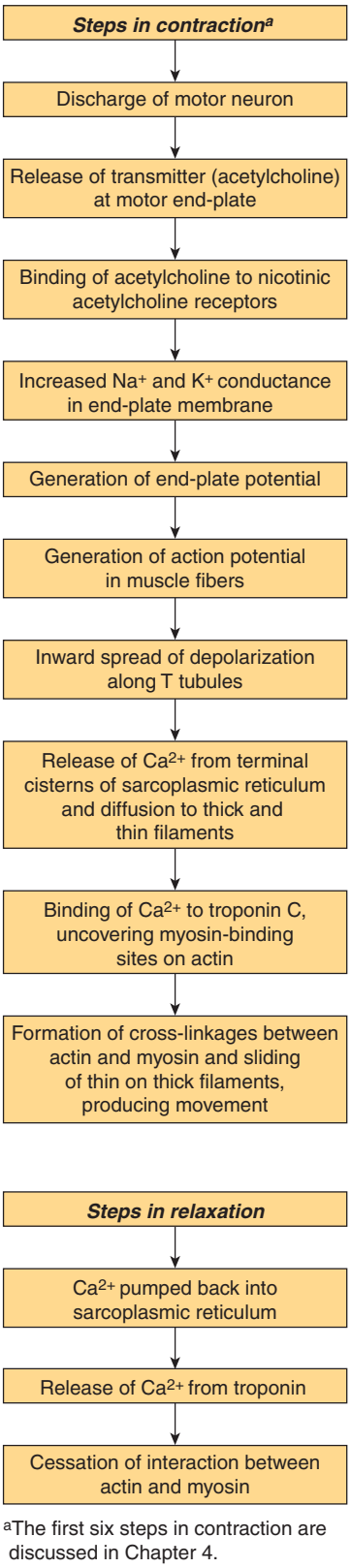
FIGURE 5–6 Power stroke of myosin in skeletal muscle. A) At rest, myosin heads are bound to adenosine diphosphate and are said to be in a "cocked" position in relation to the thin filament, which does not have Ca^{2+} bound to the troponin–tropomyosin complex. **B)** Ca^{2+} bound to the troponin–tropomyosin complex induces a conformational change in the thin filament that allows for myosin heads to cross-bridge with thin filament actin. **C)** Myosin heads rotate, move the attached actin and shorten the muscle fiber, forming the power stroke. **D)** At the end of the power stroke, ATP binds to a now exposed site, and causes a detachment from the actin filament. **E)** ATP is hydrolyzed into ADP and inorganic phosphate (P_i) and this chemical energy is used to "re-cock" the myosin head. (Based on Huxley AF, Simmons RM: Proposed mechanism of force generation in striated muscle. Nature Oct 22;233(5321):533–538, 1971 and Squire JM: Molecular mechanisms in muscular contraction. Trends Neurosci 6:409–413, 1093.)

Upon formation of the cross-bridge, ADP is released, causing a conformational change in the myosin head that moves the thin filament relative to the thick filament, comprising the cross-bridge "power stroke." ATP quickly binds to the free site on the myosin, which leads to a detachment of the myosin head from the thin filament. ATP is hydrolyzed and inorganic phosphate (P_i) released, causing a "re-cocking" of the myosin head and completing the cycle. As long as Ca^{2+} remains elevated and sufficient ATP is available, this cycle repeats. Many myosin heads cycle at or near the same time, and they cycle repeatedly, producing gross muscle contraction. Each power stroke shortens the sarcomere about 10 nm. Each thick filament has about 500 myosin heads, and each head cycles about five times per second during a rapid contraction.

The process by which depolarization of the muscle fiber initiates contraction is called **excitation–contraction coupling.** The action potential is transmitted to all the fibrils in the fiber via the T system (Figure 5–7). It triggers the release of Ca^{2+} from the terminal cisterns, the lateral sacs of the sarcoplasmic reticulum next to the T system. Depolarization of the T tubule membrane activates the sarcoplasmic reticulum via **dihydropyridine receptors (DHPR),** named for the drug dihydropyridine, which blocks them (Figure 5–8). DHPR are voltage-gated Ca^{2+} channels in the T tubule membrane. In cardiac muscle, influx of Ca^{2+} via these channels triggers the release of Ca^{2+} stored in the sarcoplasmic reticulum (calcium-induced calcium release) by activating the **ryanodine receptor (RyR).** The RyR is named after the plant alkaloid ryanodine that was used in its discovery. The RyR is a ligand-gated Ca^{2+} channel with Ca^{2+} as its natural ligand. In skeletal muscle, Ca^{2+} entry from the extracellular fluid (ECF) by this route is not required for Ca^{2+} release. Instead, the DHPR that serves as the voltage sensor unlocks release of Ca^{2+} from the nearby sarcoplasmic reticulum via physical interaction with the RyR. The released Ca^{2+} is quickly amplified through calcium-induced calcium release. Ca^{2+} is reduced in the muscle cell by the sarcoplasmic or endoplasmic reticulum Ca^{2+} ATPase (SERCA). The SERCA pump uses energy from ATP hydrolysis to remove Ca^{2+} from the cytosol back into the terminal cisterns, where it is stored until released by the next action potential. Once the Ca^{2+} concentration outside the reticulum has been lowered sufficiently, chemical interaction between myosin and actin ceases and the muscle relaxes. Note that ATP provides the energy for both contraction (at the myosin head) and relaxation (via SERCA). If transport of Ca^{2+} into the reticulum is inhibited, relaxation does not occur even though there are no more action potentials; the resulting sustained contraction is called a **contracture.** Alterations in the excitable response in muscle underscore many different pathologies (Clinical Box 5–2).

TYPES OF CONTRACTION

Muscular contraction involves shortening of the contractile elements, but because muscles have elastic and viscous elements in series with the contractile mechanism, it is possible



[a]The first six steps in contraction are discussed in Chapter 4.

FIGURE 5–7 Flow of information that leads to muscle contraction.

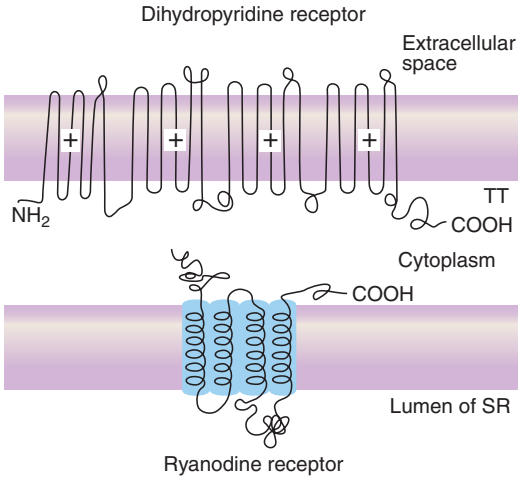


FIGURE 5–8 Relation of the T tubule (TT) to the sarcoplasmic reticulum in Ca^{2+} transport. In skeletal muscle, the voltage-gated dihydropyridine receptor in the T tubule triggers Ca^{2+} release from the sarcoplasmic reticulum (SR) via the ryanodine receptor (RyR). Upon sensing a voltage change, there is a physical interaction between the sarcolemmal-bound DHPR and the SR-bound RyR. This interaction gates the RyR and allows for Ca^{2+} release from the SR.

for contraction to occur without an appreciable decrease in the length of the whole muscle (Figure 5–9). Such a contraction is called **isometric** ("same measure" or length). Contraction against a constant load with a decrease in muscle length is **isotonic** ("same tension"). Note that because work is the product of force times distance, isotonic contractions do work, whereas isometric contractions do not. In other situations, muscle can do negative work while lengthening against a constant weight.

SUMMATION OF CONTRACTIONS

The electrical response of a muscle fiber to repeated stimulation is like that of nerve. The fiber is electrically refractory only during the rising phase and part of the falling phase of the spike potential. At this time, the contraction initiated by the first stimulus is just beginning. However, because the contractile mechanism does not have a refractory period, repeated stimulation before relaxation has occurred produces additional activation of the contractile elements and a response that is added to the contraction already present. This phenomenon is known as **summation of contractions.** The tension developed during summation is considerably greater than that during the single muscle twitch. With rapidly repeated stimulation, activation of the contractile mechanism occurs repeatedly before any relaxation has occurred, and the individual responses fuse into one continuous contraction. Such a response is called a **tetanus (tetanic contraction).** It is a **complete tetanus** when no relaxation occurs between stimuli and an **incomplete tetanus** when periods of incomplete relaxation take place between the summated stimuli. During a complete tetanus, the tension developed is about four times that developed by the individual

CLINICAL BOX 5–2

Muscle Channelopathies

Channelopathies are diseases that have as their underlying feature mutations or dysregulation of ion channels. Such diseases are frequently associated with excitable cells, including muscle. In the various forms of clinical **myotonia**, muscle relaxation is prolonged after voluntary contraction. The molecular bases of myotonias are due to dysfunction of channels that shape the action potential. Myotonia dystrophy is caused by an autosomal dominant mutation that leads to over-expression of a K^+ channel (although the mutation is *not* at the K^+ channel). A variety of myotonias are associated with mutations in Na^+ channels (eg, hyperkalemic periodic paralysis, paramyotonia congenita, or Na^+ channel congenita) or Cl^- channels (eg, dominant or recessive myotonia congenita). **Myasthenia,** defined as abnormal muscle weakness or disease, can also be related to loss of ion channel function in the muscle. In **congenital myasthenia,** the patient has an inheritable disorder of one of a group of ion channels necessary for the transmission of neuronal signaling to muscle response. Mutations in Ca^{2+} channels that allow for neuronal transmitter release or in the acetylcholine receptor nonspecific cation channels, important in recognition of neuronal transmitters, have both been shown to cause congenital myasthenia. Alterations of channel functions can also occur via autoimmune disease, such as that observed in **myasthenia gravis.** In this disease, antibodies to the nicotinic acetylcholine receptor can reduce its functional presence at the muscle membrane by up to 80%, and thus limit muscle response to neuronal transmitter release.

Channelopathies can also occur in the Ca^{2+} release channels in muscle (ryanodine receptors) that amplify the Ca^{2+} response within the cell. Such mutations can cause **malignant hyperthermia.** Patients with this conditions display normal muscle function under normal conditions. However, certain anesthetic agents, or in rare cases exposure to high environmental heat or strenuous exercise, can trigger abnormal release of Ca^{2+} from the sarcoplasmic reticulum in the muscle cell, resulting in sustained muscle contraction and heat production. In severe cases, fatality can occur.

THERAPEUTIC HIGHLIGHTS

Although the symptoms associated with each individual channelopathy may be similar, treatments for the individual diseases include a wide variety of drugs that are targeted to the individual ion channel (or proteins associated with ion channel) defect. Appropriate drug therapy helps to improve symptoms and maintain acceptable muscle function. Further interventions related to individual diseases are to avoid muscle movements that exacerbate the disease.

twitch contractions. The development of an incomplete and a complete tetanus in response to stimuli of increasing frequency is shown in Figure 5–10.

The stimulation frequency at which summation of contractions occurs is determined by the twitch duration of the particular muscle being studied. For example, if the twitch duration is 10 ms, frequencies less than 1/10 ms (100/s) cause discrete responses interrupted by complete relaxation, and frequencies greater than 100/s cause summation.

RELATION BETWEEN MUSCLE LENGTH, TENSION & VELOCITY OF CONTRACTION

Both the tension that a muscle develops when stimulated to contract isometrically (the **total tension)** and the **passive tension** exerted by the unstimulated muscle vary with the length of the muscle fiber. This relationship can be studied in a whole skeletal muscle preparation such as that shown in Figure 5–9. The length of the muscle can be varied by changing the distance between its two attachments. At each length, the passive tension is measured, the muscle is then stimulated electrically, and the total tension is measured. The difference between the two values at any length is the amount of tension actually generated by the contractile process, the **active tension.** The records obtained by plotting passive tension and total tension against muscle length are shown in Figure 5–11. Similar curves are obtained when single muscle fibers are studied. The length of the muscle at which the active tension is maximal is usually called its **resting length.** The term comes originally from experiments demonstrating that the length of many of the muscles in the body at rest is the length at which they develop maximal tension.

The observed length–tension relation in skeletal muscle can be explained by the sliding filament mechanism of muscle contraction. When the muscle fiber contracts isometrically, the tension developed is proportional to the number of cross-bridges between the actin and the myosin molecules. When muscle is stretched, the overlap between actin and myosin is reduced and the number of cross-linkages is therefore reduced. Conversely, when the muscle is appreciably shorter than resting length, the distance the thin filaments can move is reduced.

The velocity of muscle contraction varies inversely with the load on the muscle. At a given load, the velocity is maximal at the resting length and declines if the muscle is shorter or longer than this length.

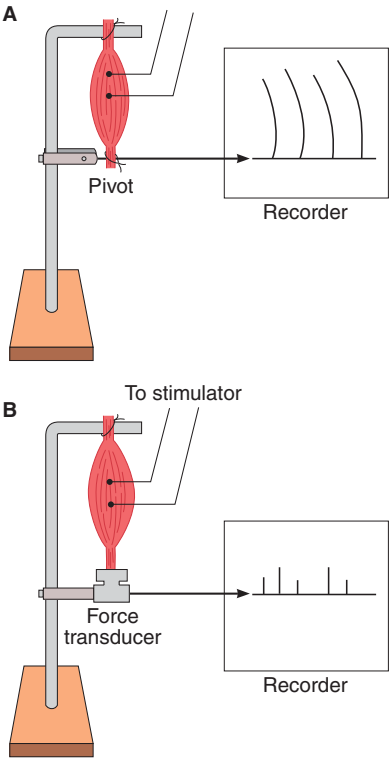


FIGURE 5–9 **A)** Muscle preparation arranged for recording isotonic contractions. **B)** Preparation arranged for recording isometric contractions. In **A,** the muscle is fastened to a writing lever that swings on a pivot. In **B,** it is attached to an electronic transducer that measures the force generated without permitting the muscle to shorten.

FIBER TYPES

Although skeletal muscle fibers resemble one another in a general way, skeletal muscle is a heterogeneous tissue made up of fibers that vary in myosin ATPase activity, contractile speed, and other properties. Muscles are frequently classified into two types, "slow" and "fast." These muscles can contain a mixture of three fiber types: type I (or SO for slow-oxidative); type IIA (FOG for fast-oxidative-glycolytic); or type IIB (FG for fast glycolytic). Some of the properties associated with type I, type IIA, and type IIB fibers are summarized in Table 5–2. Although these classification schemes are valid for muscles across many mammalian species, there are significant variations of fibers within and between muscles. For example, type I fibers in a given muscle can be larger than type IIA fibers from a different muscle in the same animal. Many of the differences in the fibers that make up muscles stem from differences in the proteins within them. Most of these are encoded by multigene families. Ten different **isoforms** of the myosin heavy chains (MHCs) have been characterized. Each of the two types of light chains also have isoforms. It appears that there is only one form of actin, but multiple isoforms of tropomyosin and all three components of troponin.

ENERGY SOURCES & METABOLISM

Muscle contraction requires energy, and muscle has been called "a machine for converting chemical energy into mechanical work." The immediate source of this energy is ATP, and this is formed by the metabolism of carbohydrates and lipids.

PHOSPHORYLCREATINE

ATP is resynthesized from ADP by the addition of a phosphate group. Some of the energy for this endothermic reaction is supplied by the breakdown of glucose to CO_2 and H_2O, but there also exists in muscle another energy-rich phosphate compound that can supply this energy for short periods. This compound is **phosphorylcreatine,** which is hydrolyzed to creatine and phosphate groups with the release of considerable energy (Figure 5–12). At rest, some ATP in the mitochondria transfers its phosphate to creatine, so that a phosphorylcreatine store is built up. During exercise, the phosphorylcreatine is hydrolyzed at the junction between the myosin heads and actin, forming ATP from ADP and thus permitting contraction to continue.

CARBOHYDRATE & LIPID BREAKDOWN

At rest and during light exercise, muscles utilize lipids in the form of free fatty acids as their energy source. As the intensity of exercise increases, lipids alone cannot supply energy fast enough and so use of carbohydrate becomes the predominant component in the muscle fuel mixture. Thus, during exercise,

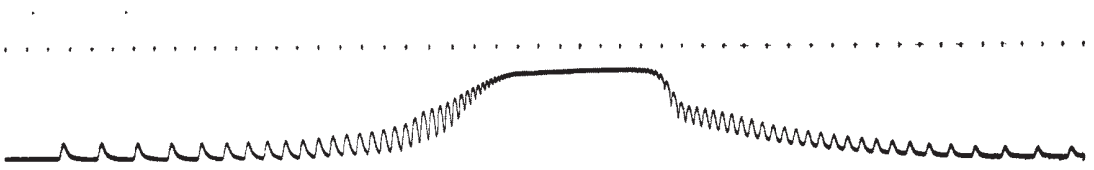


FIGURE 5–10 **Tetanus.** Isometric tension of a single muscle fiber during continuously increasing and decreasing stimulation frequency. Dots at the top are at intervals of 0.2 s. Note the development of incomplete and then complete tetanus as stimulation is increased, and the return of incomplete tetanus, then full response, as stimulation frequency is decreased.

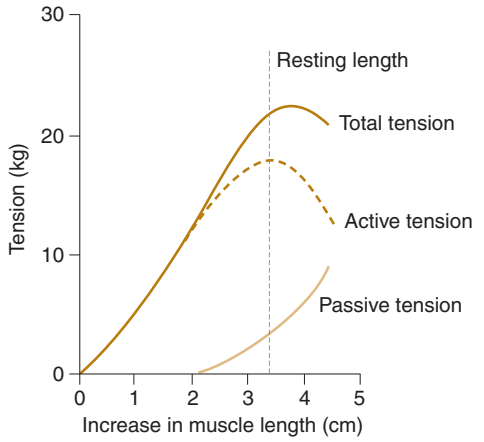


FIGURE 5–11 Length–tension relationship for the human triceps muscle. The passive tension curve measures the tension exerted by this skeletal muscle at each length when it is not stimulated. The total tension curve represents the tension developed when the muscle contracts isometrically in response to a maximal stimulus. The active tension is the difference between the two.

much of the energy for phosphorylcreatine and ATP resynthesis comes from the breakdown of glucose to CO_2 and H_2O. Glucose in the bloodstream enters cells, where it is degraded through a series of chemical reactions to pyruvate. Another source of intracellular glucose, and consequently of pyruvate, is glycogen, the carbohydrate polymer that is especially abundant in liver and skeletal muscle. When adequate O_2 is

TABLE 5–2 Classification of fiber types in skeletal muscles.

	Type 1	Type IIA	Type IIB
Other names	Slow, Oxidative (SO)	Fast, Oxidative, Glycolytic (FOG)	Fast, Glycolytic (FG)
Color	Red	Red	White
Myosin ATPase activity	Slow	Fast	Fast
Ca^{2+}-pumping capacity of sarcoplasmic reticulum	Moderate	High	High
Diameter	Small	Large	Large
Glycolytic capacity	Moderate	High	High
Oxidative capacity	High	Moderate	Low
Associated Motor Unit Type	Slow (S)	Fast Resistant to Fatigue (FR)	Fast Fatigable (FF)
Membrane potential = –90 mV			
Oxidative capacity	High	Moderate	Low

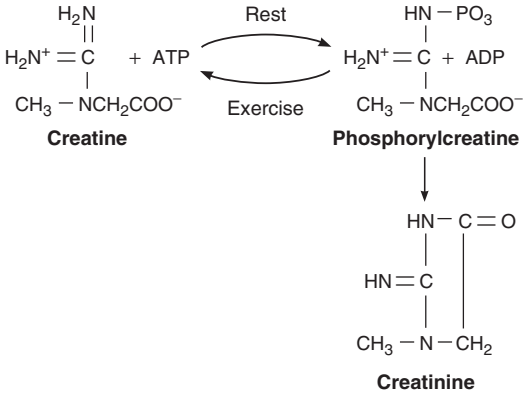


FIGURE 5–12 Creatine, phosphorylcreatine, and creatinine cycling in muscle. During periods of high activity, cycling of phosphorylcreatine allows for quick release of ATP to sustain muscle activity.

present, pyruvate enters the citric acid cycle and is metabolized—through this cycle and the so-called respiratory enzyme pathway—to CO_2 and H_2O. This process is called **aerobic glycolysis.** The metabolism of glucose or glycogen to CO_2 and H_2O forms large quantities of ATP from ADP. If O_2 supplies are insufficient, the pyruvate formed from glucose does not enter the tricarboxylic acid cycle but is reduced to lactate. This process of **anaerobic glycolysis** is associated with the net production of much smaller quantities of energy-rich phosphate bonds, but it does not require the presence of O_2. A brief overview of the various reactions involved in supplying energy to skeletal muscle is shown in Figure 5–13.

THE OXYGEN DEBT MECHANISM

During exercise, the muscle blood vessels dilate and blood flow is increased so that the available O_2 supply is increased. Up to a point, the increase in O_2 consumption is proportional to the

$$ATP + H_2O \rightarrow ADP + H_3PO_4 + 7.3\ kcal$$

$$Phosphorylcreatine + ADP \rightleftharpoons Creatine + ATP$$

$$Glucose + 2\ ATP\ (or\ glycogen + 1\ ATP) \xrightarrow{Anaerobic} 2\ Lactic\ acid + 4\ ATP$$

$$Glucose + 2\ ATP\ (or\ glycogen + 1\ ATP) \xrightarrow{Oxygen} 6\ CO_2 + 6\ H_2O + 40\ ATP$$

$$FFA \xrightarrow{Oxygen} CO_2 + H_2O + ATP$$

FIGURE 5–13 ATP turnover in muscle cells. Energy released by hydrolysis of 1 mol of ATP and reactions responsible for resynthesis of ATP. The amount of ATP formed per mole of free fatty acid (FFA) oxidized is large but varies with the size of the FFA. For example, complete oxidation of 1 mol of palmitic acid generates 140 mol of ATP.

energy expended, and all the energy needs are met by aerobic processes. However, when muscular exertion is very great, aerobic resynthesis of energy stores cannot keep pace with their utilization. Under these conditions, phosphorylcreatine is still used to resynthesize ATP. In addition, some ATP synthesis is accomplished by using the energy released by the anaerobic breakdown of glucose to lactate. Use of the anaerobic pathway is self-limiting because in spite of rapid diffusion of lactate into the bloodstream, enough accumulates in the muscles to eventually exceed the capacity of the tissue buffers and produce an enzyme-inhibiting decline in pH. However, for short periods, the presence of an anaerobic pathway for glucose breakdown permits muscular exertion of a far greater magnitude than would be possible without it. For example, in a 100-m dash that takes 10 s, 85% of the energy consumed is derived anaerobically; in a 2-mile race that takes 10 min, 20% of the energy is derived anaerobically; and in a long-distance race that takes 60 min, only 5% of the energy comes from anaerobic metabolism.

After a period of exertion is over, extra O_2 is consumed to remove the excess lactate, replenish the ATP and phosphorylcreatine stores, and replace the small amounts of O_2 that were released by myoglobin. Without replenishment of ATP, muscles enter a state of rigor (Clinical Box 5–3). The amount of extra O_2 consumed is proportional to the extent to which the energy demands during exertion exceeded the capacity for the aerobic synthesis of energy stores, that is, the extent to which an **oxygen debt** was incurred. The O_2 debt is measured experimentally by determining O_2 consumption after exercise until a constant, basal consumption is reached and subtracting the basal consumption from the total. The amount of this debt may be six times the basal O_2 consumption, which indicates that the subject is capable of six times the exertion that would have been possible without it.

HEAT PRODUCTION IN MUSCLE

Thermodynamically, the energy supplied to a muscle must equal its energy output. The energy output appears in work done by the muscle, in energy-rich phosphate bonds formed for later use, and in heat. The overall mechanical efficiency of skeletal muscle (work done/total energy expenditure) ranges up to 50% while lifting a weight during isotonic contraction and is essentially 0% during isometric contraction. Energy storage in phosphate bonds is a small factor. Consequently, heat production is considerable. The heat produced in muscle can be measured accurately with suitable thermocouples.

Resting heat, the heat given off at rest, is the external manifestation of basal metabolic processes. The heat produced in excess of resting heat during contraction is called the **initial heat.** This is made up of **activation heat,** the heat that muscle produces whenever it is contracting, and **shortening heat,** which is proportional in amount to the distance the muscle shortens. Shortening heat is apparently due to some change in the structure of the muscle during shortening.

Following contraction, heat production in excess of resting heat continues for as long as 30 min. This **recovery heat** is the heat liberated by the metabolic processes that restore the muscle to its precontraction state. The recovery heat of muscle is approximately equal to the initial heat; that is, the heat produced during recovery is equal to the heat produced during contraction.

If a muscle that has contracted isotonically is restored to its previous length, extra heat in addition to recovery heat is produced **(relaxation heat).** External work must be done on the muscle to return it to its previous length, and relaxation heat is mainly a manifestation of this work.

CLINICAL BOX 5–3

Muscle Rigor

When muscle fibers are completely depleted of ATP and phosphorylcreatine, they develop a state of rigidity called rigor. When this occurs after death, the condition is called **rigor mortis.** In rigor, almost all of the myosin heads attach to actin but in an abnormal, fixed, and resistant way. The muscles effectively are locked into place and become quite stiff to the touch.

PROPERTIES OF SKELETAL MUSCLES IN THE INTACT ORGANISM

THE MOTOR UNIT

Innervation of muscle fibers is critical to muscle function (Clinical Box 5–4). Because the axons of the spinal motor neurons supplying skeletal muscle each branch to innervate

CLINICAL BOX 5–4

Denervation of Muscle

In the intact animal healthy skeletal muscle does not contract except in response to stimulation of its motor nerve supply. Destruction of this nerve supply causes muscle atrophy. It also leads to abnormal excitability of the muscle and increases its sensitivity to circulating acetylcholine (**denervation hypersensitivity;** see Chapter 6). Fine, irregular contraction of individual fibers (**fibrillations**) appears. This is the classic picture of a **lower motor neuron lesion.** If the motor nerve regenerates, the fibrillations disappear. Usually, the contractions are not visible grossly, and they should not be confused with **fasciculations,** which are jerky, visible contractions of groups of muscle fibers that occur as a result of pathologic discharge of spinal motor neurons.

several muscle fibers, the smallest possible amount of muscle that can contract in response to the excitation of a single motor neuron is not one muscle fiber but all the fibers supplied by the neuron. Each single motor neuron and the muscle fibers it innervates constitute a **motor unit.** The number of muscle fibers in a motor unit varies. In muscles such as those of the hand and those concerned with motion of the eye (ie, muscles concerned with fine, graded, precise movement), each motor unit innervates very few (on the order of three to six) muscle fibers. On the other hand, values of 600 muscle fibers per motor unit can occur in human leg muscles. The group of muscle fibers that contribute to a motor unit can be intermixed within a muscle. That is, although they contract as a unit, they are not necessarily "neighboring" fibers within the muscle.

Each spinal motor neuron innervates only one kind of muscle fiber, so that all the muscle fibers in a motor unit are of the same type. On the basis of the type of muscle fiber they innervate, and thus on the basis of the duration of their twitch contraction, motor units are divided into S (slow), FR (fast, resistant to fatigue), and FF (fast, fatigable) units. Interestingly, there is also a gradation of innervation of these fibers, with S fibers tending to have a low innervation ratio (ie, small units) and FF fibers tending to have a high innervation ratio (ie, large units). The recruitment of motor units during muscle contraction is not random; rather it follows a general scheme, the **size principle.** In general, a specific muscle action is developed first by the recruitment of S muscle units that contract relatively slowly to produce controlled contraction. Next, FR muscle units are recruited, resulting in more powerful response over a shorter period of time. Lastly, FF muscle units are recruited for the most demanding tasks. For example, in muscles of the leg, the small, slow units are first recruited for standing. As walking motion is initiated, their recruitment of FR units increases. As this motion turns to running or jumping, the FF units are recruited. Of course, there is overlap in recruitment, but, in general, this principle holds true.

The differences between types of muscle units are not inherent but are determined by, among other things, their activity. When the nerve to a slow muscle is cut and the nerve to a fast muscle is spliced to the cut end, the fast nerve grows and innervates the previously slow muscle. However, the muscle becomes fast and corresponding changes take place in its muscle protein isoforms and myosin ATPase activity. This change is due to changes in the pattern of activity of the muscle; in stimulation experiments, changes in the expression of MHC genes and consequently of MHC isoforms can be produced by changes in the pattern of electrical activity used to stimulate the muscle. More commonly, muscle fibers can be altered by a change in activity initiated through exercise (or lack thereof). Increased activity can lead to muscle cell hypertrophy, which allows for increase in contractile strength. Type IIA and IIB fibers are most susceptible to these changes. Alternatively, inactivity can lead to muscle cell atrophy and a loss of contractile strength. Type I fibers—that is, the ones used most often—are most susceptible to these changes.

ELECTROMYOGRAPHY

Activation of motor units can be studied by electromyography, the process of recording the electrical activity of muscle. This may be done in unanaesthetized humans by using small metal disks on the skin overlying the muscle as the pick-up electrodes or by using needle or fine wire electrodes inserted into the muscle. The record obtained with such electrodes is the **electromyogram (EMG).** With needle or fine wire electrodes, it is usually possible to pick up the activity of single muscle fibers. The measured EMG depicts the potential difference between the two electrodes, which is altered by the activation of muscles in between the electrodes. A typical EMG is shown in Figure 5–14.

It has been shown by electromyography that little if any spontaneous activity occurs in the skeletal muscles of normal individuals at rest. With minimal voluntary activity a few motor units discharge, and with increasing voluntary effort, more and more are brought into play to monitor the **recruitment of motor units.** Gradation of muscle response is therefore in part a function of the number of motor units activated. In addition, the frequency of discharge in the individual nerve fibers plays a role, the tension developed during a tetanic contraction being greater than that during individual twitches. The length of the muscle is also a factor. Finally, the motor units fire asynchronously, that is, out of phase with one another. This asynchronous firing causes the individual muscle fiber responses to merge into a smooth contraction of the whole muscle. In summary, EMGs can be used to quickly (and roughly) monitor abnormal electrical activity associated with muscle responses.

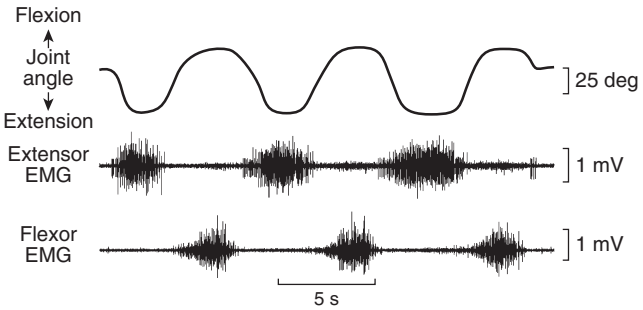


FIGURE 5–14 Relative joint angle and electromyographic tracings from human extensor pollicis longus and flexor pollicis longus during alternate flexion and extension of the distal joint of the thumb. The extensor pollicis longus and flexor pollicis longus extend and flex the distal joint of the thumb, respectively. The distal thumb joint angle (top) is superimposed over the extensor pollicis longus (middle) and flexor pollicus longus (bottom) EMGs. Note the alternate activation and rest patterns as one muscle is used for extension and the other for flexion. (Courtesy of Andrew J. Fuglevand.)

THE STRENGTH OF SKELETAL MUSCLES

Human skeletal muscle can exert 3–4 kg of tension per square centimeter of cross-sectional area. This figure is about the same as that obtained in a variety of experimental animals and seems to be constant for mammalian species. Because many of the muscles in humans have a relatively large cross-sectional area, the tension they can develop is quite large. The gastrocnemius, for example, not only supports the weight of the whole body during climbing but resists a force several times this great when the foot hits the ground during running or jumping. An even more striking example is the gluteus maximus, which can exert a tension of 1200 kg. The total tension that could be developed if all muscles in the body of an adult man pulled together is approximately 22,000 kg (nearly 25 tons).

BODY MECHANICS

Body movements are generally organized in such a way that they take maximal advantage of the physiologic principles outlined above. For example, the attachments of the muscles in the body are such that many of them are normally at or near their resting length when they start to contract. In muscles that extend over more than one joint, movement at one joint may compensate for movement at another in such a way that relatively little shortening of the muscle occurs during contraction. Nearly isometric contractions of this type permit development of maximal tension per contraction. The hamstring muscles extend from the pelvis over the hip joint and the knee joint to the tibia and fibula. Hamstring contraction produces flexion of the leg on the thigh. If the thigh is flexed on the pelvis at the same time, the lengthening of the hamstrings across the hip joint tends to compensate for the shortening across the knee joint. In the course of various activities, the body moves in a way that takes advantage of this. Such factors as momentum and balance are integrated into body movement in ways that make possible maximal motion with minimal muscular exertion. One net effect is that the stress put on tendons and bones rarely exceeds 50% of their failure strength, protecting them from damage.

In walking, each limb passes rhythmically through a support or stance phase when the foot is on the ground and a swing phase when the foot is off the ground. The support phases of the two legs overlap, so that two periods of double support occur during each cycle. There is a brief burst of activity in the leg flexors at the start of each step, and then the leg is swung forward with little more active muscular contraction. Therefore, the muscles are active for only a fraction of each step, and walking for long periods causes relatively little fatigue.

A young adult walking at a comfortable pace moves at a velocity of about 80 m/min and generates a power output of 150–175 W per step. A group of young adults asked to walk at their most comfortable rate selected a velocity close to 80 m/min, and it was found that they had selected the velocity at which their energy output was minimal. Walking more rapidly or more slowly took more energy.

CARDIAC MUSCLE MORPHOLOGY

The striations in cardiac muscle are similar to those in skeletal muscle, and Z lines are present. Large numbers of elongated mitochondria are in close contact with the muscle fibrils. The muscle fibers branch and interdigitate, but each is a complete unit surrounded by a cell membrane. Where the end of one muscle fiber abuts on another, the membranes of both fibers parallel each other through an extensive series of folds. These areas, which always occur at Z lines, are called **intercalated disks** (Figure 5–15). They provide a strong union between fibers, maintaining cell-to-cell cohesion, so that the pull of one contractile cell can be transmitted along its axis to the next. Along the sides of the muscle fibers next to the disks, the cell membranes of adjacent fibers fuse for considerable distances, forming gap junctions. These junctions provide low-resistance bridges for the spread of excitation from one fiber to another. They permit cardiac muscle to function as if it were a syncytium, even though no protoplasmic bridges are present between cells. The T system in cardiac muscle is located at the Z lines rather than at the A–I junction, where it is located in mammalian skeletal muscle.

ELECTRICAL PROPERTIES

RESTING MEMBRANE & ACTION POTENTIALS

The resting membrane potential of individual mammalian cardiac muscle cells is about –80 mV. Stimulation produces a propagated action potential that is responsible for initiating contraction. Although action potentials vary among the cardiomyocytes in different regions of the heart (discussed in Chapter 29), the action potential of a typical ventricular cardiomyocyte can be used as an example (Figure 5–16). Depolarization proceeds rapidly and an overshoot of the zero potential is present, as in skeletal muscle and nerve, but this is followed by a plateau before the membrane potential returns to the baseline. In mammalian hearts, depolarization lasts about 2 ms, but the plateau phase and repolarization last 200 ms or more. Repolarization is therefore not complete until the contraction is half over.

As in other excitable tissues, changes in the external K^+ concentration affect the resting membrane potential of cardiac muscle, whereas changes in the external Na^+ concentration affect the magnitude of the action potential. The initial rapid depolarization and the overshoot (phase 0) are due to opening of voltage-gated Na^+ channels similar to that occurring in nerve and skeletal muscle (Figure 5–17). The initial rapid repolarization (phase 1) is due to closure of Na^+ channels and opening of one type of K^+ channel. The subsequent prolonged plateau (phase 2) is due to a slower but prolonged opening of voltage-gated Ca^{2+} channels. Final repolarization (phase 3) to the resting membrane potential (phase 4) is due

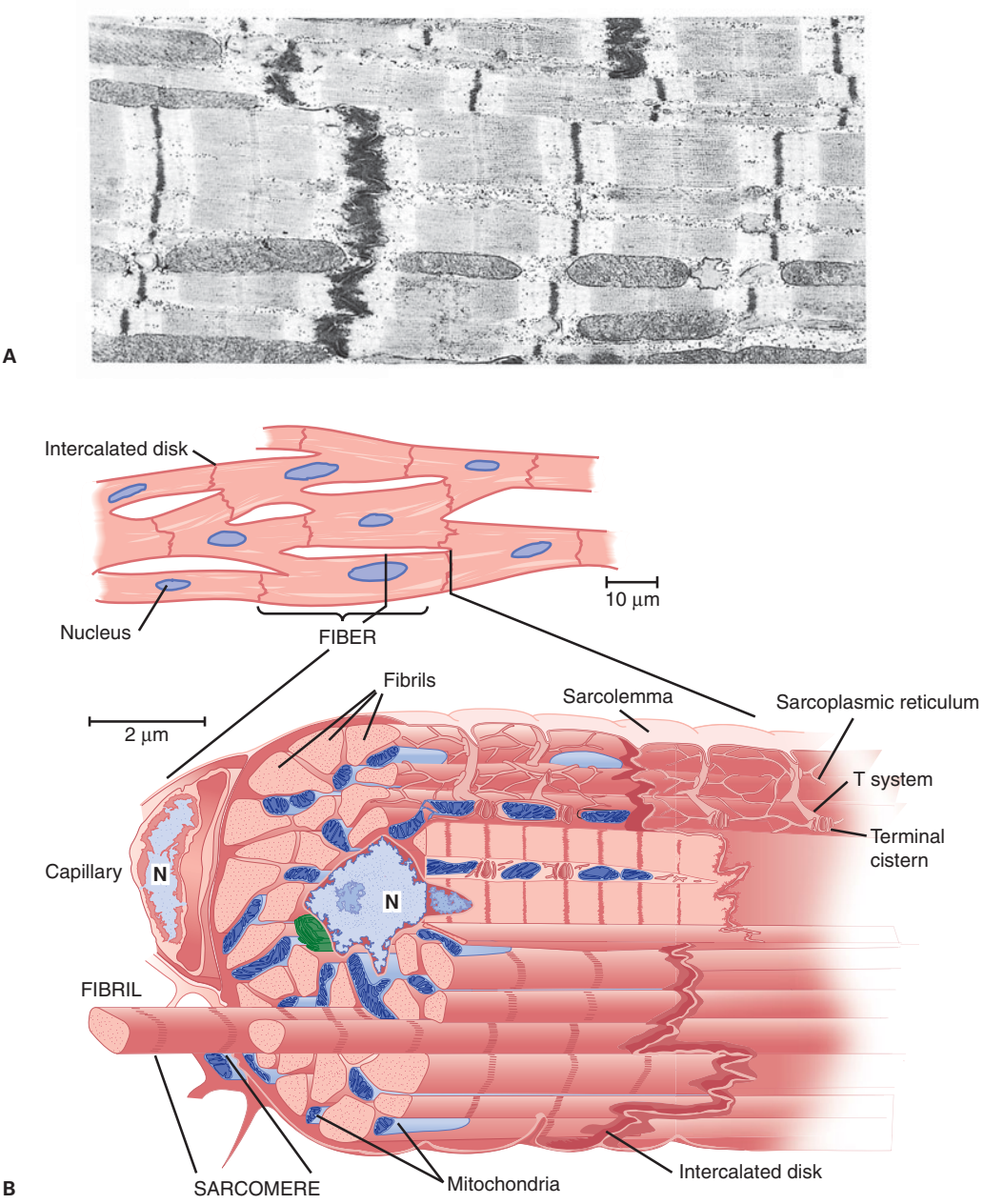


FIGURE 5–15 Cardiac muscle. A) Electronmicrograph of cardiac muscle. Note the similarity of the A-I regions seen in the skeletal muscle EM of Figure 3–2. The fuzzy thick lines are intercalated disks and function similarly to the Z-lines but occur at cell membranes (× 12,000). (Reproduced with permission from Bloom W, Fawcett DW: *A Textbook of Histology,* 10th ed. Saunders, 1975.) **B)** Artist interpretation of cardiac muscle as seen under the light microscope (top) and the electron microscope (bottom). Again, note the similarity to skeletal muscle structure. N, nucleus. (Reproduced with permission from Braunwald E, Ross J, Sonnenblick EH: Mechanisms of contraction of the normal and failing heart. *N Engl J Med* 1967;277:794.)

to closure of the Ca^{2+} channels and a slow, delayed increase of K^+ efflux through various types of K^+ channels. Cardiac myocytes contain at least two types of Ca^{2+} channels (T- and L-types), but the Ca^{2+} current is mostly due to opening of the slower L-type Ca^{2+} channels. Mutations or dysfunction in any of these channels lead to serious pathologies of the heart (eg, Clinical Box 5–5).

MECHANICAL PROPERTIES

CONTRACTILE RESPONSE

The contractile response of cardiac muscle begins just after the start of depolarization and lasts about 1.5 times as long as the action potential (Figure 5–16). The role of Ca^{2+} in excitation–

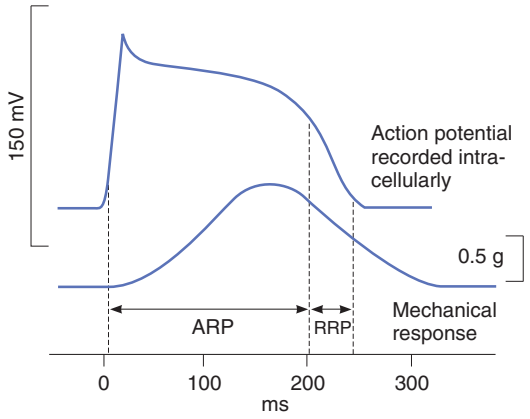


FIGURE 5–16 Comparison of action potentials and contractile response of a mammalian cardiac muscle fiber in a typical ventricular cell. In the top trace, the intracellular recording of the action potential shows the quick depolarization and extended recovery. In the bottom trace, the mechanical response is matched to the extracellular and intracellular electrical activities. Note that in the absolute refractory period (ARP), the cardiac myocyte cannot be excited, whereas in the relative refractory period (RRP) minimal excitation can occur.

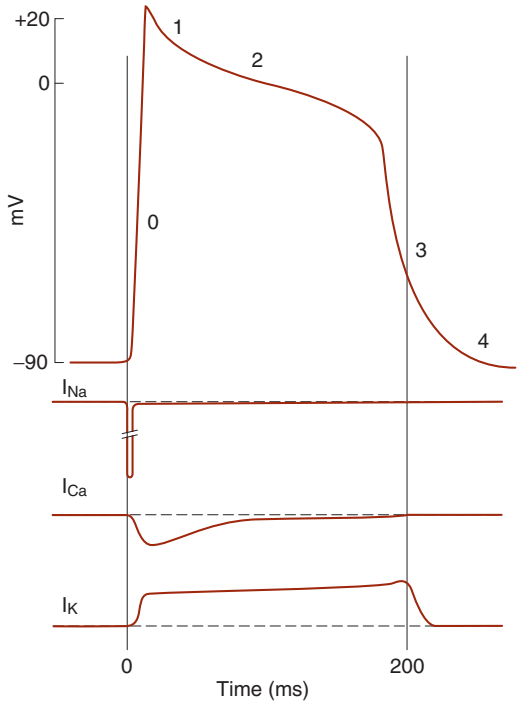


FIGURE 5–17 Dissection of the cardiac action potential. Top: The action potential of a cardiac muscle fiber can be broken down into several phases: 0, depolarization; 1, initial rapid repolarization; 2, plateau phase; 3, late rapid repolarization; 4, baseline. Bottom: Diagrammatic summary of Na^+, Ca^{2+}, and cumulative K+ currents during the action potential. As is convention, inward currents are downward, and outward currents are upward.

contraction coupling is similar to its role in skeletal muscle (see above). However, it is the influx of extracellular Ca^{2+} through the voltage-sensitive DHPR in the T system that triggers calcium-induced calcium release through the RyR at the sarcoplasmic reticulum. Because there is a net influx of Ca^{2+} during activation, there is also a more prominent role for plasma membrane Ca^{2+} ATPases and the Na^+/Ca^{2+} exchanger in recovery of intracellular Ca^{2+} concentrations. Specific effects of drugs that indirectly alter Ca^{2+} concentrations are discussed in Clinical Box 5–6.

During phases 0 to 2 and about half of phase 3 (until the membrane potential reaches approximately –50 mV during repolarization), cardiac muscle cannot be excited again; that is, it is in its **absolute refractory period.** It remains relatively refractory until phase 4. Therefore, tetanus of the type seen in skeletal muscle cannot occur. Of course, tetanization of cardiac muscle for any length of time would have lethal consequences, and in this sense, the fact that cardiac muscle cannot be tetanized is a safety feature.

ISOFORMS

Cardiac muscle is generally slow and has relatively low ATPase activity. Its fibers are dependent on oxidative metabolism and hence on a continuous supply of O_2. The human heart contains both the α and the β isoforms of the myosin heavy chain (α MHC and β MHC). β MHC has lower myosin ATPase activity than α MHC. Both are present in the atria, with the α isoform predominating, whereas the β isoform predominates in the ventricle. The spatial differences in expression contribute to the well-coordinated contraction of the heart.

CORRELATION BETWEEN MUSCLE FIBER LENGTH & TENSION

The relation between initial fiber length and total tension in cardiac muscle is similar to that in skeletal muscle; there is a resting length at which the tension developed on stimulation is maximal. In the body, the initial length of the fibers is determined by the degree of diastolic filling of the heart, and the pressure developed in the ventricle is proportional to the volume of the ventricle at the end of the filling phase **(Starling's law of the heart).** The developed tension (Figure 5–18) increases as the diastolic volume increases until it reaches a maximum, then tends to decrease. However, unlike skeletal muscle, the decrease in developed tension at high degrees of stretch is not due to a decrease in the number of cross-bridges between actin and myosin, because even severely dilated hearts are not stretched to this degree. The decrease is instead due to beginning disruption of the myocardial fibers.

The force of contraction of cardiac muscle can be also increased by catecholamines, and this increase occurs without a change in muscle length. This positive ionotropic effect of catecholamines is mediated via innervated β_1-adrenergic receptors, cyclic AMP, and their effects on Ca^{2+} homeostasis. The heart also contains noninnervated β_2-adrenergic receptors,

CLINICAL BOX 5–5

Long QT Syndrome

Long QT syndrome (LQTS) is defined as a prolongation of the QT interval observed on an electrocardiogram. LQTS can lead to irregular heartbeats and subsequent fainting, seizure, cardiac arrest, or even death. Although certain medications can lead to LQTS, it is more frequently associated with genetic mutations in a variety of cardiac-expressed ion channels. Mutations in cardiac-expressed voltage gated K^+ channel genes (KCNQ1 or KCNH2) account for most of the mutation-based cases of LQTS (~90%). Mutations in cardiac-expressed voltage-gated Na^+ channels (eg, SCN5A) or cardiac-expressed Ca^{2+} channels (eg, CACNA1C) have also been associated with the disease. The fact that mutations in diverse channels all can result in the prolongation of the QT interval and subsequent pathology underlies the intricate interplay of these channels in shaping the heart's electrical response.

THERAPEUTIC HIGHLIGHTS

Patients with long QT syndrome (LQTS) should avoid drugs that prolong the QT interval or reduce their serum K^+ or Mg^{2+} levels; any K^+ or Mg^{2+} deficiencies should be corrected. Drug interventions in asymptomatic patients remain somewhat controversial, although patients with congenital defects that lead to LQTS are considered candidates for intervention independent of symptoms. In general, β-blockers have been used for LQTS to reduce the risk of cardiac arrhythmias. More specific and effective treatments can be introduced once the underlying cause of LQTS is identified.

CLINICAL BOX 5–6

Glycolysidic Drugs & Cardiac Contractions

Oubain and other digitalis glycosides are commonly used to treat failing hearts. These drugs have the effect of increasing the strength of cardiac contractions. Although there is discussion as to full mechanisms, a working hypothesis is based on the ability of these drugs to inhibit the Na, K ATPase in cell membranes of the cardiomyocytes. The block of the Na, K ATPase in cardiomyocytes would result in an increased intracellular Na^+ concentration. Such an increase would result in a decreased Na^+ influx and hence Ca^{2+} efflux via the Na^+-Ca^{2+} exchange antiport during the Ca^{2+} recovery period. The resulting increase in intracellular Ca^{2+} concentration in turn increases the strength of contraction of the cardiac muscle. With this mechanism in mind, these drugs can also be quite toxic. Overinhibition of the Na, K ATPase would result in a depolarized cell that could slow conduction, or even spontaneously activate. Alternatively, an overly increased Ca^{2+} concentration could also have ill effects on cardiomyocyte physiology.

which also act via cyclic AMP, but their ionotropic effect is smaller and is maximal in the atria. Cyclic AMP activates protein kinase A, and this leads to phosphorylation of the voltage-dependent Ca^{2+} channels, causing them to spend more time in the open state. Cyclic AMP also increases the active transport of Ca^{2+} to the sarcoplasmic reticulum, thus accelerating relaxation and consequently shortening systole. This is important when the cardiac rate is increased because it permits adequate diastolic filling (see Chapter 30).

METABOLISM

Mammalian hearts have an abundant blood supply, numerous mitochondria, and a high content of myoglobin, a muscle pigment that can function as an O_2 storage mechanism. Normally, less than 1% of the total energy liberated is provided by anaerobic metabolism. During hypoxia, this figure may increase to nearly 10%; but under totally anaerobic conditions, the energy liberated is inadequate to sustain ventricular contractions. Under basal conditions, 35% of the caloric needs of the human heart are provided by carbohydrate, 5% by ketones and amino acids, and 60% by fat. However, the proportions of substrates utilized vary greatly with the nutritional state. After ingestion of large amounts of glucose, more lactate

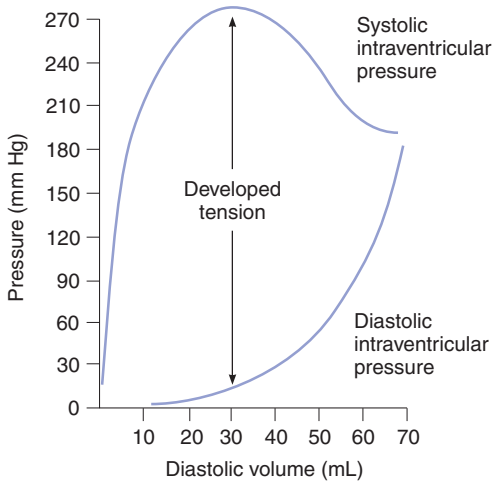


FIGURE 5–18 Length–tension relationship for cardiac muscle. Comparison of the systolic intraventricular pressure (top trace) and diastolic intraventricular pressure (bottom trace) display the developed tension in the cardiomyocyte. Values shown are for canine heart.

and pyruvate are used; during prolonged starvation, more fat is used. Circulating free fatty acids normally account for almost 50% of the lipid utilized. In untreated diabetics, the carbohydrate utilization of cardiac muscle is reduced and that of fat is increased.

SMOOTH MUSCLE MORPHOLOGY

Smooth muscle is distinguished anatomically from skeletal and cardiac muscle because it lacks visible cross-striations. Actin and myosin-II are present, and they slide on each other to produce contraction. However, they are not arranged in regular arrays, as in skeletal and cardiac muscle, and so the striations are absent. Instead of Z lines, there are **dense bodies** in the cytoplasm and attached to the cell membrane, and these are bound by α-actinin to actin filaments. Smooth muscle also contains tropomyosin, but troponin appears to be absent. The isoforms of actin and myosin differ from those in skeletal muscle. A sarcoplasmic reticulum is present, but it is less extensive than those observed in skeletal or cardiac muscle. In general, smooth muscles contain few mitochondria and depend, to a large extent, on glycolysis for their metabolic needs.

TYPES

There is considerable variation in the structure and function of smooth muscle in different parts of the body. In general, smooth muscle can be divided into **unitary** (or **visceral**) **smooth muscle** and **multiunit smooth muscle.** Unitary smooth muscle occurs in large sheets, has many low-resistance gap junctional connections between individual muscle cells, and functions in a syncytial fashion. Unitary smooth muscle is found primarily in the walls of hollow viscera. The musculature of the intestine, the uterus, and the ureters are examples. Multiunit smooth muscle is made up of individual units with few (or no) gap junctional bridges. It is found in structures such as the iris of the eye, in which fine, graded contractions occur. It is not under voluntary control, but it has many functional similarities to skeletal muscle. Each multiunit smooth muscle cell has en passant endings of nerve fibers, but in unitary smooth muscle there are en passant junctions on fewer cells, with excitation spreading to other cells by gap junctions. In addition, these cells respond to hormones and other circulating substances. Blood vessels have both unitary and multiunit smooth muscle in their walls.

ELECTRICAL & MECHANICAL ACTIVITY

Unitary smooth muscle is characterized by the instability of its membrane potential and by the fact that it shows continuous, irregular contractions that are independent of its nerve supply. This maintained state of partial contraction is called **tonus,** or **tone.** The membrane potential has no true "resting" value, being relatively low when the tissue is active and higher when it is inhibited, but in periods of relative quiescence values for resting potential are on the order of –20 to –65 mV. Smooth muscle cells can display divergent electrical activity (eg, Figure 5–19). There are slow sine wave-like fluctuations a few millivolts in magnitude and spikes that sometimes overshoot the zero potential line and sometimes do not. In many tissues, the spikes have a duration of about 50 ms, whereas in some tissues the action potentials have a prolonged plateau during repolarization, like the action potentials in cardiac muscle. As in the other muscle types, there are significant contributions of K^+, Na^+, and Ca^{2+} channels and Na, K ATPase to this electrical activity. However, discussion of contributions to individual smooth muscle types is beyond the scope of this text.

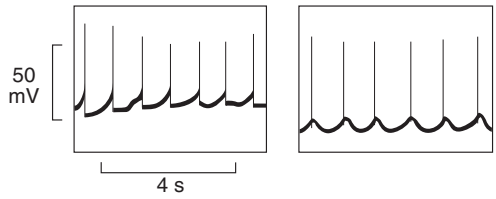


FIGURE 5–19 Electrical activity of individual smooth muscle cells in the guinea pig taenia coli. Left: Pacemaker-like activity with spikes firing at each peak. **Right:** Sinusoidal fluctuation of membrane potential with firing on the rising phase of each wave. In other fibers, spikes can occur on the falling phase of sinusoidal fluctuations and there can be mixtures of sinusoidal and pacemaker potentials in the same fiber.

Because of the continuous activity, it is difficult to study the relation between the electrical and mechanical events in unitary smooth muscle, but in some relatively inactive preparations, a single spike can be generated. In such preparations, the excitation–contraction coupling in unitary smooth muscle can occur with as much as a 500 ms delay. Thus, it is a very slow process compared with that in skeletal and cardiac muscle, in which the time from initial depolarization to initiation of contraction is less than 10 ms. Unlike unitary smooth muscle, multiunit smooth muscle is nonsyncytial and contractions do not spread widely through it. Because of this, the contractions of multiunit smooth muscle are more discrete, fine, and localized than those of unitary smooth muscle.

MOLECULAR BASIS OF CONTRACTION

As in skeletal and cardiac muscle, Ca^{2+} plays a prominent role in the initiation of contraction of smooth muscle. However, the source of Ca^{2+} increase can be quite different in unitary smooth muscle. Depending on the activating stimulus, Ca^{2+} increase can be due to influx through voltage- or ligand-gated plasma membrane channels, efflux from intracellular stores through the RyR, efflux from intracellular stores through the **inositol trisphosphate receptor (IP_3R)** Ca^{2+} channel, or via a combination of these channels. In addition, the lack of troponin in

smooth muscle prevents Ca^{2+} activation via troponin binding. Rather, myosin in smooth muscle must be phosphorylated for activation of the myosin ATPase. Phosphorylation and dephosphorylation of myosin also occur in skeletal muscle, but phosphorylation is not necessary for activation of the ATPase. In smooth muscle, Ca^{2+} binds to calmodulin, and the resulting complex activates **calmodulin-dependent myosin light chain kinase.** This enzyme catalyzes the phosphorylation of the myosin light chain on serine at position 19, increasing its ATPase activity.

Myosin is dephosphorylated by **myosin light chain phosphatase** in the cell. However, dephosphorylation of myosin light chain kinase does not necessarily lead to relaxation of the smooth muscle. Various mechanisms are involved. One appears to be a latch bridge mechanism by which myosin cross-bridges remain attached to actin for some time after the cytoplasmic Ca^{2+} concentration falls. This produces sustained contraction with little expenditure of energy, which is especially important in vascular smooth muscle. Relaxation of the muscle presumably occurs when the Ca^{2+}-calmodulin complex finally dissociates or when some other mechanism comes into play. The events leading to contraction and relaxation of unitary smooth muscle are summarized in Figure 5–20. The events in multiunit smooth muscle are generally similar.

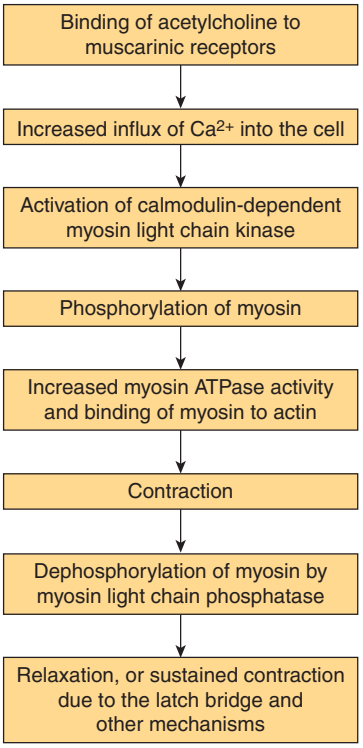


FIGURE 5–20 Sequence of events in contraction and relaxation of smooth muscle. Flow chart illustrates many of the molecular changes that occur from the initiation of contraction to its relaxation. Note the distinct differences from skeletal and cardiac muscle excitation.

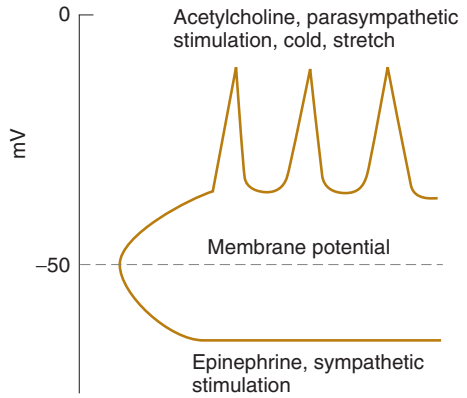


FIGURE 5–21 Effects of various agents on the membrane potential of intestinal smooth muscle. Drugs and hormones can alter firing of smooth muscle action potentials by raising (top trace) or lowering (bottom trace) resting membrane potential.

Unitary smooth muscle is unique in that, unlike other types of muscle, it contracts when stretched in the absence of any extrinsic innervation. Stretch is followed by a decline in membrane potential, an increase in the frequency of spikes, and a general increase in tone.

If epinephrine or norepinephrine is added to a preparation of intestinal smooth muscle arranged for recording of intracellular potentials in vitro, the membrane potential usually becomes larger, the spikes decrease in frequency, and the muscle relaxes (Figure 5–21). Norepinephrine is the chemical mediator released at noradrenergic nerve endings, and stimulation of the noradrenergic nerves to the preparation produces inhibitory potentials. Acetylcholine has an effect opposite to that of norepinephrine on the membrane potential and contractile activity of intestinal smooth muscle. If acetylcholine is added to the fluid bathing a smooth muscle preparation in vitro, the membrane potential decreases and the spikes become more frequent. The muscle becomes more active, with an increase in tonic tension and the number of rhythmic contractions. The effect is mediated by phospholipase C, which produces IP_3 and allows for Ca^{2+} release through IP_3 receptors. In the intact animal, stimulation of cholinergic nerves causes release of acetylcholine, excitatory potentials, and increased intestinal contractions.

Like unitary smooth muscle, multiunit smooth muscle is very sensitive to circulating chemical substances and is normally activated by chemical mediators (acetylcholine and norepinephrine) released at the endings of its motor nerves. Norepinephrine in particular tends to persist in the muscle and to cause repeated firing of the muscle after a single stimulus rather than a single action potential. Therefore, the contractile response produced is usually an irregular tetanus rather than a single twitch. When a single twitch response is obtained, it resembles the twitch contraction of skeletal muscle except that its duration is 10 times as long.

CLINICAL BOX 5–7

Common Drugs That Act on Smooth Muscle

Overexcitation of smooth muscle in the airways, such as that observed during an asthma attack, can lead to bronchoconstriction. Inhalers that deliver drugs to the conducting airway are commonly used to offset this smooth muscle bronchoconstriction, as well as other symptoms in the asthmatic airways. The rapid effects of drugs in inhalers are related to smooth muscle relaxation. Rapid response inhaler drugs (eg, ventolin, albuterol, sambuterol) frequently target β-adrenergic receptors in the airway smooth muscle to elicit a relaxation. Although these β-adrenergic receptor agonists targeting the smooth muscle do not treat all symptoms associated with asthma (eg, inflammation and increased mucus), they act rapidly and frequently allow for sufficient opening of the conducting airway to restore airflow, and thus allow for other treatments to reduce airway obstruction.

Smooth muscle is also a target for drugs developed to increase blood flow. As discussed in the text, NO is a natural signaling molecule that relaxes smooth muscle by raising cGMP. This signaling pathway is naturally down-regulated by the action of **phosphodiesterase (PDE)**, which transforms cGMP into a nonsignaling form, GMP. The drugs sildenafil, tadalafil, and vardenafil are all specific inhibitors of PDE V, an isoform found mainly in the smooth muscle in the corpus cavernosum of the penis (see Chapters 25 and 32). Thus, oral administration of these drugs can block the action of PDE V, increasing blood flow in a very limited region in the body and offsetting erectile dysfunction.

RELAXATION

In addition to cellular mechanisms that increase contraction of smooth muscle, there are cellular mechanisms that lead to its relaxation (Clinical Box 5–7). This is especially important in smooth muscle that surrounds the blood vessels to increase blood flow. It was long known that endothelial cells that line the inside of blood cells could release a substance that relaxed smooth muscle **(endothelial derived relaxing factor, EDRF).** EDRF was later identified as the gaseous second messenger molecule, **nitric oxide (NO).** NO produced in endothelial cells is free to diffuse into the smooth muscle for its effects. Once in muscle, NO directly activates a soluble guanylate cyclase to produce another second messenger molecule, **cyclic guanosine monophosphate (cGMP).** This molecule can activate cGMP-specific protein kinases that can affect ion channels, Ca^{2+} homeostasis, or phosphatases, or all of those mentioned, leading to smooth muscle relaxation (see Chapters 7 and 32).

FUNCTION OF THE NERVE SUPPLY TO SMOOTH MUSCLE

The effects of acetylcholine and norepinephrine on unitary smooth muscle serve to emphasize two of its important properties: (1) its spontaneous activity in the absence of nervous stimulation and (2) its sensitivity to chemical agents released from nerves locally or brought to it in the circulation. In mammals, unitary muscle usually has a dual nerve supply from the two divisions of the autonomic nervous system. The function of the nerve supply is not to initiate activity in the muscle but rather to modify it. Stimulation of one division of the autonomic nervous system usually increases smooth muscle activity, whereas stimulation of the other decreases it. In some organs, noradrenergic stimulation increases and cholinergic stimulation decreases smooth muscle activity; in others, the reverse is true.

FORCE GENERATION & PLASTICITY OF SMOOTH MUSCLE

Smooth muscle displays a unique economy when compared to skeletal muscle. Despite approximately 20% of the myosin content and a 100-fold difference in ATP use when compared with skeletal muscle, they can generate similar force per cross-sectional area. One of the tradeoffs of obtaining force under these conditions is the noticeably slower contractions when compared to skeletal muscle. There are several known reasons for these noticeable changes, including unique isoforms of myosin and contractile-related proteins expressed in smooth muscle and their distinct regulation (discussed above). The unique architecture of the smooth cell and its coordinated units also likely contribute to these changes.

Another special characteristic of smooth muscle is the variability of the tension it exerts at any given length. If a unitary smooth muscle is stretched, it first exerts increased tension. However, if the muscle is held at the greater length after stretching, the tension gradually decreases. Sometimes the tension falls to or below the level exerted before the muscle was stretched. It is consequently impossible to correlate length and developed tension accurately, and no resting length can be assigned. In some ways, therefore, smooth muscle behaves more like a viscous mass than a rigidly structured tissue, and it is this property that is referred to as the **plasticity** of smooth muscle.

The consequences of plasticity can be demonstrated in humans. For example, the tension exerted by the smooth muscle walls of the bladder can be measured at different degrees of distention as fluid is infused into the bladder via a catheter. Initially, tension increases relatively little as volume is increased because of the plasticity of the bladder wall. However, a point is eventually reached at which the bladder contracts forcefully (see Chapter 37).

CHAPTER SUMMARY

- There are three main types of muscle cells: skeletal, cardiac, and smooth.
- Skeletal muscle is a true syncytium under voluntary control. Skeletal muscles receive electrical stimuli from neurons to elicit contraction: "excitation–contraction coupling." Action potentials in muscle cells are developed largely through coordination of Na^+, K^+, and Ca^{2+} channels. Contraction in skeletal muscle cells is coordinated through Ca^{2+} regulation of the actomyosin system that gives the muscle its classic striated pattern under the microscope.
- There are several different types of skeletal muscle fibers (I, IIA, IIB) that have distinct properties in terms of protein makeup and force generation. Skeletal muscle fibers are arranged into motor units of like fibers within a muscle. Skeletal motor units are recruited in a specific pattern as the need for more force is increased.
- Cardiac muscle is a collection of individual cells (cardiomyocytes) that are linked as a syncytium by gap junctional communication. Cardiac muscle cells also undergo excitation–contraction coupling. Pacemaker cells in the heart can initiate propagated action potentials. Cardiac muscle cells also have a striated, actomyosin system that underlies contraction.
- Smooth muscle exists as individual cells and are frequently under control of the autonomic nervous system.
- There are two broad categories of smooth muscle cells: unitary and multiunit. Unitary smooth muscle contraction is synchronized by gap junctional communication to coordinate contraction among many cells. Multiunit smooth muscle contraction is coordinated by motor units, functionally similar to skeletal muscle.
- Smooth muscle cells contract through an actomyosin system, but do not have well-organized striations. Unlike skeletal and cardiac muscle, Ca^{2+} regulation of contraction is primarily through phosphorylation–dephosphorylation reactions.

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. The action potential of skeletal muscle
   A. has a prolonged plateau phase.
   B. spreads inward to all parts of the muscle via the T tubules.
   C. causes the immediate uptake of Ca^{2+} into the lateral sacs of the sarcoplasmic reticulum.
   D. is longer than the action potential of cardiac muscle.
   E. is not essential for contraction.
2. The functions of tropomyosin in skeletal muscle include
   A. sliding on actin to produce shortening.
   B. releasing Ca^{2+} after initiation of contraction.
   C. binding to myosin during contraction.
   D. acting as a "relaxing protein" at rest by covering up the sites where myosin binds to actin.
   E. generating ATP, which it passes to the contractile mechanism.
3. The cross-bridges of the sarcomere in skeletal muscle are made up of
   A. actin.
   B. myosin.
   C. troponin.
   D. tropomyosin.
   E. myelin.
4. The contractile response in skeletal muscle
   A. starts after the action potential is over.
   B. does not last as long as the action potential.
   C. produces more tension when the muscle contracts isometrically than when the muscle contracts isotonically.
   D. produces more work when the muscle contracts isometrically than when the muscle contracts isotonically.
   E. decreases in magnitude with repeated stimulation.
5. Gap junctions
   A. are absent in cardiac muscle.
   B. are present but of little functional importance in cardiac muscle.
   C. are present and provide the pathway for rapid spread of excitation from one cardiac muscle fiber to another.
   D. are absent in smooth muscle.
   E. connect the sarcotubular system to individual skeletal muscle cells.

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CHAPTER 6

Synaptic & Junctional Transmission

OBJECTIVES

After studying this chapter, you should be able to:

- Describe the main morphologic features of synapses.
- Distinguish between chemical and electrical transmission at synapses.
- Describe fast and slow excitatory and inhibitory postsynaptic potentials, outline the ionic fluxes that underlie them, and explain how the potentials interact to generate action potentials.
- Define and give examples of direct inhibition, indirect inhibition, presynaptic inhibition, and postsynaptic inhibition.
- Describe the neuromuscular junction, and explain how action potentials in the motor neuron at the junction lead to contraction of the skeletal muscle.
- Define denervation hypersensitivity.

INTRODUCTION

The "all-or-none" type of conduction seen in axons and skeletal muscle has been discussed in Chapters 4 and 5. Impulses are transmitted from one nerve cell to another cell at **synapses.** These are the junctions where the axon or some other portion of one cell (the **presynaptic cell**) terminates on the dendrites, soma, or axon of another neuron (Figure 6–1) or, in some cases, a muscle or gland cell (the **postsynaptic cell**). Cell-to-cell communication occurs across either a **chemical** or **electrical synapse.** At chemical synapses, a **synaptic cleft** separates the terminal of the presynaptic cell from the postsynaptic cell. An impulse in the presynaptic axon causes secretion of a chemical that diffuses across the synaptic cleft and binds to receptors on the surface of the postsynaptic cell. This triggers events that open or close channels in the membrane of the postsynaptic cell. In electrical synapses, the membranes of the presynaptic and postsynaptic neurons come close together, and gap junctions form between the cells (see Chapter 2). Like the intercellular junctions in other tissues, these junctions form low-resistance bridges through which ions can pass with relative ease. There are also a few conjoint synapses in which transmission is both electrical and chemical.

Regardless of the type of synapse, transmission is not a simple transmission of an action potential from the presynaptic to the postsynaptic cell. The effects of discharge at individual synaptic endings can be excitatory or inhibitory, and when the postsynaptic cell is a neuron, the summation of all the excitatory and inhibitory effects determines whether an action potential is generated. Thus, synaptic transmission is a complex process that permits the grading and adjustment of neural activity necessary for normal function. Because most synaptic transmission is chemical, consideration in this chapter is limited to chemical transmission unless otherwise specified.

Transmission from nerve to muscle resembles chemical synaptic transmission from one neuron to another. The **neuromuscular junction,** the specialized area where a motor nerve terminates on a skeletal muscle fiber, is the site of a stereotyped transmission process. The contacts between autonomic neurons and smooth and cardiac muscle are less specialized, and transmission in these locations is a more diffuse process. These forms of transmission are also considered in this chapter.

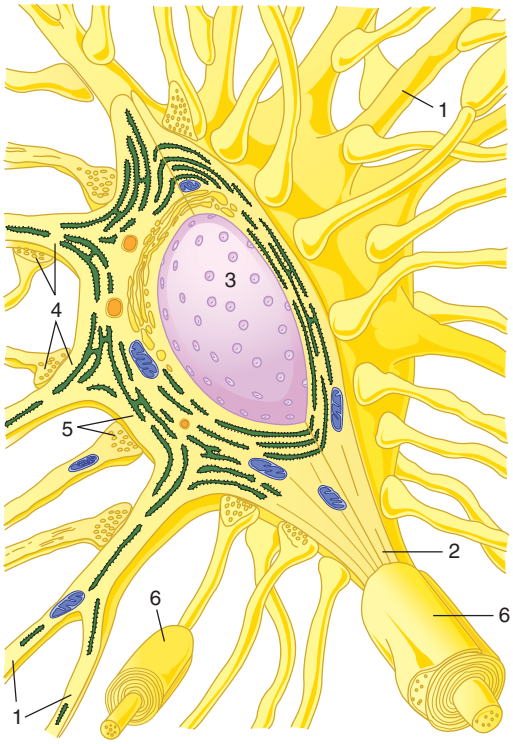

FIGURE 6–1 Synapses on a typical motor neuron. The neuron has dendrites **(1),** an axon **(2),** and a prominent nucleus **(3).** Note that rough endoplasmic reticulum extends into the dendrites but not into the axon. Many different axons converge on the neuron, and their terminal boutons form axodendritic **(4)** and axosomatic **(5)** synapses. **(6)** Myelin sheath. (Reproduced with permission from Krstic RV: *Ultrastructure of the Mammalian Cell.* Springer, 1979.)

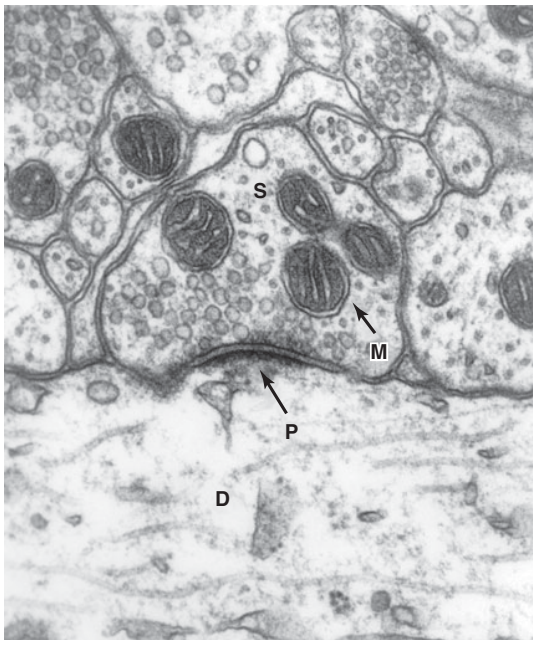

FIGURE 6–2 Electronmicrograph of synaptic knob (S) ending on the shaft of a dendrite (D) in the central nervous system. P, postsynaptic density; M, mitochondrion. (×56,000). (Courtesy of DM McDonald.)

SYNAPTIC TRANSMISSION: FUNCTIONAL ANATOMY

The anatomic structure of synapses varies considerably in the different parts of the mammalian nervous system. The ends of the presynaptic fibers are generally enlarged to form **terminal boutons or synaptic knobs** (Figure 6–2). In the cerebral and cerebellar cortex, endings are commonly located on dendrites and frequently on **dendritic spines,** which are small knobs projecting from dendrites (Figure 6–3). In some instances, the terminal branches of the axon of the presynaptic neuron form a basket or net around the soma of the postsynaptic cell (eg, basket cells of the cerebellum). In other locations, they intertwine with the dendrites of the postsynaptic cell (eg, climbing fibers of the cerebellum) or end on the dendrites directly (eg, apical dendrites of cortical pyramidal cells). Some end on axons of postsynaptic neurons (axoaxonal endings). On average, each neuron divides to form over 2000 synaptic endings, and because the human central nervous system (CNS) has 10^{11} neurons, it follows that there are about 2×10^{14} synapses. Obviously, therefore, communication between neurons is extremely complex. Synapses are dynamic structures, increasing and decreasing in complexity and number with use and experience.

It has been calculated that in the cerebral cortex, 98% of the synapses are on dendrites and only 2% are on cell bodies. In the spinal cord, the proportion of endings on dendrites is less; there are about 8000 endings on the dendrites of a typical spinal neuron and about 2000 on the cell body, making the soma appear encrusted with endings.

FUNCTIONS OF SYNAPTIC ELEMENTS

Each presynaptic terminal of a chemical synapse is separated from the postsynaptic structure by a synaptic cleft that is 20–40 nm wide. Across the synaptic cleft are many neurotransmitter receptors in the postsynaptic membrane, and usually a postsynaptic thickening called the **postsynaptic density** (Figures 6–2 and 6–3). The postsynaptic density is an ordered complex of specific receptors, binding proteins, and enzymes induced by postsynaptic effects.

Inside the presynaptic terminal are many mitochondria, as well as many membrane-enclosed vesicles, which contain neurotransmitters. There are three kinds of **synaptic vesicles:** small, clear synaptic vesicles that contain acetylcholine, glycine, GABA, or glutamate; small vesicles with a dense core that contain catecholamines; and large vesicles with a dense core that contain neuropeptides. The vesicles and the proteins contained in their walls are synthesized in the neuronal cell body and transported along the axon to the endings by fast axoplasmic transport. The neuropeptides in the large

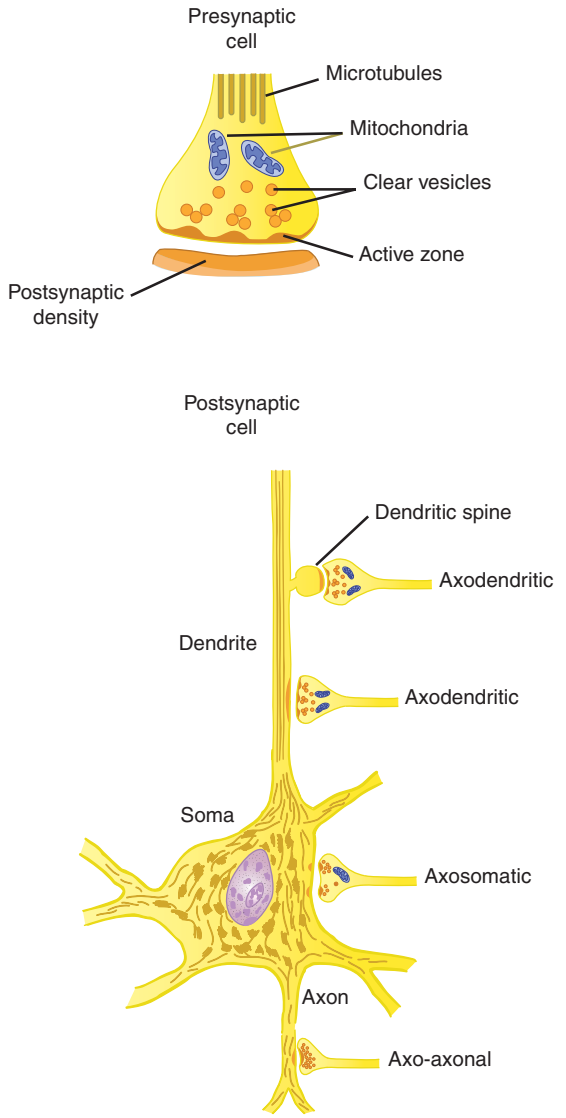

FIGURE 6–3 Axodendritic, axoaxonal, and axosomatic synapses. Many presynaptic neurons terminate on dendritic spines, as shown at the top, but some also end directly on the shafts of dendrites. Note the presence of clear and granulated synaptic vesicles in endings and clustering of clear vesicles at active zones.

dense-core vesicles must also be produced by the protein-synthesizing machinery in the cell body. However, the small clear vesicles and the small dense-core vesicles recycle in the nerve ending. These vesicles fuse with the cell membrane and release transmitters through exocytosis and are then recovered by endocytosis to be refilled locally. In some instances, they enter endosomes and are budded off the endosome and refilled, starting the cycle over again. The steps involved are shown in Figure 6–4. More commonly, however, the synaptic vesicle discharges its contents through a small hole in the cell membrane, then the opening reseals rapidly and the main vesicle stays inside the cell **(kiss-and-run discharge).** In this way, the full endocytotic process is short-circuited.

The large dense-core vesicles are located throughout the presynaptic terminals that contain them and release their neuropeptide contents by exocytosis from all parts of the terminal. On the other hand, the small vesicles are located near the synaptic cleft and fuse to the membrane, discharging their contents very rapidly into the cleft at areas of membrane thickening called **active zones** (Figure 6–3). The active zones contain many proteins and rows of Ca^{2+} channels.

The Ca^{2+} that triggers exocytosis of transmitters enters the presynaptic neurons, and transmitter release starts within 200 μs. Therefore, it is not surprising that the voltage-gated Ca^{2+} channels are very close to the release sites at the active zones. In addition, the transmitter must be released close to the postsynaptic receptors to be effective on the postsynaptic neuron. This orderly organization of the synapse depends in part on **neurexins,** proteins bound to the membrane of the presynaptic neuron that bind neurexin receptors in the membrane of the postsynaptic neuron. In many vertebrates, neurexins are produced by a single gene that codes for the α isoform. However, in mice and humans they are encoded by three genes, and both α and β isoforms are produced. Each of the genes has two regulatory regions and extensive alternative splicing of their mRNAs. In this way, over 1000 different neurexins are produced. This raises the possibility that the neurexins not only hold synapses together, but also provide a mechanism for the production of synaptic specificity.

As noted in Chapter 2, vesicle budding, fusion, and discharge of contents with subsequent retrieval of vesicle membrane are fundamental processes occurring in most, if not all, cells. Thus, neurotransmitter secretion at synapses and the accompanying membrane retrieval are specialized forms of the general processes of exocytosis and endocytosis. The details of the processes by which synaptic vesicles fuse with the cell membrane are still being worked out. They involve the **v-snare** protein **synaptobrevin** in the vesicle membrane locking with the **t-snare** protein **syntaxin** in the cell membrane; a multiprotein complex regulated by small GTPases such as Rab3 is also involved in the process (Figure 6–5). The one-way gate at the synapses is necessary for orderly neural function.

Several deadly toxins that block neurotransmitter release are zinc endopeptidases that cleave and hence inactivate proteins in the fusion-exocytosis complex. Clinical Box 6–1 describes how neurotoxins from bacteria called *Clostridium tetani* and *Clostridium botulinum* can disrupt neurotransmitter release in either the CNS or at the neuromuscular junction.

ELECTRICAL EVENTS IN POSTSYNAPTIC NEURONS

EXCITATORY & INHIBITORY POSTSYNAPTIC POTENTIALS

Penetration of an α-motor neuron is a good example of a technique used to study postsynaptic electrical activity. It is achieved by advancing a microelectrode through the ventral portion of the spinal cord. Puncture of a cell membrane is signaled by the

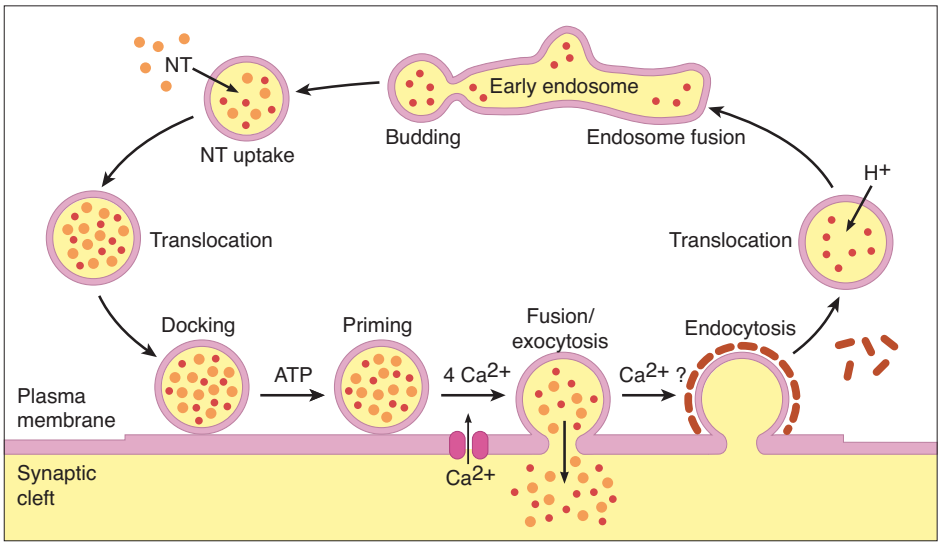

FIGURE 6–4 Small synaptic vesicle cycle in presynaptic nerve terminals. Vesicles bud off the early endosome and then fill with neurotransmitter (NT; top left). They then move to the plasma membrane, dock, and become primed. Upon arrival of an action potential at the ending, Ca^{2+} influx triggers fusion and exocytosis of the granule contents to the synaptic cleft. The vesicle wall is then coated with clathrin and taken up by endocytosis. In the cytoplasm, it fuses with the early endosome, and the cycle is ready to repeat. (Reproduced with permission from Südhof TC: The synaptic vesicle cycle: A cascade of protein-protein interactions. Nature 1995;375:645.)

appearance of a steady 70 mV potential difference between the microelectrode and an electrode outside the cell. The cell can be identified as a spinal motor neuron by stimulating the appropriate ventral root and observing the electrical activity of the cell. Such stimulation initiates an antidromic impulse (see Chapter 4) that is conducted to the soma and stops at that point. Therefore, the presence of an action potential in the cell after antidromic stimulation indicates that the cell that has been penetrated is an α-motor neuron. Stimulation of a dorsal root afferent (sensory neuron) can be used to study both excitatory and inhibitory events in α-motor neurons (Figure 6–6).

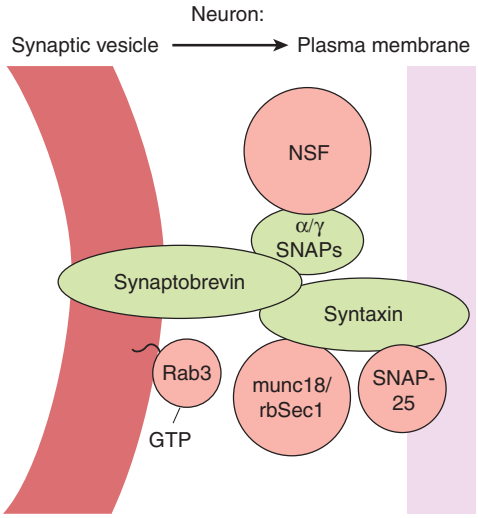

FIGURE 6–5 Main proteins that interact to produce synaptic vesicle docking and fusion in nerve endings. The processes by which synaptic vesicles fuse with the cell involve the v-snare protein synaptobrevin in the vesicle membrane locking with the t-snare protein syntaxin in the cell membrane; a multiprotein complex regulated by small GTPases such as Rab3 is also involved in the process. (Reproduced with permission from Ferro-Novick S, John R: Vesicle fusion from yeast to man. Nature 1994;370:191.)

Once an impulse reaches the presynaptic terminals, a response can be obtained in the postsynaptic neuron after a **synaptic delay.** The delay is due to the time it takes for the synaptic mediator to be released and to act on the receptors on the membrane of the postsynaptic cell. Because of it, conduction along a chain of neurons is slower if there are many synapses compared to if there are only a few synapses. Because the minimum time for transmission across one synapse is 0.5 ms, it is also possible to determine whether a given reflex pathway is **monosynaptic** or **polysynaptic** (contains more than one synapse) by measuring the synaptic delay.

A single stimulus applied to the sensory nerves characteristically does not lead to the formation of a propagated action potential in the postsynaptic neuron. Instead, the stimulation produces either a transient partial depolarization or a transient hyperpolarization. The initial depolarizing response produced by a single stimulus to the proper input begins about 0.5 ms after the afferent impulse enters the spinal cord. It reaches its peak 11.5 ms later and then declines exponentially. During this potential, the excitability of the neuron to other stimuli is increased, and consequently the potential is called an **excitatory postsynaptic potential (EPSP)** (Figure 6–6).

The EPSP is produced by depolarization of the postsynaptic cell membrane immediately under the presynaptic ending. The excitatory transmitter opens Na^+ or Ca^{2+} channels in the postsynaptic membrane, producing an inward current. The area of current flow thus created is so small that it does

CLINICAL BOX 6–1

Botulinum and Tetanus Toxins

Clostridia are gram-positive bacteria. Two varieties, *Clostridium tetani* and *Clostridium botulinum,* produce some of the most potent biological toxins **(tetanus toxin** and **botulinum toxin)** known to affect humans. These neurotoxins act by preventing the release of neurotransmitters in the CNS and at the neuromuscular junction. Tetanus toxin binds irreversibly to the presynaptic membrane of the neuromuscular junction and uses retrograde axonal transport to travel to the cell body of the motor neuron in the spinal cord. From there it is picked up by the terminals of presynaptic inhibitory interneurons. The toxin attaches to **gangliosides** in these terminals and blocks the release of glycine and GABA. As a result, the activity of motor neurons is markedly increased. Clinically, tetanus toxin causes spastic paralysis; the characteristic symptom of "lockjaw" involves spasms of the masseter muscle. Botulism can result from ingestion of contaminated food, colonization of the gastrointestinal tract in an infant, or wound infection. Botulinum toxins are actually a family of seven neurotoxins, but it is mainly botulinum toxins A, B, and E that are toxic to humans. Botulinum toxins A and E cleave synaptosome-associated protein **(SNAP-25).** This is a presynaptic membrane protein needed for fusion of synaptic vesicles containing acetylcholine to the terminal membrane, an important step in transmitter release. Botulinum toxin B cleaves **synaptobrevin,** a vesicle-associated membrane protein **(VAMP).** By blocking acetylcholine release at the neuromuscular junction, these toxins cause flaccid paralysis. Symptoms can include ptosis, diplopia, dysarthria, dysphonia, and dysphagia.

THERAPEUTIC HIGHLIGHTS

Tetanus can be prevented by treatment with **tetanus toxoid vaccine.** The widespread use of this vaccine in the U.S. beginning in the mid 1940s has led to a marked decline in the incidence of tetanus toxicity. The incidence of botulinum toxicity is also low (about 100 cases per year in the U.S.), but in those individuals that are affected, the fatality rate is 5–10%. An antitoxin is available for treatment, and those who are at risk for respiratory failure are placed on a ventilator. On the positive side, local injection of small doses of botulinum toxin (**botox**) has proven to be effective in the treatment of a wide variety of conditions characterized by muscle hyperactivity. Examples include injection into the lower esophageal sphincter to relieve achalasia and injection into facial muscles to remove wrinkles.

not drain off enough positive charge to depolarize the whole membrane. Instead, an EPSP is inscribed. The EPSP due to activity in one synaptic knob is small, but the depolarizations produced by each of the active knobs summate.

EPSPs are produced by stimulation of some inputs, but stimulation of other inputs produces hyperpolarizing responses. Like the EPSPs, they peak 11.5 ms after the stimulus and decrease exponentially. During this potential, the excitability of the neuron to other stimuli is decreased; consequently, it is called an **inhibitory postsynaptic potential (IPSP)** (Figure 6–6).

An IPSP can be produced by a localized increase in Cl^- transport. When an inhibitory synaptic knob becomes active, the released transmitter triggers the opening of Cl^- channels in the area of the postsynaptic cell membrane under the knob. Cl^- moves down its concentration gradient. The net effect is the transfer of negative charge into the cell, so that the membrane potential increases.

The decreased excitability of the nerve cell during the IPSP is due to movement of the membrane potential away from the firing level. Consequently, more excitatory (depolarizing) activity is necessary to reach the firing level. The fact that an IPSP is mediated by Cl^- can be demonstrated by repeating the stimulus while varying the resting membrane potential of the postsynaptic cell. When the membrane potential is at the equilibrium potential for chloride (E_{Cl}), the postsynaptic potential disappears (Figure 6–7), and at more negative membrane potentials, it becomes positive **(reversal potential).**

Because IPSPs are net hyperpolarizations, they can be produced by alterations in other ion channels in the neuron. For example, they can be produced by opening of K^+ channels, with movement of K^+ out of the postsynaptic cell, or by closure of Na^+ or Ca^{2+} channels.

SLOW POSTSYNAPTIC POTENTIALS

In addition to the EPSPs and IPSPs described previously, slow EPSPs and IPSPs have been described in autonomic ganglia, cardiac and smooth muscle, and cortical neurons. These postsynaptic potentials have a latency of 100–500 ms and last several seconds. The slow EPSPs are generally due to decreases in K^+ conductance, and the slow IPSPs are due to increases in K^+ conductance.

ELECTRICAL TRANSMISSION

At synaptic junctions where transmission is electrical, the impulse reaching the presynaptic terminal generates an EPSP in the postsynaptic cell that, because of the low-resistance bridge between the two, has a much shorter latency than the EPSP at a synapse where transmission is chemical. In conjoint synapses, both a short-latency response and a longer-latency, chemically mediated postsynaptic response can occur.

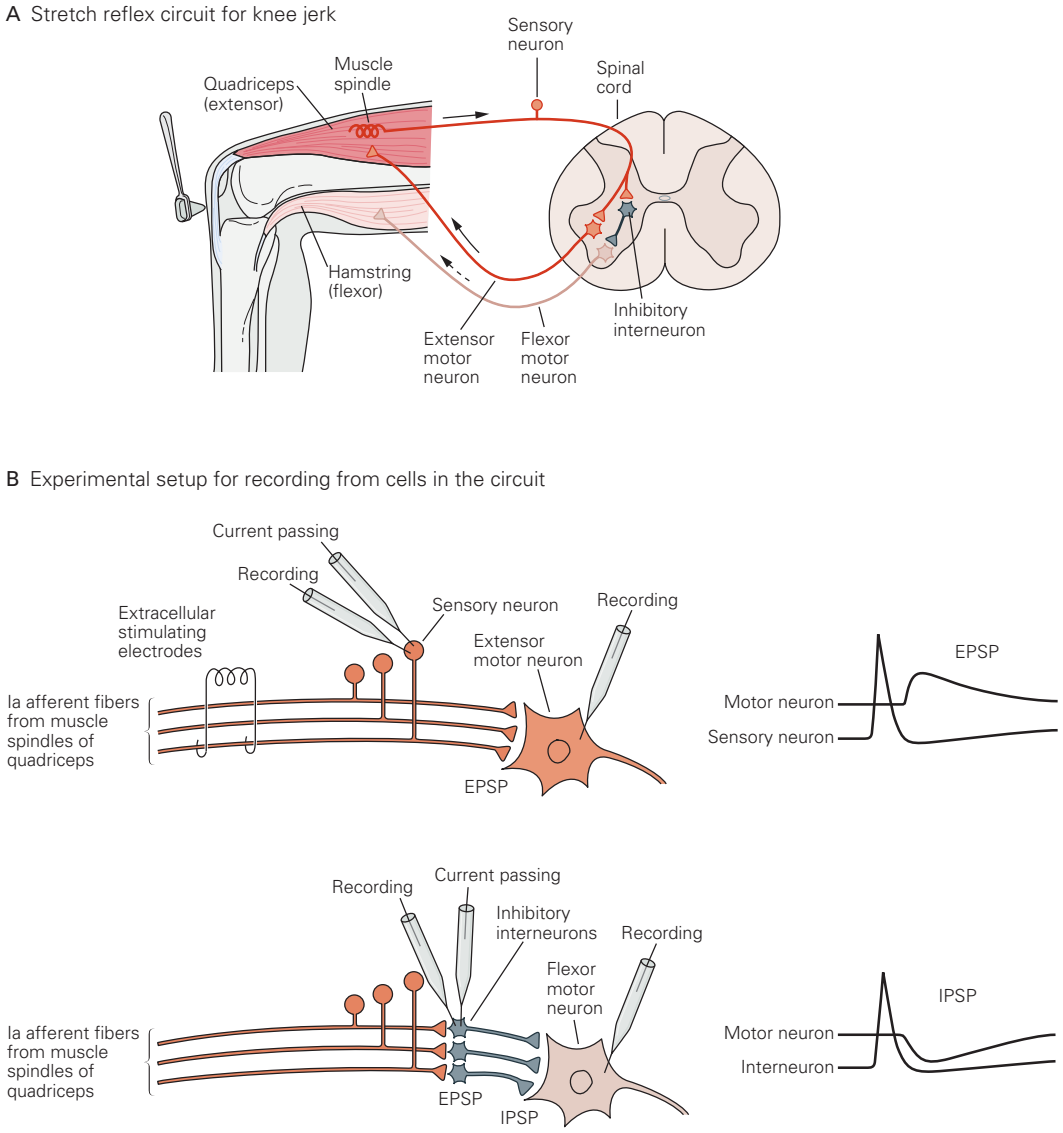

FIGURE 6–6 Excitatory and inhibitory synaptic connections mediating the stretch reflex provide an example of typical circuits within the CNS. A) The stretch receptor sensory neuron of the quadriceps muscle makes an excitatory connection with the extensor motor neuron of the same muscle and an inhibitory interneuron projecting to flexor motor neurons supplying the antagonistic hamstring muscle. **B)** Experimental setup to study excitation and inhibition of the extensor motor neuron. Top panel shows two approaches to elicit an excitatory (depolarizing) postsynaptic potential or EPSP in the extensor motor neuron–electrical stimulation of the whole Ia afferent nerve using extracellular electrodes and intracellular current passing through an electrode inserted into the cell body of a sensory neuron. Bottom panel shows that current passing through an inhibitory interneuron elicits an inhibitory (hyperpolarizing) postsynaptic potential or IPSP in the flexor motor neuron. (From Kandel ER, Schwartz JH, Jessell TM [editors]: *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.)

GENERATION OF AN ACTION POTENTIAL IN THE POSTSYNAPTIC NEURON

The constant interplay of excitatory and inhibitory activity on the postsynaptic neuron produces a fluctuating membrane potential that is the algebraic sum of the hyperpolarizing and depolarizing activities. The soma of the neuron thus acts as an integrator. When the level of depolarization reaches the threshold voltage, a propagated action potential will occur. However, the discharge of the neuron is slightly more complicated than this. In motor neurons, the portion of the cell with the lowest threshold for the production of an action potential is the **initial segment,** the portion of the axon at and just beyond the axon hillock. This unmyelinated segment is depolarized or hyperpolarized electrotonically by the current sinks and sources under the excitatory and inhibitory synaptic knobs. It is the first part of the neuron to fire, and its discharge

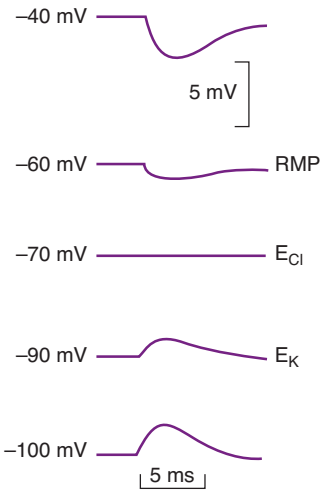

FIGURE 6–7 IPSP is due to increased Cl^- influx during stimulation. This can be demonstrated by repeating the stimulus while varying the resting membrane potential (RMP) of the postsynaptic cell. When the membrane potential is at E_{Cl}, the potential disappears, and at more negative membrane potentials (eg, E_K and below), it becomes positive (reversal potential).

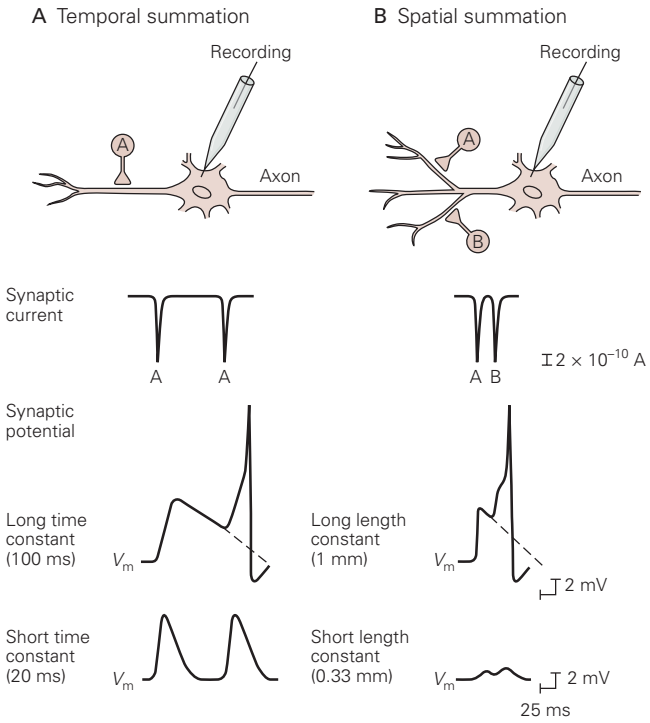

FIGURE 6–8 Central neurons integrate a variety of synaptic inputs through temporal and spatial summation. A) The time constant of the postsynaptic neuron affects the amplitude of the depolarization caused by consecutive EPSPs produced by a single presynaptic neuron. In cases of a long time constant, if a second EPSP is elicited before the first EPSP decays, the two potentials summate to induce an action potential. **B)** The length constant of a postsynaptic cell affects the amplitude of two EPSPs produced by two presynaptic neurons, A and B. If the length constant is long, the depolarization induced at two points on the neuron can spread to the trigger zone with minimal decrement so that the two potentials summate and an action potential is elicited. (From Kandel ER, Schwartz JH, Jessell TM [editors]: *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.)

is propagated in two directions: down the axon and back into the soma. Retrograde firing of the soma in this fashion probably has value in wiping the slate clean for subsequent renewal of the interplay of excitatory and inhibitory activity on the cell.

TEMPORAL & SPATIAL SUMMATION OF POSTSYNAPTIC POTENTIALS

Two passive membrane properties of a neuron affect the ability of postsynaptic potentials to summate to elicit an action potential (Figure 6–8). The **time constant** of a neuron determines the time course of the synaptic potential, and the **length constant** of a neuron determines the degree to which a depolarizing current is reduced as it spreads passively. Figure 6–8 also shows how the time constant of the postsynaptic neuron can affect the amplitude of the depolarization caused by consecutive EPSPs produced by a single presynaptic neuron. The longer the time constant, the greater is the chance for two potentials to summate to induce an action potential. If a second EPSP is elicited before the first EPSP decays, the two potentials summate and, as in this example, their additive effects are sufficient to induce an action potential in the postsynaptic neuron **(temporal summation).** Figure 6–8 also shows how the length constant of a postsynaptic neuron can affect the amplitude of two EPSPs produced by different presynaptic neurons in a process called **spatial summation.** If a neuron has a long length constant, the membrane depolarization induced by input arriving at two points on the neuron can spread to the trigger zone of the neuron with minimal decrement. The two potentials can summate and induce an action potential.

FUNCTION OF THE DENDRITES

For many years, the standard view was that dendrites were simply the sites of current sources or sinks that electrotonically change the membrane potential at the initial segment; that is, they were regarded merely as extensions of the soma that expand the area available for integration. When the dendritic tree of a neuron is extensive and has multiple presynaptic knobs ending on it, there is room for a great interplay of inhibitory and excitatory activity.

It is now well established that dendrites contribute to neural function in more complex ways. Action potentials can be recorded in dendrites. In many instances, these are initiated in the initial segment and conducted in a retrograde fashion, but propagated action potentials are initiated in some dendrites. Further research has demonstrated the malleability of dendritic spines. Dendritic spines appear, change, and even disappear over a time scale of minutes and hours, not days and months. Also, although protein synthesis occurs mainly in the soma

with its nucleus, strands of mRNA migrate into the dendrites. There, each can become associated with a single ribosome in a dendritic spine and produce proteins, which alters the effects of input from individual synapses on the spine. These changes in dendritic spines have been implicated in motivation, learning, and long-term memory.

INHIBITION & FACILITATION AT SYNAPSES

Inhibition in the CNS can be postsynaptic or presynaptic. The neurons responsible for postsynaptic and presynaptic inhibition are compared in Figure 6–9. **Postsynaptic inhibition** during the course of an IPSP is called **direct inhibition** because it is not a consequence of previous discharges of the postsynaptic neuron. There are various forms of **indirect inhibition,** which is inhibition due to the effects of previous postsynaptic neuron discharge. For example, the postsynaptic cell can be refractory to excitation because it has just fired and is in its refractory period. During after-hyperpolarization it is also less excitable. In spinal neurons, especially after repeated firing, this after-hyperpolarization may be large and prolonged.

POSTSYNAPTIC INHIBITION

Postsynaptic inhibition occurs when an inhibitory transmitter (eg, glycine, GABA) is released from a presynaptic nerve terminal onto the postsynaptic neuron. Various pathways in the nervous system are known to mediate postsynaptic inhibition, and one illustrative example is presented here. Afferent fibers from the muscle spindles (stretch receptors) in skeletal muscle project directly to the spinal motor neurons of the motor units supplying the same muscle (Figure 6–6). Impulses in this afferent fiber cause EPSPs and, with summation, propagated responses in the postsynaptic motor neurons. At the same time, IPSPs are produced in motor neurons supplying the antagonistic muscles which have an inhibitory interneuron interposed between the afferent fiber and the motor neuron. Therefore, activity in the afferent fibers from the muscle spindles excites the motor neurons supplying the muscle from which the impulses come, and inhibits the motor neurons supplying its antagonists **(reciprocal innervation).** These reflexes are considered in more detail in Chapter 12.

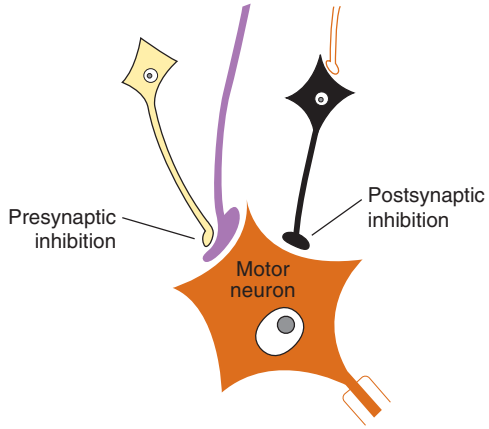

FIGURE 6–9 Comparison of neurons producing presynaptic and postsynaptic inhibition. Presynaptic inhibition is a process mediated by neurons whose terminals are on excitatory nerve endings, forming axoaxonal synapses, and reducing transmitter release form the excitatory neuron. Postsynaptic inhibition occurs when an inhibitory transmitter (eg, glycine, GABA) is released from a presynaptic nerve terminal onto the postsynaptic neuron.

PRESYNAPTIC INHIBITION & FACILITATION

Another type of inhibition occurring in the CNS is **presynaptic inhibition,** a process mediated by neurons whose terminals are on excitatory endings, forming **axoaxonal synapses** (Figure 6–3). Three mechanisms of presynaptic inhibition have been described. First, activation of the presynaptic receptors increases Cl^- conductance, and this has been shown to decrease the size of the action potentials reaching the excitatory ending (Figure 6–10). This in turn reduces Ca^{2+} entry and consequently the amount of excitatory transmitter released. Voltage-gated K^+ channels are also opened, and the resulting K^+ efflux also causes a decrease in Ca^{2+} influx. Finally, there is evidence for direct inhibition of transmitter release independent of Ca^{2+} influx into the excitatory ending.

The first transmitter shown to produce presynaptic inhibition was GABA. Acting via $GABA_A$ receptors, GABA increases Cl^- conductance. $GABA_B$ receptors are also present in the spinal cord and appear to mediate presynaptic inhibition via a G protein that produces an increase in K^+ conductance. Baclofen, a $GABA_B$ agonist, is effective in the treatment of the spasticity of spinal cord injury and multiple sclerosis, particularly when administered intrathecally via an implanted pump. Other transmitters also mediate presynaptic inhibition by G protein-mediated effects on Ca^{2+} channels and K^+ channels.

Conversely, **presynaptic facilitation** is produced when the action potential is prolonged (Figure 6–10) and the Ca^{2+} channels are open for a longer period. The molecular events responsible for the production of presynaptic facilitation mediated by serotonin in the sea snail *Aplysia* have been worked out in detail. Serotonin released at an axoaxonal ending increases intraneuronal cAMP levels, and the resulting phosphorylation of one group of K^+ channels closes the channels, slowing repolarization and prolonging the action potential.

ORGANIZATION OF INHIBITORY SYSTEMS

Presynaptic inhibition and postsynaptic inhibition are usually produced by stimulation of certain systems converging on a given postsynaptic neuron. Neurons may also inhibit themselves in a negative feedback fashion (negative feedback

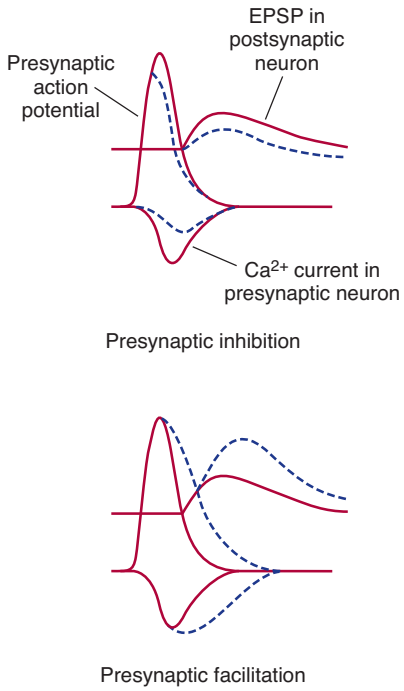

FIGURE 6–10 Effects of presynaptic inhibition and facilitation on the action potential and the Ca^{2+} current in the presynaptic neuron and the EPSP in the postsynaptic neuron. In each case, the solid lines are the controls and the dashed lines the records obtained during inhibition or facilitation. Presynaptic inhibition occurs when activation of presynaptic receptors increases Cl^- conductance which decreases the size of the action potential. This reduces Ca^{2+} entry and thus the amount of excitatory transmitter released. Presynaptic facilitation is produced when the action potential is prolonged and the Ca^{2+} channels are open for a longer duration. (Modified from Kandel ER, Schwartz JH, Jessell TM [editors]: *Principles of Neural Science,* 4th ed. McGraw-Hill, 2000.)

inhibition). For instance, a spinal motor neuron emits a recurrent collateral that synapses with an inhibitory interneuron, which then terminates on the cell body of the spinal neuron and other spinal motor neurons (Figure 6–11). This particular inhibitory neuron is sometimes called a **Renshaw cell** after its discoverer. Impulses generated in the motor neuron activate the inhibitory interneuron to secrete the inhibitory neurotransmitter **glycine,** and this reduces or stops the discharge of the motor neuron. Similar inhibition via recurrent collaterals is seen in the cerebral cortex and limbic system. Presynaptic inhibition due to descending pathways that terminate on afferent pathways in the dorsal horn may be involved in the gating of pain transmission.

Another type of inhibition is seen in the cerebellum. In this part of the brain, stimulation of basket cells produces IPSPs in the Purkinje cells. However, the basket cells and the Purkinje cells are excited by the same parallel-fiber excitatory input (see Chapter 12). This arrangement, which has been called feed-forward inhibition, presumably limits the duration of the excitation produced by any given afferent volley.

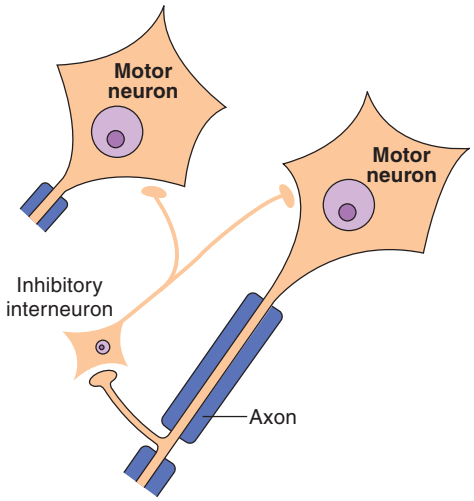

FIGURE 6–11 Negative feedback inhibition of a spinal motor neuron via an inhibitory interneuron. The axon of a spinal motor neuron has a recurrent collateral that synapses on an inhibitory interneuron that terminates on the cell body of the same and other motor neurons. The inhibitory interneuron is called a Renshaw cell and its neurotransmitter is glycine.

NEUROMUSCULAR TRANSMISSION

NEUROMUSCULAR JUNCTION

As the axon supplying a skeletal muscle fiber approaches its termination, it loses its myelin sheath and divides into a number of terminal boutons (Figure 6–12). The terminal contains many small, clear vesicles that contain acetylcholine, the transmitter at these junctions. The endings fit into **junctional folds,** which are depressions in the **motor end plate,** the thickened portion of the muscle membrane at the junction. The space between the nerve and the thickened muscle membrane is comparable to the synaptic cleft at neuron-to-neuron synapses. The whole structure is known as the **neuromuscular junction.** Only one nerve fiber ends on each end plate, with no convergence of multiple inputs.

SEQUENCE OF EVENTS DURING TRANSMISSION

The events occurring during transmission of impulses from the motor nerve to the muscle are somewhat similar to those occurring at neuron-to-neuron synapses (Figure 6–13). The impulse arriving in the end of the motor neuron increases the permeability of its endings to Ca^{2+}. Ca^{2+} enters the endings and triggers a marked increase in exocytosis of the acetylcholine-containing synaptic vesicles. The acetylcholine diffuses to nicotinic cholinergic (N_M) receptors that are concentrated at the tops of the junctional folds of the membrane of the motor end plate. Binding of acetylcholine to these receptors increases

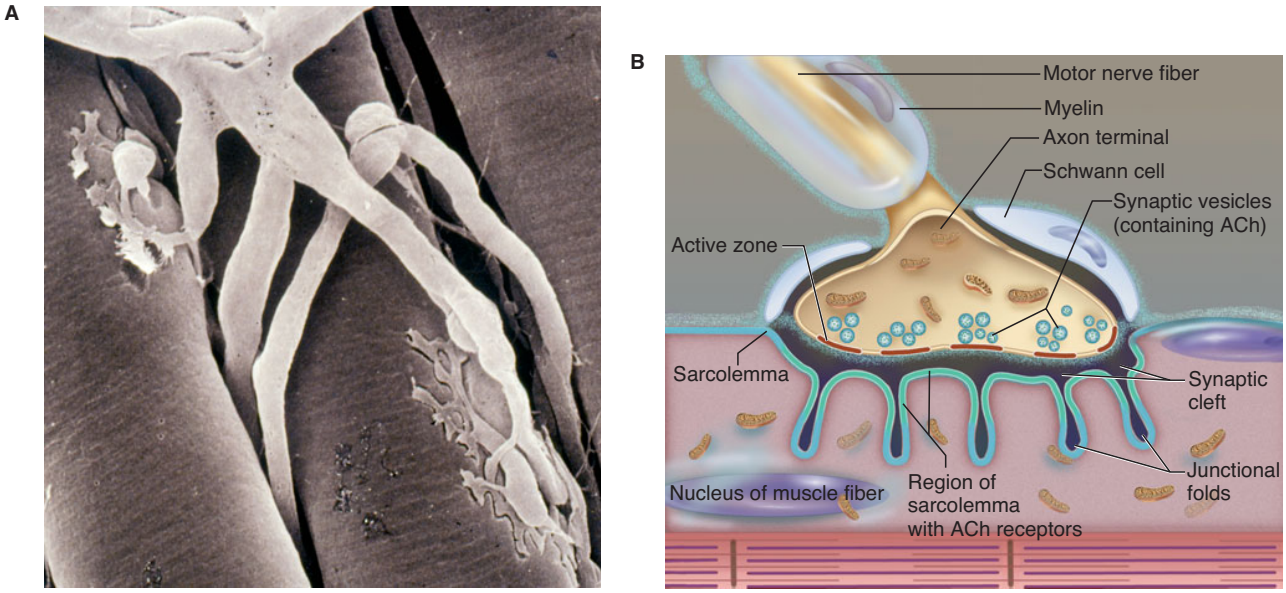

FIGURE 6–12 The neuromuscular junction. A) Scanning electronmicrograph showing branching of motor axons with terminals embedded in grooves in the muscle fiber's surface. **B)** Structure of a neuromuscular junction. (From Widmaier EP, Raff H, Strang KT: *Vanders Human Physiology.* McGraw-Hill, 2008.)

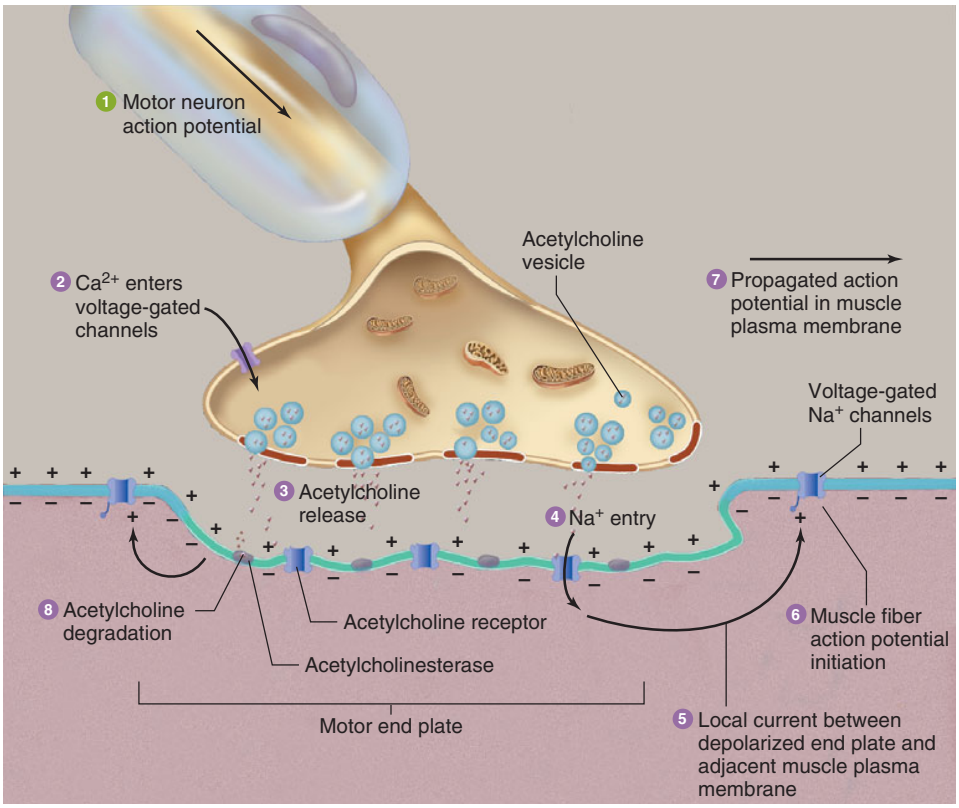

FIGURE 6–13 Events at the neuromuscular junction that lead to an action potential in the muscle fiber plasma membrane. The impulse arriving in the end of the motor neuron increases the permeability of its endings to Ca^{2+} which enters the endings and triggers exocytosis of the acetylcholine (ACh)-containing synaptic vesicles. ACh diffuses and binds to nicotinic cholinergic (N_M) receptors in the motor end plate which increases Na^+ and K^+ conductance. The resultant influx of Na^+ produces the end plate potential. The current sink created by this local potential depolarizes the adjacent muscle membrane to its firing level. Action potentials are generated on either side of the end plate and are conducted away from the end plate in both directions along the muscle fiber and the muscle contracts. ACh is then removed from the synaptic cleft by acetylcholinesterase. (From Widmaier EP, Raff H, Strang KT: *Vanders Human Physiology.* McGraw-Hill, 2008.)

the Na^+ and K^+ conductance, and the resultant influx of Na^+ produces a depolarizing potential, the **end plate potential.** The current sink created by this local potential depolarizes the adjacent muscle membrane to its firing level. Action potentials are generated on either side of the end plate and are conducted away from the end plate in both directions along the muscle fiber. The muscle action potential, in turn, initiates muscle contraction, as described in Chapter 5. Acetylcholine is then removed from the synaptic cleft by acetylcholinesterase, which is present in high concentration at the neuromuscular junction.

An average human end plate contains about 15–40 million acetylcholine receptors. Each nerve impulse releases acetylcholine from about 60 synaptic vesicles, and each vesicle contains about 10,000 molecules of the neurotransmitter. This amount is enough to activate about 10 times the number of N_M receptors needed to produce a full end plate potential. Therefore, a propagated action potential in the muscle is regularly produced, and this large response obscures the end plate potential. However, the end plate potential can be seen if the 10-fold safety factor is overcome and the potential is reduced to a size that is insufficient to activate the adjacent muscle membrane. This can be accomplished by administration of small doses of curare, a drug that competes with acetylcholine for binding to N_M receptors. The response is then recorded only at the end plate region and decreases exponentially away from it. Under these conditions, end plate potentials can be shown to undergo temporal summation.

QUANTAL RELEASE OF TRANSMITTER

Small quanta (packets) of acetylcholine are released randomly from the nerve cell membrane at rest. Each produces a minute depolarizing spike called a **miniature end plate potential,** which is about 0.5 mV in amplitude. The size of the quanta of acetylcholine released in this way varies directly with the Ca^{2+} concentration and inversely with the Mg^{2+} concentration at the end plate. When a nerve impulse reaches the ending, the number of quanta released increases by several orders of magnitude, and the result is the large end plate potential that exceeds the firing level of the muscle fiber. Quantal release of acetylcholine similar to that seen at the myoneural junction has been observed at other cholinergic synapses, and quantal release of other transmitters occurs at noradrenergic, glutamatergic, and other synaptic junctions. Two diseases of the neuromuscular junction, myasthenia gravis and Lambert-Eaton syndrome, are described in Clinical Box 6–2 and Clinical Box 6–3, respectively.

CLINICAL BOX 6–2

Myasthenia Gravis

Myasthenia gravis is a serious and sometimes fatal disease in which skeletal muscles are weak and tire easily. It occurs in 25 to 125 of every 1 million people worldwide and can occur at any age but seems to have a bimodal distribution, with peak occurrences in individuals in their 20s (mainly women) and 60s (mainly men). It is caused by the formation of circulating antibodies to the muscle type of **nicotinic cholinergic receptors.** These antibodies destroy some of the receptors and bind others to neighboring receptors, triggering their removal by endocytosis. Normally, the number of quanta released from the motor nerve terminal declines with successive repetitive stimuli. In myasthenia gravis, neuromuscular transmission fails at these low levels of quantal release. This leads to the major clinical feature of the disease, muscle fatigue with sustained or repeated activity. There are two major forms of the disease. In one form, the extraocular muscles are primarily affected. In the second form, there is a generalized skeletal muscle weakness. In severe cases, all muscles, including the diaphragm, can become weak and respiratory failure and death can ensue. The major structural abnormality in myasthenia gravis is the appearance of sparse, shallow, and abnormally wide or absent synaptic clefts in the motor end plate. Studies show that the postsynaptic membrane has a reduced response to acetylcholine and a 70–90% decrease in the number of receptors per end plate in affected muscles. Patients with mysathenia gravis have a greater than normal tendency to also have rheumatoid arthritis, systemic lupus erythematosus, and polymyositis. About 30% of mysathenia gravis patients have a maternal relative with an autoimmune disorder. These associations suggest that individuals with myasthenia gravis share a genetic predisposition to autoimmune disease. The thymus may play a role in the pathogenesis of the disease by supplying helper T cells sensitized against thymic proteins that cross-react with acetylcholine receptors. In most patients, the thymus is hyperplastic; and 10–15% have a thymoma.

THERAPEUTIC HIGHLIGHTS

Muscle weakness due to myasthenia gravis improves after a period of rest or after administration of an **acetylcholinesterase inhibitor** such as **neostigmine** or **pyridostigmine.** Cholinesterase inhibitors prevent metabolism of acetylcholine and can thus compensate for the normal decline in released neurotransmitters during repeated stimulation. **Immunosuppressive drugs** (eg, **prednisone, azathioprine,** or **cyclosporine**) can suppress antibody production and have been shown to improve muscle strength in some patients with myasthenia gravis. **Thymectomy** is indicated especially if a thymoma is suspected in the development of myasthenia gravis. Even in those without thymoma, thymectomy induces remission in 35% and improves symptoms in another 45% of patients.

CLINICAL BOX 6–3

Lambert–Eaton Syndrome

In a relatively rare condition called **Lambert–Eaton Syndrome (LEMS),** muscle weakness is caused by an autoimmune attack against one of the voltage-gated Ca^{2+} channels in the nerve endings at the neuromuscular junction. This decreases the normal Ca^{2+} influx that causes acetylcholine release. The incidence of LEMS in the U.S. is about 1 case per 100,000 people; it is usually an adult-onset disease that appears to have a similar occurrence in men and women. Proximal muscles of the lower extremities are primarily affected, producing a waddling gait and difficulty raising the arms. Repetitive stimulation of the motor nerve facilitates accumulation of Ca^{2+} in the nerve terminal and increases acetylcholine release, leading to an increase in muscle strength. This is in contrast to myasthenia gravis in which symptoms are exacerbated by repetitive stimulation. About 40% of patients with LEMS also have cancer, especially small cell cancer of the lung. One theory is that antibodies that have been produced to attack the cancer cells may also attack Ca^{2+} channels, leading to LEMS. LEMS has also been associated with lymphosarcoma, malignant thymoma, and cancer of the breast, stomach, colon, prostate, bladder, kidney, or gall bladder. Clinical signs usually precede the diagnosis of cancer. A syndrome similar to LEMS can occur after the use of **aminoglycoside antibiotics,** which also impair Ca^{2+} channel function.

THERAPEUTIC HIGHLIGHTS

Since there is a high comorbidity with small cell lung cancer, the first treatment strategy is to determine whether the individual also has cancer and, if so, to treat that appropriately. In patients without cancer, **immunotherapy** is initiated. **Prednisone** administration, **plasmapheresis,** and **intravenous immunoglobulin** are some examples of effective therapies for LEMS. Also, the use of **aminopyridines** facilitates the release of acetylcholine in the neuromuscular junction and can improve muscle strength in LEMS patients. This class of drugs causes blockade of presynaptic K^+ channels and promote activation of voltage-gated Ca^{2+} channels. Acetylcholinesterase inhibitors can be used but often do not ameliorate the symptoms of LEMS.

NERVE ENDINGS IN SMOOTH & CARDIAC MUSCLE

The postganglionic neurons in the various smooth muscles that have been studied in detail branch extensively and come in close contact with the muscle cells (**Figure 6–14**). Some of these nerve fibers contain clear vesicles and are cholinergic, whereas others contain the characteristic dense-core vesicles that contain norepinephrine. There are no recognizable end plates or other postsynaptic specializations. The nerve fibers run along the membranes of the muscle cells and sometimes groove their surfaces. The multiple branches of the noradrenergic and, presumably, the cholinergic neurons are beaded with enlargements **(varicosities)** and contain synaptic vesicles (Figure 6–14). In noradrenergic neurons, the varicosities are about 5 μm apart, with up to 20,000 varicosities per neuron. Transmitter is apparently liberated at each varicosity, that is, at many locations along each axon. This arrangement permits one neuron to innervate many effector cells. The type of contact in which a neuron forms a synapse on the surface of another neuron or a smooth muscle cell and then passes on to make similar contacts with other cells is called a **synapse en passant.**

In the heart, cholinergic and noradrenergic nerve fibers end on the sinoatrial node, the atrioventricular node, and the bundle of His (see Chapter 29). Noradrenergic fibers also innervate the ventricular muscle. The exact nature of the endings on nodal tissue is not known. In the ventricle, the contacts between the noradrenergic fibers and the cardiac muscle fibers resemble those found in smooth muscle.

JUNCTIONAL POTENTIALS

In smooth muscles in which noradrenergic discharge is excitatory, stimulation of the noradrenergic nerves produces discrete partial depolarizations that look like small end plate potentials and are called **excitatory junction potentials (EJPs).** These potentials summate with repeated stimuli. Similar EJPs are seen in tissues excited by cholinergic discharges. In tissues inhibited by noradrenergic stimuli, hyperpolarizing **inhibitory junction potentials (IJPs)** are produced by stimulation of the noradrenergic nerves. Junctional potentials spread electrotonically.

DENERVATION SUPERSENSITIVITY

When the motor nerve to skeletal muscle is cut and allowed to degenerate, the muscle gradually becomes extremely sensitive to acetylcholine. This is called **denervation hypersensitivity** or **supersensitivity.** Normally nicotinic receptors are located only in the vicinity of the motor end plate where the axon of the motor nerve terminates. When the motor nerve is severed,

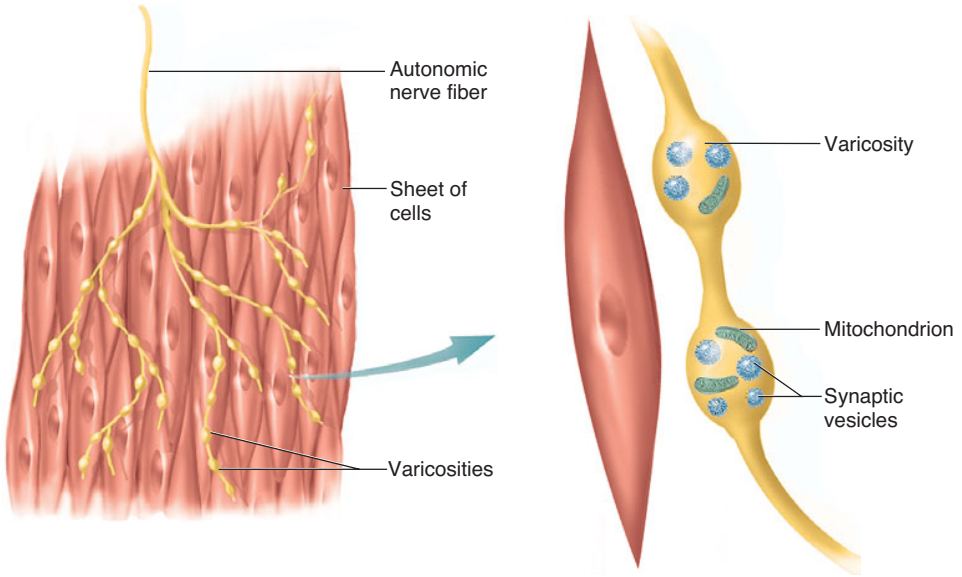

FIGURE 6–14 Endings of postganglionic autonomic neurons on smooth muscle. The nerve fibers run along the membranes of the smooth muscle cells and sometimes groove their surfaces. The multiple branches of postganglionic neurons are beaded with enlargements (varicosities) and contain synaptic vesicles. Neurotransmitter is released from the varicosities and diffuses to receptors on smooth muscle cell plasma membranes. (From Widmaier EP, Raff H, Strang KT: *Vanders Human Physiology*. McGraw-Hill, 2008.)

there is a marked proliferation of nicotinic receptors over a wide region of the neuromuscular junction. Denervation supersensitivity also occurs at autonomic junctions. Smooth muscle, unlike skeletal muscle, does not atrophy when denervated, but it becomes hyperresponsive to the chemical mediator that normally activates it. This hyperresponsiveness can be demonstrated by using pharmacological tools rather than actual nerve section. Prolonged use of a drug such as reserpine can be used to deplete transmitter stores and prevent the target organ from being exposed to norepinephrine for an extended period. Once the drug usage is stopped, smooth muscle and cardiac muscle will be supersensitive to subsequent release of the neurotransmitter.

The reactions triggered by section of an axon are summarized in Figure 6–15. Hypersensitivity of the postsynaptic structure to the transmitter previously secreted by the axon endings is a general phenomenon, largely due to the synthesis or activation of more receptors. Both orthograde degeneration **(wallerian degeneration)** and retrograde degeneration of the axon stump to the nearest collateral **(sustaining collateral)** will occur. There are a series of changes in the cell body that leads to a decrease in Nissl substance **(chromatolysis).** The nerve then starts to regrow, with multiple small branches projecting along the path the axon previously followed **(regenerative sprouting).** Axons sometimes grow back to their original targets, especially in locations like the neuromuscular junction. However, nerve regeneration is generally limited because axons often become entangled in the area of tissue damage at the site where they were disrupted. This difficulty has been reduced by administration of **neurotrophins** (see Chapter 4).

Denervation hypersensitivity has multiple causes. As noted in Chapter 2, a deficiency of a given chemical messenger generally produces an upregulation of its receptors. Another factor is a lack of reuptake of secreted neurotransmitters.

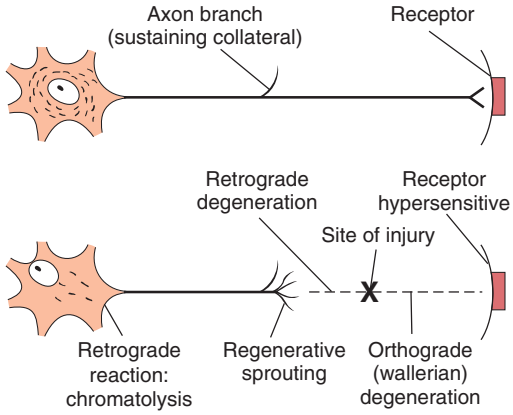

FIGURE 6–15 Summary of changes occurring in a neuron and the structure it innervates when its axon is crushed or cut at the point marked X. Hypersensitivity of the postsynaptic structure to the transmitter previously secreted by the axon occurs largely due to the synthesis or activation of more receptors. There is both orthograde (wallerian) degeneration from the point of damage to the terminal and retrograde degeneration of the axon stump to the nearest collateral (sustaining collateral). Changes also occur in the cell body, including chromatolysis. The nerve starts to regrow, with multiple small branches projecting along the path the axon previously followed (regenerative sprouting).

CHAPTER SUMMARY

- The terminals of the presynaptic fibers have enlargements called terminal boutons or synaptic knobs. The presynaptic terminal is separated from the postsynaptic structure by a synaptic cleft. The postsynaptic membrane contains neurotransmitter receptors and usually a postsynaptic thickening called the postsynaptic density.
- At chemical synapses, an impulse in the presynaptic axon causes secretion of a neurotransmitter that diffuses across the synaptic cleft and binds to postsynaptic receptors, triggering events that open or close channels in the membrane of the postsynaptic cell. At electrical synapses, the membranes of the presynaptic and postsynaptic neurons come close together, and gap junctions form low-resistance bridges through which ions pass with relative ease from one neuron to the next.
- An EPSP is produced by depolarization of the postsynaptic cell after a latency of 0.5 ms; the excitatory transmitter opens Na^+ or Ca^{2+} ion channels in the postsynaptic membrane, producing an inward current. An IPSP is produced by a hyperpolarization of the postsynaptic cell; it can be produced by a localized increase in Cl^- transport. Slow EPSPs and IPSPs occur after a latency of 100–500 ms in autonomic ganglia, cardiac, and smooth muscle, and cortical neurons. The slow EPSPs are due to decreases in K^+ conductance, and the slow IPSPs are due to increases in K^+ conductance.
- Postsynaptic inhibition during the course of an IPSP is called direct inhibition. Indirect inhibition is due to the effects of previous postsynaptic neuron discharge; for example, the postsynaptic cell cannot be activated during its refractory period. Presynaptic inhibition is a process mediated by neurons whose terminals are on excitatory endings, forming axoaxonal synapses; in response to activation of the presynaptic terminal. Activation of the presynaptic receptors can increase Cl^- conductance, decreasing the size of the action potentials reaching the excitatory ending, and reducing Ca^{2+} entry and the amount of excitatory transmitter released.
- The axon terminal of motor neurons synapses on the motor end plate on the skeletal muscle membrane to form the neuromuscular junction. The impulse arriving in the motor nerve terminal leads to the entry of Ca^{2+} which triggers the exocytosis of the acetylcholine-containing synaptic vesicles. The acetylcholine diffuses and binds to nicotinic cholinergic receptors on the motor end plate, causing an increase in Na^+ and K^+ conductance; the influx of Na^+ induces the end plate potential and subsequent depolarization of the adjacent muscle membrane. Action potentials are generated and conducted along the muscle fiber, leading in turn to muscle contraction.
- When a nerve is damaged and then degenerates, the postsynaptic structure gradually becomes extremely sensitive to the transmitter released by the nerve. This is called denervation hypersensitivity or supersensitivity.

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. Which of the following electrophysiological events is correctly paired with the change in ionic currents causing the event?
   A. Fast inhibitory postsynaptic potentials (IPSPs) and closing of Cl^- channels.
   B. Fast excitatory postsynaptic potentials (EPSPs) and an increase in Ca^{2+} conductance.
   C. End plate potential and an increase in Na^+ conductance.
   D. Presynaptic inhibition and closure of voltage-gated K^+ channels.
   E. Slow EPSPs and an increase in K^+ conductance.
2. Which of the following physiological processes is not correctly paired with a structure?
   A. Electrical transmission : gap junction
   B. Negative feedback inhibition : Renshaw cell
   C. Synaptic vesicle docking and fusion : presynaptic nerve terminal
   D. End plate potential : muscarinic cholinergic receptor
   E. Action potential generation : initial segment
3. Initiation of an action potential in skeletal muscle
   A. requires spatial facilitation.
   B. requires temporal facilitation.
   C. is inhibited by a high concentration of Ca^{2+} at the neuromuscular junction.
   D. requires the release of norepinephrine.
   E. requires the release of acetylcholine.
4. A 35-year-old woman sees her physician to report muscle weakness in the extraocular eye muscles and muscles of the extremities. She states that she feels fine when she gets up in the morning, but the weakness begins soon after she becomes active. The weakness is improved by rest. Sensation appears normal. The physician treats her with an anticholinesterase inhibitor, and she notes immediate return of muscle strength. Her physician diagnoses her with
   A. Lambert–Eaton syndrome.
   B. myasthenia gravis.
   C. multiple sclerosis.
   D. Parkinson disease.
   E. muscular dystrophy.
5. A 55-year-old female had an autonomic neuropathy which disrupted the sympathetic nerve supply to the pupillary dilator muscle of her right eye. While having her eyes examined, the ophthalmologist placed phenylephrine in her eyes. The right eye became much more dilated than the left eye. This suggests that
   A. the sympathetic nerve to the right eye had regenerated.
   B. the parasympathetic nerve supply to the right eye remained intact and compensated for the loss of the sympathetic nerve.
   C. phenylephrine blocked the pupillary constrictor muscle of the right eye.
   D. denervation supersensitivity had developed.
   E. the left eye also had nerve damage and so was not responding as expected.

6. A 47-year-old female was admitted to the hospital after reporting that she had been experiencing nausea and vomiting for about two days and then developed severe muscle weakness and neurological symptoms including ptosis and dysphagia. She indicated she had eaten at a restaurant the evening before the symptoms began. Lab tests were positive for *Clostridium botulinum*. Neurotoxins
   A. block the reuptake of neurotransmitters into presynaptic terminals.
   B. such as tetanus toxin bind reversibly to the presynaptic membrane at the neuromuscular junction.
   C. reach the cell body of the motor neuron by diffusion into the spinal cord.
   D. exert all of their adverse effects by acting centrally rather than peripherally.
   E. such as botulinum toxin prevent the release of acetylcholine from motor neurons due to cleavage of either synaptosome-associated proteins or vesicle-associated membrane proteins.

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