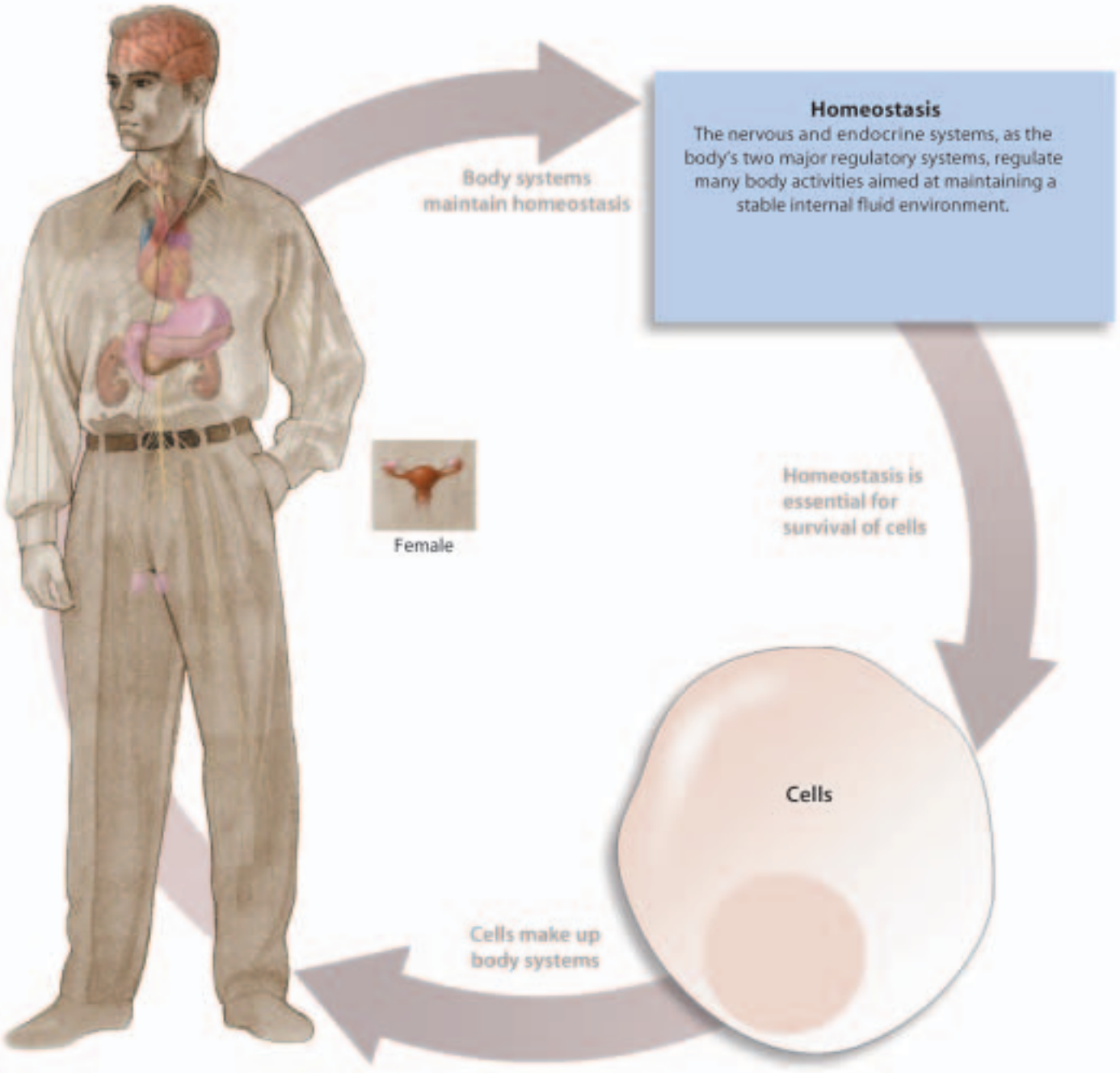
## Nervous and Endocrine Systems




To maintain homeostasis, cells must work together in a coordinated fashion toward common goals. The two major regulatory systems of the body that help ensure life-sustaining coordinated responses are the nervous and endocrine systems. **Neural communication** is accomplished by means of nerve cells, or neurons, which are specialized for rapid electrical signaling and for secreting neurotransmitters, short-distance chemical messengers that act on nearby target organs. The nervous system exerts rapid control over most of the body's muscular and glandular activities. **Hormonal communication** is accomplished by hormones, which are long-distance chemical messengers secreted by the endocrine glands into the blood. The blood carries the hormones to distant target sites, where they regulate processes that require duration rather than speed, such as metabolic activities, water and electrolyte balance, and growth.

# Principles of Neural and Hormonal Communication

CHAPTER 4

CONTENTS AT A GLANCE




Click on the Tutorials menu of the CD-ROM for a tutorial on Neuronal Physiology and Hormonal Communication.

Communication is critical for the survival of the society of cells that collectively compose the body. The ability of cells to communicate with each other is essential for coordination of their diverse activities to maintain homeostasis as well as to control growth and development of the body as a whole. In this chapter, we will consider the molecular and cellular means by which the two major regulatory systems of the body—the nervous and endocrine systems—communicate with the cells/tissues/organs/systems whose activities they control. We will begin with neural communication, then turn our attention to hormonal communication, and conclude with a general comparison of the action modes of the nervous and endocrine systems.

## INTRODUCTION TO NEURAL COMMUNICATION

All body cells display a membrane potential, which is a separation of positive and negative charges across the membrane, as discussed in the preceding chapter. This potential is related to the uneven distribution of $Na^+$, $K^+$, and large intracellular protein anions between the intracellular fluid (ICF) and extracellular fluid (ECF), and to the differential permeability of the plasma membrane to these ions (see pp. 61–66).

### Nerve and muscle are excitable tissues.

Two types of cells, *nerve cells* and *muscle cells*, have developed a specialized use for this membrane potential. They can undergo transient, rapid changes in their membrane potentials. These fluctuations in potential serve as electrical signals. The constant membrane potential that exists when a nerve or muscle cell is not displaying rapid changes in potential is referred to as the *resting potential*. In Chapter 3 you learned that the resting potential of a typical nerve cell is −70 mV.

Nerve and muscle are considered **excitable tissues** because when excited they change their resting

potential to produce electrical signals. Nerve cells, which are known as *neurons,* use these electrical signals to receive, process, initiate, and transmit messages. In muscle cells, these electrical signals initiate contraction. Thus electrical signals are critical to the function of the nervous system as well as all muscles. In this chapter, we will consider how neurons undergo changes in potential to accomplish their function. Muscle cells are discussed in later chapters.

## Membrane potential decreases during depolarization and increases during hyperpolarization.

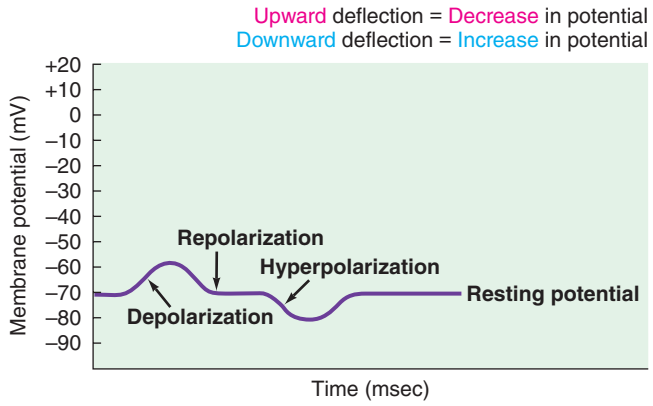
Before you can understand what electrical signals are and how they are created, it will help to become familiar with the following terms, used to describe changes in potential, as graphically represented on ● Figure 4-1:

1. **Polarization:** Charges are separated across the plasma membrane, so that the membrane has potential. Any time the value of the membrane potential is other than 0 mV, in either the positive or negative direction, the membrane is in a state of polarization. Recall that the magnitude of the potential is directly proportional to the number of positive and negative charges separated by the membrane and that the sign of the potential (+ or −) always designates whether excess positive or excess negative charges are present, respectively, on the inside of the membrane.
2. **Depolarization:** A change in potential that makes the membrane less polarized (less negative) than at resting potential. Depolarization decreases membrane potential, moving it closer to 0 mV (for example, a change from −70 mV to −60 mV); fewer charges are separated than at resting potential.
3. **Repolarization:** The membrane returns to resting potential after having been depolarized.
4. **Hyperpolarization:** A change in potential that makes the membrane more polarized (more negative) than at resting potential. Hyperpolarization increases membrane potential, moving it even farther from 0 mV (for instance, a change from −70 mV to −80 mV); more charges are separated than at resting potential.

One possibly confusing point should be clarified. On the device used for recording rapid changes in potential, a *decrease* in potential (that is, the inside being less negative than at resting) is represented as an upward deflection, whereas an *increase* in potential (that is, the inside being more negative than at resting) is represented by a *downward* deflection.

● **FIGURE 4-1**

**Types of changes in membrane potential**




## Electrical signals are produced by changes in ion movement across the plasma membrane.

Changes in membrane potential are brought about by changes in ion movement across the membrane. For example, if the net inward flow of positively charged ions increases compared to the resting state, the membrane becomes depolarized (less negative inside). By contrast, if the net outward flow of positively charged ions increases compared to the resting state, the membrane becomes hyperpolarized (more negative inside).

Changes in ion movement in turn are brought about by changes in membrane permeability in response to *triggering events.* Depending on the type of electrical signal, a triggering event might be (1) a change in the electrical field in the vicinity of an excitable membrane; (2) an interaction of a chemical messenger with a surface receptor on a nerve or muscle cell membrane; (3) a stimulus, such as sound waves stimulating specialized nerve cells in your ear; or (4) a spontaneous change of potential caused by inherent imbalances in the leak–pump cycle. (You will learn more about the nature of these various triggering events as our discussion of electrical signals continues.)

Because the water-soluble ions responsible for carrying charge cannot penetrate the plasma membrane's lipid bilayer, these charges can only cross the membrane through channels specific for them. Membrane channels may be either *leak channels* or *gated channels.* **Leak channels** are open all the time, thus permitting unregulated leakage of their chosen ion across the membrane through the channels. **Gated channels**, in contrast, have gates that can alternately be open, permitting ion passage through the channel, or closed, preventing ion passage through the channels. Gate opening and closing results from a change in the three-dimensional conformation (shape) of the protein that forms the gated channel. There are four kinds of gated channels, depending on the factor that induces the change in channel conformation: (1) **voltage-gated channels**, which open or close in response to changes in membrane potential; (2) **chemically gated channels**, which change conformation in response to the binding of a specific chemical messenger with a membrane receptor in close association with the channel; (3) **mechanically gated channels**, which respond to stretching or other mechanical deformation; and (4) **thermally gated channels**, which respond to local changes in temperature (heat or cold).

Thus, triggering events alter membrane permeability and consequently alter ion flow across the membrane by opening or closing the gates guarding particular ion channels. These

ion movements redistribute charge across the membrane, causing membrane potential to fluctuate.

There are two basic forms of electrical signals: (1) *graded potentials,* which serve as short-distance signals; and (2) *action potentials,* which signal over long distances. We are now going to examine these types of signals in more detail, beginning with graded potentials, and then will explore how nerve cells use these signals to convey messages.

## GRADED POTENTIALS

**Graded potentials** are local changes in membrane potential that occur in varying grades or degrees of magnitude or strength. For example, membrane potential could change from −70 mV to −60 mV (a 10-mV graded potential) or from −70 mV to −50 mV (a 20-mV graded potential).

### The stronger a triggering event, the larger the resultant graded potential.

Graded potentials are usually produced by a specific triggering event that causes gated ion channels to open in a specialized region of the excitable cell membrane. Most commonly, gated $Na^+$ channels open, leading to the inward movement of $Na^+$ down its concentration and electrical gradients. The resultant depolarization—the graded potential—is confined to this small, specialized region of the total plasma membrane.

The magnitude of this initial graded potential (that is, the difference between the new potential and the resting potential) is related to the magnitude of the triggering event: *The stronger the triggering event, the more gated channels that open, the greater the positive charge entering the cell, and the larger the depolarizing graded potential at the point of origin. Also, the longer the duration of the triggering event, the longer the duration of the graded potential.*

### Graded potentials spread by passive current flow.

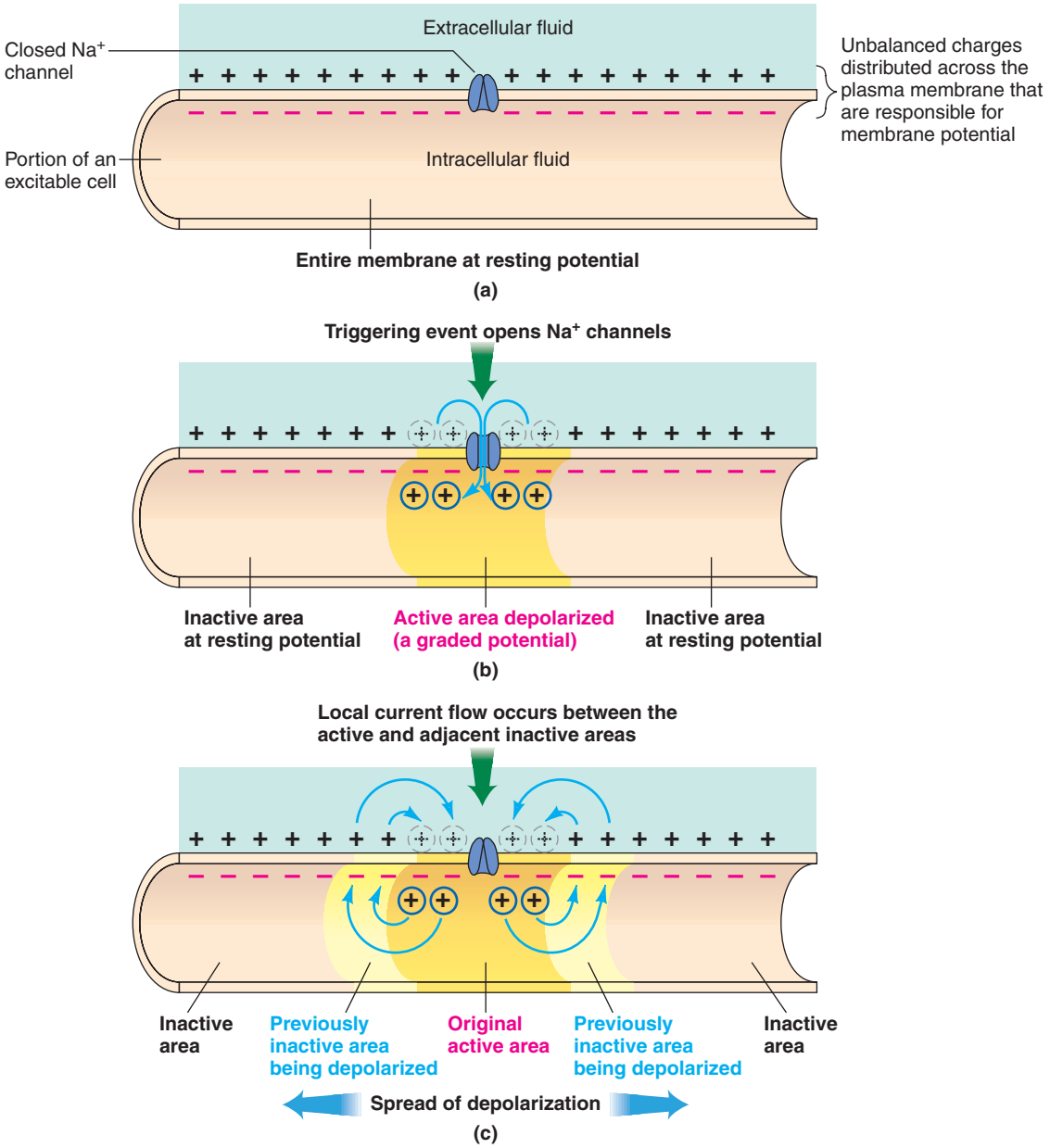
When a graded potential occurs locally in a nerve or muscle cell membrane, the remainder of the membrane is still at resting potential. The temporarily depolarized region is called an *active area.* Note from ● Figure 4-2 that inside the cell, the active area is relatively more positive than the neighboring *inactive areas* that are still at resting potential. Outside the cell, the active area is relatively less positive than these adjacent areas. Because of this difference in potential, electrical charges, in this case carried by ions, passively flow between the active and adjacent resting regions on both the inside and outside of the membrane. Any flow of electrical charges is called a **current.** By convention, the direction of current flow is always designated by the direction in which the positive charges are moving (● Figure 4-2c). On the inside, positive charges flow through the ICF away from the relatively more positive depolarized active region toward the more negative adjacent resting regions. Similarly, outside the cell positive charges flow through the ECF from the more positive adjacent inactive regions toward the relatively more negative active region. Ion movement (that is, current) is occurring *along* the membrane between regions next to each other on the same side of the membrane. This flow is in contrast to ion movement *across* the membrane through ion channels.

As a result of local current flow between an active depolarized area and an adjacent inactive area, the potential changes in the previously inactive area. Positive charges have flowed into this adjacent area on the inside, while simultaneously positive charges have flowed out of this area on the outside. Thus at this adjacent site the inside is more positive (or less negative), and the outside is less positive (or more negative) than before (● Figure 4-2c). Stated differently, the previously inactive adjacent region has been depolarized, so the graded potential has spread. This area's potential now differs from that of the inactive region immediately next to it on the other side, inducing further current flow at this new site, and so on. In this manner, current spreads in both directions away from the initial site of the potential change.

The amount of current that flows between two areas depends on the difference in potential between the areas and on the resistance of the material through which the charges are moving. **Resistance** is the hindrance to electrical charge movement. The greater the difference in potential, the greater the current flow. The lower the resistance, the greater the current flow. *Conductors* have low resistance, providing little hindrance to current flow. Electrical wires and the ICF and ECF are all good conductors, so current readily flows through them. *Insulators* have high resistance and greatly hinder movement of charge. The plastic surrounding electrical wires has high resistance, as do body lipids. Thus current does not flow across the plasma membrane's lipid bilayer. Current, carried by ions, can move across the membrane only through ion channels.

### Graded potentials die out over short distances.

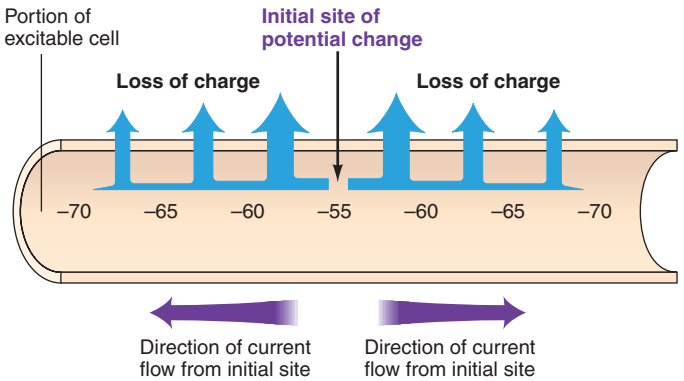
The passive current flow between active and adjacent inactive areas is similar to the means by which current is carried through electrical wires. We know from experience that current leaks out of an electrical wire with dangerous results unless the wire is covered with an insulating material such as plastic. (People can get an electric shock if they touch a bare wire.) Likewise, current is lost across the plasma membrane as charge-carrying ions leak through the "uninsulated" parts of the membrane, that is, through open channels. Because of this current loss, the magnitude of the local current progressively diminishes with increasing distance from the initial site of origin (● Figure 4-3). Thus the magnitude of the graded potential continues to decrease the farther it moves away from the initial active area. Another way of saying this is that the spread of a graded potential is *decremental* (gradually decreases) (● Figure 4-4). Note that in ● Figure 4-3, the magnitude of the initial change in potential is 15 mV (a change from −70 mV to −55 mV), then decreases as it moves along the membrane to a change in potential of 10 mV (from −70 mV




● **FIGURE 4-2**

**Current flow during a graded potential.** (a) The membrane of an excitable cell at resting potential. (b) A triggering event opens $Na^+$ channels, leading to the $Na^+$ entry that brings about depolarization. The adjacent inactive areas are still at resting potential. (c) Local current flow occurs between the active and adjacent inactive areas. This local current flow results in depolarization of the previously inactive areas. In this way, the depolarization spreads away from its point of origin.

PhysioEdge For an interaction related to this figure, see Media Exercise 4.2: Graded Potentials and Action Potentials on the CD-ROM.

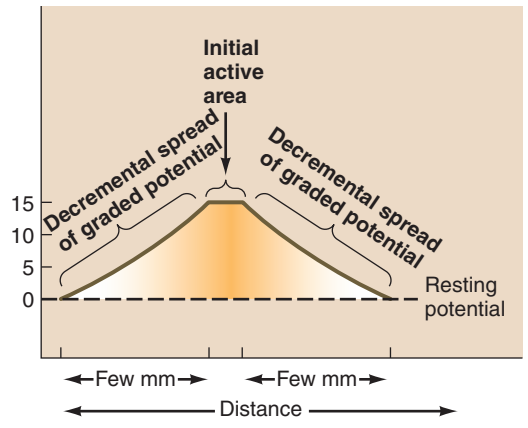



* Numbers refer to the local potential in mV at various points along the membrane.

● **FIGURE 4-3**

**Current loss across the plasma membrane.** Leakage of charge-carrying ions across the plasma membrane results in progressive loss of current with increasing distance from the initial site of potential change.

Change in membrane potential in mV relative to resting potential—i.e., magnitude of electrical signal




● **FIGURE 4-4**

**Decremental spread of graded potentials.** Because of leaks in current, the magnitude of a graded potential continues to decrease as it passively spreads from the initial active area. The potential dies out altogether within a few millimeters of its site of initiation.

to −60 mV), and continues to diminish the farther it moves away from the initial active area, until there is no longer a change in potential. In this way, these local currents die out within a few millimeters from the initial site of change in potential and consequently can function as signals for only very short distances.

Although graded potentials have limited signaling distance, they are critically important to the body's function, as explained in later chapters. The following are all graded potentials: *postsynaptic potentials, receptor potentials, end-plate potentials, pacemaker potentials,* and *slow-wave potentials*. These terms are unfamiliar to you now, but you will become well acquainted with them as we continue discussing nerve and muscle physiology. We are including this list here because it is the only place all these graded potentials will be grouped together. For now it's enough to say that for the most part, excitable cells produce one of these types of graded potentials in response to a triggering event. In turn, graded potentials can initiate *action potentials,* the long-distance signals, in an excitable cell.

## ACTION POTENTIALS

**Action potentials** are brief, rapid, large (100 mV) changes in membrane potential during which the potential actually reverses, so that the inside of the excitable cell transiently becomes more positive than the outside. As with a graded potential, a single action potential involves only a small portion of the total excitable cell membrane. Unlike graded potentials, however, action potentials are conducted, or propagated, throughout the entire membrane in *nondecremental* fashion; that is, they do not diminish in strength as they travel from their site of initiation throughout the remainder of the cell membrane. Thus action potentials can serve as faithful long-distance signals. Think about the nerve cell that brings about contraction of muscle cells in your big toe. If you want to wiggle your big toe, commands are sent from your brain down your spinal cord to initiate an action potential at the beginning of this nerve cell, which is located in the spinal cord. This action potential travels in undiminishing fashion all the way down the nerve cell's long axon, which runs through your leg to terminate on your big-toe muscle cells. The signal has not weakened or died off, being instead preserved at full strength from beginning to end.

Let's now consider the changes in potential during an action potential and the permeability and ion movements responsible for generating this change in potential, before we turn our attention to the means by which action potentials spread throughout the cell membrane in undiminishing fashion.

### During an action potential, the membrane potential rapidly, transiently reverses.

If of sufficient magnitude, a graded potential can initiate an action potential before the graded potential dies off. (Later you will discover the means by which this initiation is accomplished for the various types of graded potentials.) Typically, the portion of the excitable membrane where graded potentials are produced in response to a triggering event does not undergo action potentials. Instead, the graded potential, by electrical or chemical means, brings about depolarization of adjacent portions of the membrane where action potentials can take place. For convenience in this discussion, we will now jump from the triggering event to the depolarization of the membrane portion that is to undergo an action potential, without considering the involvement of the intervening graded potential.

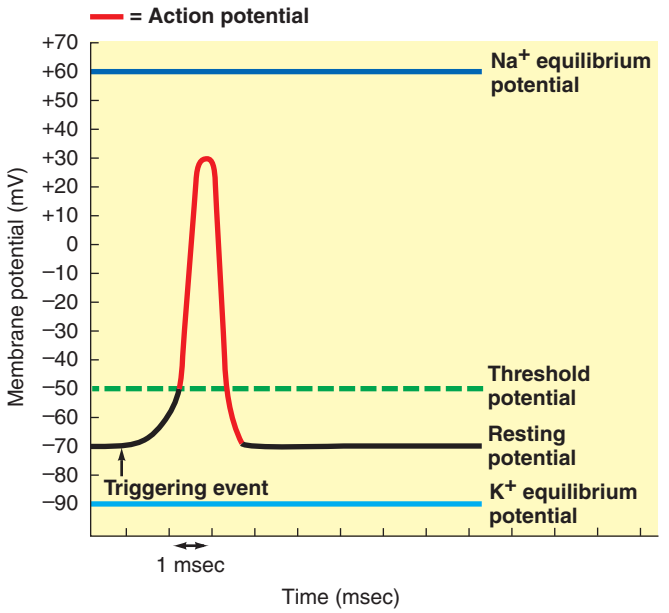
To initiate an action potential, a triggering event causes the membrane to depolarize from the resting potential of −70 mV (● Figure 4-5). Depolarization proceeds slowly at first, until it reaches a critical level known as **threshold potential**, typically between −50 and −55 mV. At threshold potential, an explosive depolarization takes place. A recording of the potential at this time shows a sharp upward deflection to +30 mV as the potential rapidly reverses itself so that the inside of the cell becomes positive compared to the outside. Just as rapidly, the membrane repolarizes, dropping back to resting potential.

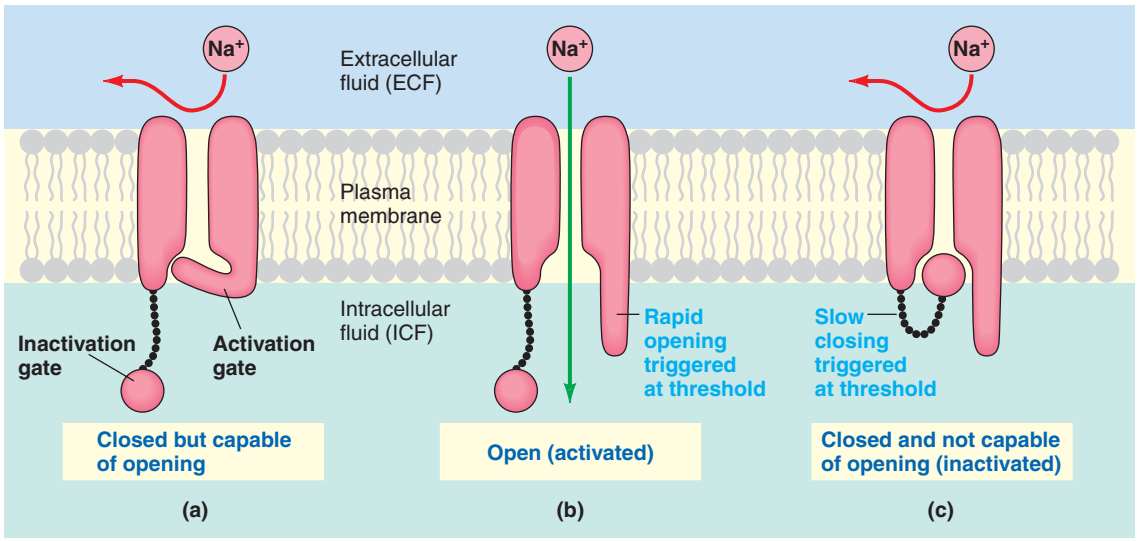
The entire rapid change in potential from threshold to peak and then back to resting is called the *action potential.* Unlike the variable duration of a graded potential, the duration of an action potential is always the same in a given excitable cell. In a nerve cell, an action potential lasts for only 1 msec (0.001 sec). It lasts longer in muscle, with the duration depending on the muscle type. Often an action potential is referred to as a **spike**, because of its spikelike recorded appearance. Alternatively, when an excitable membrane is trig-

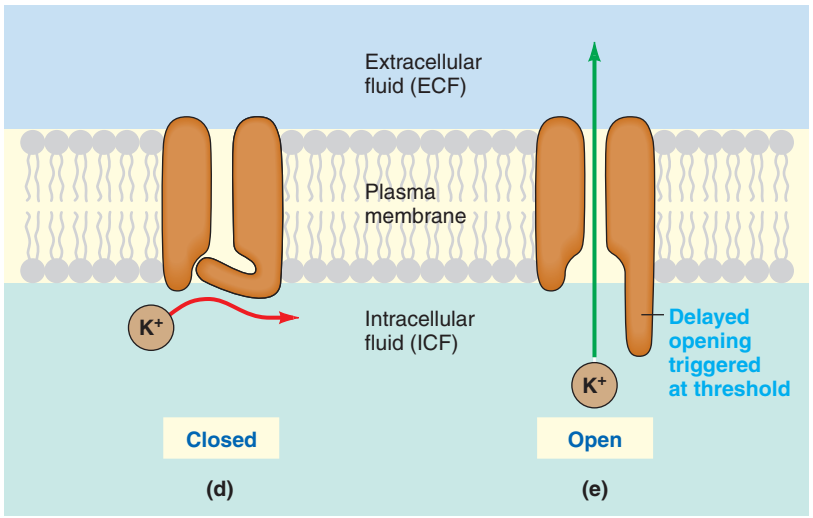
● **FIGURE 4-5**

**Changes in membrane potential during an action potential**

PhysioEdge For an animation related to this figure, click the Action Potential tab in the Neuronal Physiology and Hormonal Communication tutorial on the CD-ROM.






● **FIGURE 4-6**

**Conformations of voltage-gated sodium and potassium channels**

PhysioEdge For an animation of this figure, click the Voltage-gated Ion Channels tab in the Neuronal Physiology and Hormonal Communication tutorial on the CD-ROM.

gered to undergo an action potential, it is said to **fire**. Thus the terms *action potential, spike,* and *firing* all refer to the same phenomenon of rapid reversal of membrane potential.

If threshold potential is not reached by the initial triggered depolarization, no action potential takes place. Thus threshold is a critical all-or-none point. Either the membrane is depolarized to threshold and an action potential takes place, or threshold is not reached in response to the depolarizing event and no action potential occurs.

## Marked changes in membrane permeability and ion movement lead to an action potential.

How is the membrane potential, which is usually maintained at a constant resting level, thrown out of balance to such an extent as to produce an action potential? Recall that $K^+$ makes the greatest contribution to the establishment of the resting potential, because the membrane at rest is considerably more permeable to $K^+$ than to $Na^+$ (see p. 64). During an action potential, marked changes in membrane permeability to $Na^+$ and $K^+$ take place, permitting rapid fluxes of these ions down their electrochemical gradients. These ion movements carry the current responsible for the potential changes that occur during an action potential. Action potentials take place as a result of the triggered opening and subsequent closing of two specific types of channels: voltage-gated $Na^+$ channels and voltage-gated $K^+$ channels.

### VOLTAGE-GATED $Na^+$ AND $K^+$ CHANNELS

Voltage-gated membrane channels consist of proteins that have a number of charged groups. The electric field (potential) surrounding the channels can exert a distorting force on the channel structure as charged portions of the channel proteins are electrically attracted or repelled by charges in the fluids surrounding the membrane. Unlike the majority of membrane proteins, which remain stable despite fluctuations in membrane potential, the voltage-gated channel proteins are especially sensitive to voltage changes. Small distortions in channel shape induced by potential changes can cause them to flip to another conformation. Here again is an example of how subtle changes in structure can profoundly influence function.

The voltage-gated $Na^+$ channel has two gates: an *activation gate* and an *inactivation gate* (● Figure 4-6). The activation gate guards the channel by opening and closing like a hinged door. The inactivation gate consists of a ball-and-chain–like sequence of amino acids. This gate is open when the ball is dangling free on its chain and closed when the ball binds to its receptor located at the channel opening, thus

blocking the opening. Both gates must be open to permit passage of $Na^+$ through the channel, and closure of either gate prevents passage. This voltage-gated $Na^+$ channel can exist in three different conformations: (1) *closed but capable of opening* (activation gate closed, inactivation gate open, ● Figure 4-6a); (2) *open,* or *activated* (both gates open, ● Figure 4-6b); and (3) *closed and not capable of opening* (activation gate open, inactivation gate closed, ● Figure 4-6c).

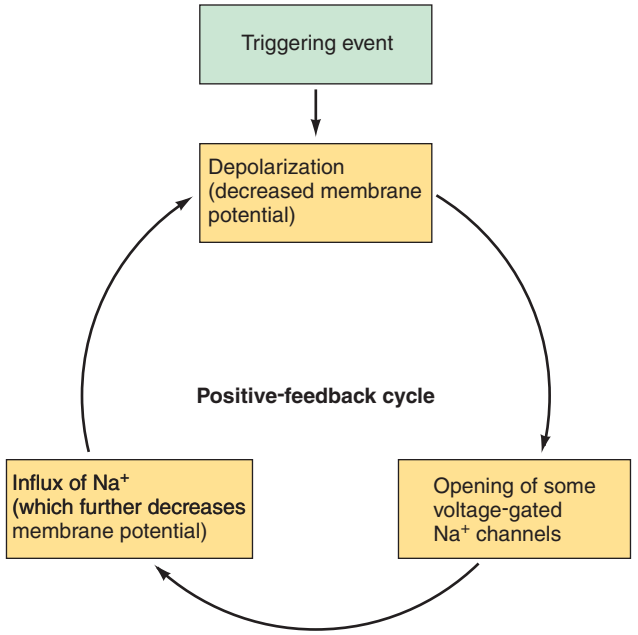
The voltage-gated $K^+$ channel is simpler. It has only one gate, which can be either open or closed (● Figure 4-6d and e). These voltage-gated $Na^+$ and $K^+$ channels exist in addition to the $Na^+$–$K^+$ pump and the leak channels for these ions (described in Chapter 3).

## CHANGES IN PERMEABILITY AND ION MOVEMENT DURING AN ACTION POTENTIAL

At resting potential (−70 mV), all the voltage-gated $Na^+$ and $K^+$ channels are closed, with the $Na^+$ channels' activation gates being closed and their inactivation gates being open; that is, the voltage-gated $Na^+$ channels are in their "closed but capable of opening" conformation. Therefore, passage of $Na^+$ and $K^+$ does not occur through these voltage-gated channels at resting potential. However, because of the presence of many $K^+$ leak channels and very few $Na^+$ leak channels, the resting membrane is 50 to 75 times more permeable to $K^+$ than to $Na^+$.

When a membrane starts to depolarize toward threshold as a result of a triggering event, the activation gates of some of its voltage-gated $Na^+$ channels open. Now both gates of these activated channels are open. Because both the concentration and electrical gradients for $Na^+$ favor its movement into the cell, $Na^+$ starts to move in. The inward movement of positively charged $Na^+$ depolarizes the membrane further, thereby opening even more voltage-gated $Na^+$ channels and allowing more $Na^+$ to enter, and so on, in a positive-feedback cycle (● Figure 4-7).

At threshold potential, there is an explosive increase in $Na^+$ permeability, which is symbolized as $P_{Na^+}$, as the membrane swiftly becomes 600 times more permeable to $Na^+$ than to $K^+$. Each individual channel is either closed or open and cannot be partially open. However, the delicately poised gating mechanisms of the various voltage-gated $Na^+$ channels are jolted open by slightly different voltage changes. During the early depolarizing phase, more and more of the $Na^+$ channels open as the potential progressively decreases. At threshold, enough $Na^+$ gates have opened to set off the positive feedback cycle that rapidly causes the remaining $Na^+$ gates to swing open. Now $Na^+$ permeability dominates the membrane, in contrast to the $K^+$ domination at resting potential. Thus at threshold $Na^+$ rushes into the cell, rapidly eliminating the internal negativity and even making the inside of the cell more positive than the outside as the membrane potential is driven toward the $Na^+$ equilibrium potential (which is +60 mV; see p. 64). The potential reaches +30 mV, close to the $Na^+$ equilibrium potential. The potential does not become any more positive, because at the peak of the action potential the $Na^+$ channels start to close to the inactivated state and $P_{Na^+}$ starts to fall to its low resting value.




● **FIGURE 4-7**

**Positive-feedback cycle responsible for opening $Na^+$ channels at threshold**

What causes the $Na^+$ channels to close? When the membrane potential reaches threshold, two closely related events take place in the gates of each $Na^+$ channel. First the activation gates are triggered to *open rapidly,* in response to the depolarization, converting the channel to its open (activated) conformation (● Figure 4-6b). Surprisingly, this channel opening initiates the process of channel closing. The conformational change that opens the channel also allows the inactivation gate's ball to bind to its receptor at the channel opening, thereby physically blocking the mouth of the channel. However, this closure process takes time, so the inactivation gate *closes slowly* compared to the rapidity of channel opening. Meanwhile, during the 0.5-msec delay after the activation gate opens and before the inactivation gate closes, both gates are open, and $Na^+$ rushes into the cell through these open channels, bringing the action potential to its peak. Then the inactivation gate closes, membrane permeability to $Na^+$ plummets to its low resting value, and further $Na^+$ entry is prevented. The channel remains in this inactivated conformation until the membrane potential has been restored to its resting value.

Simultaneous with inactivation of $Na^+$ channels, the voltage-gated $K^+$ channels start to slowly open, with maximum opening occurring at the peak of the action potential. Opening of the $K^+$ channel gate is a delayed voltage-gated response triggered by the initial depolarization to threshold. Thus three action-potential–related events occur at threshold: (1) the rapid opening of the $Na^+$ activation gates, which permits $Na^+$ to enter, moving the potential from threshold to its positive peak; (2) the slow closing of the $Na^+$ inactivation gates, which halts further $Na^+$ entry after a brief time delay, thus keeping the potential from rising any further; and

(3) the slow opening of the $K^+$ gates, which is responsible for the potential plummeting from its peak back to resting.

Opening of the voltage-gated $K^+$ channels greatly increases $K^+$ permeability (designated $P_{K^+}$) to about 300 times the resting $P_{Na^+}$ at the peak of the action potential. This marked increase in $P_{K^+}$ causes $K^+$ to rush out of the cell down its concentration and electrical gradients, carrying positive charges back to the outside. Note that at the peak of the action potential, the positive potential inside the cell tends to repel the positive $K^+$ ions, so the electrical gradient for $K^+$ is outward, unlike at resting potential. The outward movement of $K^+$ rapidly restores the negative resting potential.

To review (● Figure 4-8), *the rising phase of the action potential* (from threshold to +30 mV) *is due to* $Na^+$ *influx* ($Na^+$ entering the cell) induced by an explosive increase in $P_{Na^+}$ at threshold. The *falling phase* (from +30 mV to resting potential) *is brought about largely by* $K^+$ *efflux* ($K^+$ leaving the cell) caused by the marked increase in $P_{K^+}$ occurring simultaneously with the inactivation of the $Na^+$ channels at the peak of the action potential.

As the potential returns to resting, the changing voltage shifts the $Na^+$ channels to their "closed but capable of opening" conformation, with the activation gate closed and the inactivation gate open. Now the channel is reset, ready to respond to another triggering event. The newly opened voltage-gated $K^+$ channels also close, so the membrane returns to the resting number of open $K^+$ leak channels. The membrane remains at resting potential until another triggering event alters the gated $Na^+$ and $K^+$ channels.

## The $Na^+$–$K^+$ pump gradually restores the concentration gradients disrupted by action potentials.

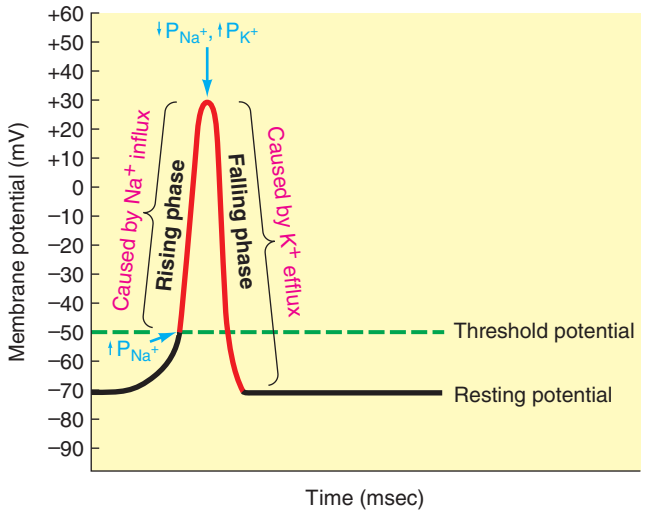
At the completion of an action potential, the membrane potential has been restored to its resting condition, but the ion distribution has been altered slightly. Sodium has entered the cell during the rising phase, and a comparable amount of $K^+$ has left during the falling phase. The $Na^+$–$K^+$ pump restores these ions to their original locations in the long run, but not after each action potential.

The active pumping process takes much longer to restore $Na^+$ and $K^+$ to their original locations than it takes for the passive fluxes of these ions during an action potential. However, the membrane does not need to wait until the $Na^+$–$K^+$ pump slowly restores the concentration gradients before it can undergo another action potential. Actually, the movement of only relatively few of the total number of $Na^+$ and $K^+$ ions present causes the large swings in potential that occur during an action potential. Only about 1 out of 100,000 $K^+$ ions present in the cell leaves during an action potential, while a comparable number of $Na^+$ ions enters from the ECF. The movement of this extremely small proportion of the total $Na^+$ and $K^+$ during a single action potential produces dramatic 100-mV changes in potential (between −70 mV and +30 mV), but only infinitesimal changes in the ICF and ECF concentrations of these ions. Much more $K^+$ is still inside the cell than outside, and $Na^+$ is still predominantly an extracellular cation. Consequently, the $Na^+$ and $K^+$ concentration gradients still exist, so repeated action potentials can occur without the pump having to keep pace to restore the gradients.

Were it not for the pump, of course, even tiny fluxes accompanying repeated action potentials would eventually "run down" the concentration gradients so that further action potentials would be impossible. If the concentrations of $Na^+$ and $K^+$ were equal between the ECF and ICF, changes in permeability to these ions would not bring about ion fluxes, so no change in potential would occur. Thus the $Na^+$–$K^+$ pump is critical to maintaining the concentration gradients in the long run. However, it does not have to perform its role between action potentials, nor is it directly involved in the ion fluxes or potential changes that occur during an action potential.

● **FIGURE 4-8**

**Permeability changes and ion fluxes during an action potential**




## Action potentials are propagated from the axon hillock to the axon terminals.

A single action potential involves only a small patch of the total surface membrane of an excitable cell. But if action potentials are to serve as long-distance signals, they cannot be merely isolated events occurring in a limited area of a nerve or muscle cell membrane. Mechanisms must exist to conduct or spread the action potential throughout the entire cell membrane. Furthermore, the signal must be transmitted from one cell to the next cell (for example, along specific nerve pathways). To explain how these mechanisms are accomplished, we will first begin with a brief look at neuronal structure. Then we will examine how an action potential (nerve impulse) is conducted throughout a nerve cell, before we turn our attention to how the signal is passed to another cell.

A single nerve cell, or **neuron**, typically consists of three basic parts: the *cell body,* the *dendrites,* and the *axon,* although there are variations in structure, depending on the location and function of the neuron. The nucleus and organelles are

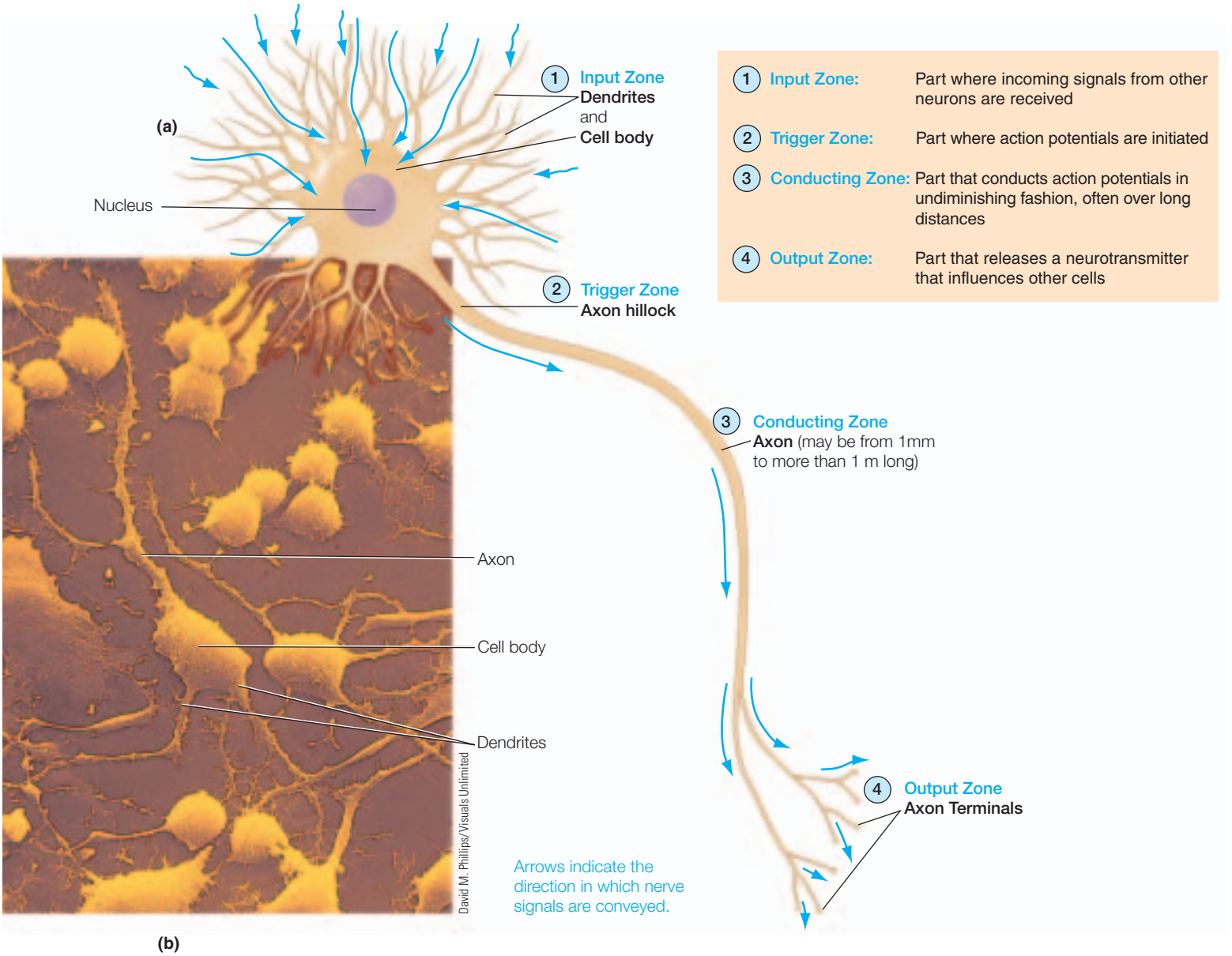
housed in the **cell body**, from which numerous extensions known as **dendrites** typically project like antennae to increase the surface area available for receiving signals from other nerve cells (● Figure 4-9). Some neurons have up to 400,000 of these elongated surface extensions. Dendrites carry signals *toward* the cell body. In most neurons the plasma membrane of the dendrites and cell body contains protein receptors for binding chemical messengers from other neurons. Therefore, the dendrites and cell body are the neuron's *input zone,* because these components receive and integrate incoming signals. This is the region where graded potentials are produced in response to triggering events, in this case, incoming chemical messengers.

The **axon**, or **nerve fiber**, is a single, elongated, tubular extension that conducts action potentials *away from* the cell body and eventually terminates at other cells. The axon frequently gives off side branches along its course. The first portion of the axon plus the region of the cell body from which the axon leaves is known as the **axon hillock**. The axon hillock is the neuron's *trigger zone,* because it is the site where action potentials are triggered, or initiated, by the graded potential if it is of sufficient magnitude. The action potentials

● **FIGURE 4-9**

**Anatomy of the most abundant structural type of neuron (nerve cell).** (a) Most but not all neurons consist of the basic parts represented in the figure. (b) An electron micrograph highlighting the cell body, dendrites, and part of the axon of a neuron within the central nervous system.

PhysioEdge For an animation of this figure, click the Neuronal Anatomy and Conduction of the Action Potential tab in the Neuronal Physiology and Hormonal Communication tutorial on the CD-ROM.



are then conducted along the axon from the axon hillock to the typically highly branched ending at the **axon terminals**. These terminals release chemical messengers that simultaneously influence numerous other cells with which they come into close association. Functionally, therefore, the axon is the *conducting zone* of the neuron, and the axon terminals constitute its *output zone*. (The major exception to this typical neuronal structure and functional organization is neurons specialized to carry sensory information, a topic described in a later chapter.)

Axons vary in length from less than a millimeter in neurons that communicate only with neighboring cells to longer than a meter in neurons that communicate with distant parts of the nervous system or with peripheral organs. For example, the axon of the nerve cell innervating your big toe must traverse the distance from the origin of its cell body within the spinal cord in the lower region of your back all the way down your leg to your toe.

Action potentials can be initiated only in portions of the membrane that have an abundance of voltage-gated $Na^+$ channels that can be triggered to open by a depolarizing event. Typically, regions of excitable cells where graded potentials take place do not undergo action potentials, because voltage-gated $Na^+$ channels are sparse there. Therefore, sites specialized for graded potentials do not undergo action potentials, even though they might be considerably depolarized. However, graded potentials can, before dying out, trigger action potentials in adjacent portions of the membrane by bringing these more sensitive regions to threshold through local current flow spreading from the site of the graded potential. In a typical neuron, for example, graded potentials are generated in the dendrites and cell body in response to incoming signals. If these graded potentials have sufficient magnitude by the time they have spread to the axon hillock, they initiate an action potential at this triggering zone.

## Once initiated, action potentials are conducted throughout a nerve fiber.

Once an action potential is initiated at the axon hillock, no further triggering event is necessary to activate the remainder of the nerve fiber. The impulse is automatically conducted throughout the neuron without further stimulation by one of two methods of propagation: *contiguous conduction* or *saltatory conduction*.

**Contiguous conduction** involves the spread of the action potential along every patch of membrane down the length of the axon (*contiguous* means "touching" or "next to in sequence.") This process is illustrated in ● Figure 4-10. You are viewing a schematic representation of a longitudinal section of the axon hillock and the portion of the axon immediately beyond it. The membrane at the axon hillock is at the peak of an action potential. The inside of the cell is positive in this active area, because $Na^+$ has already rushed into the nerve cell at this point. The remainder of the axon, still at resting potential and negative inside, is considered inactive. For the action potential to spread from the active to the inactive areas, the inactive areas must somehow be depolarized to threshold before they can undergo an action potential. This depolarization is accomplished by local current flow between the area already undergoing an action potential and the adjacent inactive area, similar to the current flow responsible for the spread of graded potentials. Because opposite charges attract, current can flow locally between the active area and the neighboring inactive area on both the inside and the outside of the membrane. This local current flow in effect neutralizes or eliminates some of the unbalanced charges in the inactive area; that is, it reduces the number of opposite charges separated across the membrane, reducing the potential in this area. This depolarizing effect quickly brings the involved inactive area to threshold, at which time the voltage-gated $Na^+$ channels in this region of the membrane are all thrown open, leading to an action potential in this previously inactive area. Meanwhile, the original active area returns to resting potential as a result of $K^+$ efflux.

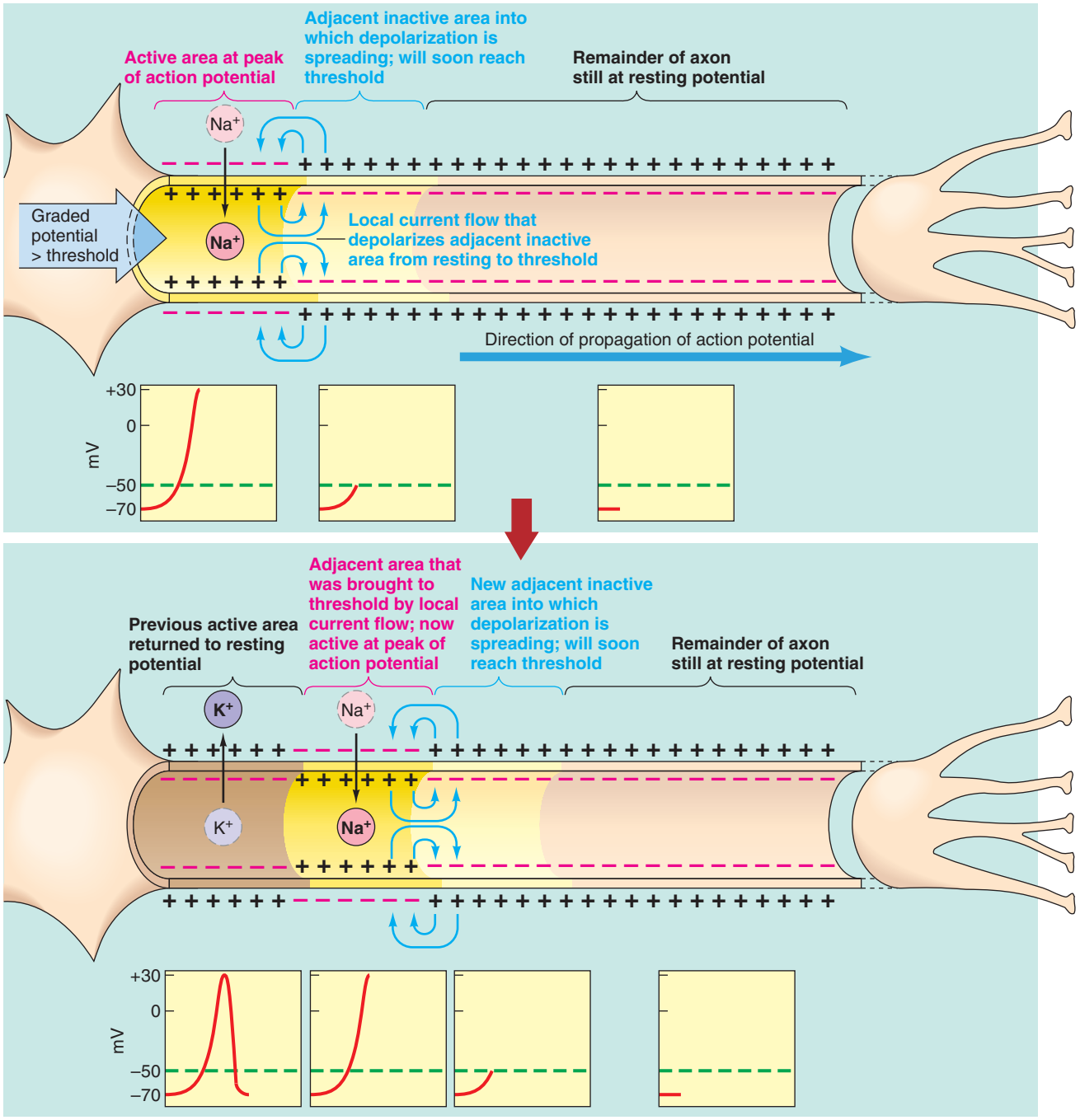
In turn, beyond the new active area is another inactive area, so the same thing happens again. This cycle repeats itself in a chain reaction until the action potential has spread to the end of the axon. *Once an action potential is initiated in one part of a nerve cell membrane, a self-perpetuating cycle is initiated so that the action potential is propagated along the rest of the fiber automatically.* In this way, the axon is like a firecracker fuse that needs to be lit at only one end. Once ignited, the fire spreads down the fuse; it is not necessary to hold a match to every separate section of the fuse.

Note that the original action potential does not travel along the membrane. Instead, it triggers an identical new action potential in the adjacent area of the membrane, with this process being repeated along the axon's length. An analogy is the "wave" at a stadium. Each section of spectators stands up (the rising phase of an action potential), then sits down (the falling phase) in sequence one after another as the wave moves around the stadium. The wave, not individual spectators, travels around the stadium. Similarly, new action potentials arise sequentially down the axon. Each new action potential in the conduction process is a fresh local event that depends on the induced permeability changes and electrochemical gradients, which are virtually identical down the length of the axon. Therefore, the last action potential at the end of the axon is identical to the original one, no matter how long the axon. Thus an action potential is spread along the axon in undiminished fashion. In this way, action potentials can serve as long-distance signals without attenuation or distortion.

This nondecremental propagation of an action potential contrasts with the decremental spread of a graded potential, which dies out over a very short distance because it cannot regenerate itself. ▲ Table 4-1 summarizes the differences between graded potentials and action potentials, some of which are yet to be discussed.

## The refractory period ensures one-way propagation of the action potential.

What ensures the one-way propagation of an action potential away from the initial site of activation? Note from ● Figure 4-11 that once the action potential has been regenerated




**● FIGURE 4-10**

**Contiguous conduction.** Local current flow between the active area at the peak of an action potential and the adjacent inactive area still at resting potential reduces the potential in this contiguous inactive area to threshold, which triggers an action potential in the previously inactive area. The original active area returns to resting potential, and the new active area induces an action potential in the next adjacent inactive area by local current flow as the cycle repeats itself down the length of the axon.

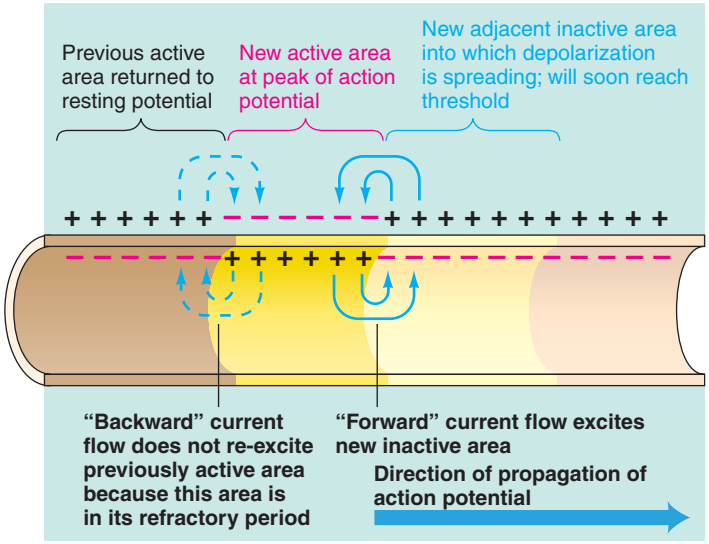
PhysioEdge For an animation of this figure, click the Neuronal Anatomy and Conduction of the Action Potential tab in the Neuronal Physiology and Hormonal Communication tutorial on the CD-ROM.

at a new neighboring site (now positive inside) and the original active area has returned to resting (once again negative inside), the close proximity of opposite charges between these two areas is conducive to local current flow taking place in the backward direction, as well as in the forward direction into as yet unexcited portions of the membrane. If such backward current flow were able to bring the just inactivated area to threshold, another action potential would be initiated here, which would spread both forward and backward, initiating still other action potentials, and so on. But if action poten-

**▲ TABLE 4-1**

Comparison of Graded Potentials and Action Potentials

| GRADED POTENTIALS | ACTION POTENTIALS |
|---|---|
| Graded potential change; magnitude varies with magnitude of triggering event | All-or-none membrane response; magnitude of triggering event coded in frequency rather than amplitude of action potentials |
| Duration varies with duration of triggering event | Constant duration |
| Decremental conduction; magnitude diminishes with distance from initial site | Propagated throughout membrane in undiminishing fashion |
| Passive spread to neighboring inactive areas of membrane | Self-regeneration in neighboring inactive areas of membrane |
| No refractory period | Refractory period |
| Can be summed | Summation impossible |
| Can be depolarization or hyperpolarization | Always depolarization and reversal of charges |
| Triggered by stimulus, by combination of neurotransmitter with receptor, or by spontaneous shifts in leak–pump cycle | Triggered by depolarization to threshold, usually through spread of graded potential |
| Occurs in specialized regions of membrane designed to respond to triggering event | Occurs in regions of membrane with abundance of voltage-gated $Na^+$ channels |



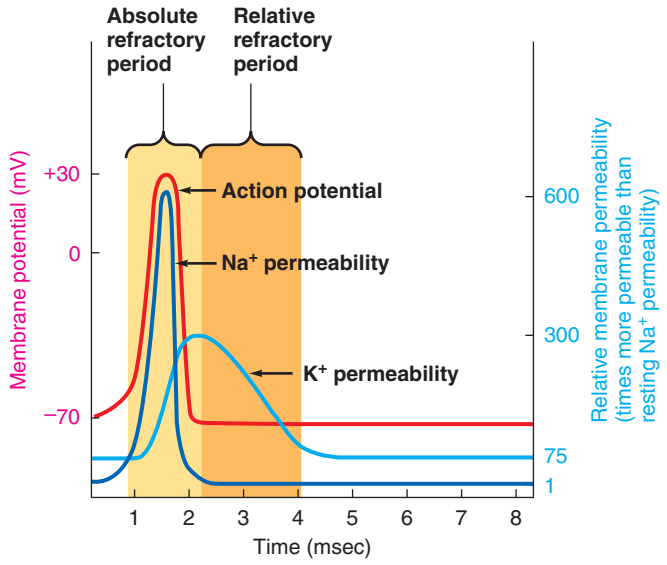

**● FIGURE 4-11**

**Value of the refractory period.** "Backward" current flow is prevented by the refractory period. During an action potential and slightly beyond, an area cannot be restimulated by normal events to undergo another action potential. Thus the refractory period ensures that an action potential can be propagated only in the forward direction along the axon.

tials were to move in both directions, the situation would be chaotic, with numerous action potentials bouncing back and forth along the axon until the nerve cell eventually fatigued. Fortunately, neurons are saved from this fate of oscillating action potentials by the **refractory period**, during which a new action potential cannot be initiated by normal events in a region that has just undergone an action potential.

The refractory period has two components: the *absolute refractory period* and the *relative refractory period*. During the time that a particular patch of axonal membrane is undergoing an action potential, it cannot initiate another action potential, no matter how strongly a triggering event stimulates it. This time period when a recently activated patch of membrane is completely refractory (meaning "stubborn," or unresponsive) to further stimulation is known as the **absolute refractory period** (● Figure 4-12). Once the voltage-gated $Na^+$ channels have flipped to their open, or activated, state, they cannot be triggered to open again in response to another depolarizing triggering event, no matter how strong, until resting potential is restored and the channels are reset to their original positions. Accordingly, the absolute refractory period lasts the entire time from opening of the voltage-gated $Na^+$ channels' activation gates at threshold, through closure of their inactivation gates at the peak of the action potential, until the return to resting potential when the channels' activation gates close and inactivation gates open once again; that is, until the channels are in their "closed but capable of opening" conformation. Only then can they respond to another depolarization with an explosive increase in $P_{Na^+}$ to initiate another action potential. Because of this absolute refractory period, one action potential must be over before another can be initiated at the same site. Action potentials cannot overlap or be added one on top of another "piggyback fashion."

Following the absolute refractory period is a **relative refractory period**, during which a second action potential can be produced only by a triggering event considerably stronger than is usually necessary. The relative refractory period occurs during the time when the voltage-gated $K^+$ channels that opened at the peak of the action potential are in the process of closing. During the relative refractory period, $Na^+$




● **FIGURE 4-12**

**Absolute and relative refractory periods.** During the absolute refractory period, the portion of the membrane that has just undergone an action potential cannot be restimulated. This period corresponds to the time during which the $Na^+$ gates are not in their resting conformation. During the relative refractory period, the membrane can be restimulated only by a stronger stimulus than is usually necessary. This period corresponds to the time during which the $K^+$ gates opened during the action potential have not yet closed.

entry in response to another triggering event is opposed by a persistent outward leak of $K^+$ through its not-yet-closed channels, and thus a greater-than-normal depolarizing triggering event is needed to bring the membrane to threshold during the relative refractory period.

By the time the original site has recovered from its refractory period and is capable of being restimulated by normal current flow, the action potential has been rapidly propagated in the forward direction only and is so far away that it can no longer influence the original site. Thus, *the refractory period ensures the one-way propagation of the action potential down the axon away from the initial site of activation.*

## Action potentials occur in all-or-none fashion.

If any portion of the neuronal membrane is depolarized to threshold, an action potential is initiated and relayed along the membrane in undiminished fashion. Furthermore, once threshold has been reached the resultant action potential always goes to maximal height. The reason for this effect is that the changes in voltage during an action potential result from ion movements down concentration and electrical gradients, and these gradients are not affected by the strength of the depolarizing triggering event. A triggering event stronger than one necessary to bring the membrane to threshold does not produce a larger action potential. However, a triggering event that fails to depolarize the membrane to threshold does not trigger an action potential at all. Thus *an excitable membrane either responds to a triggering event with a maximal action potential that spreads nondecrementally throughout the membrane, or it does not respond with an action potential at all.* This property is called the **all-or-none law.**

This all-or-none concept is analogous to firing a gun. Either the trigger is not pulled sufficiently to fire the bullet (threshold is not reached), or it is pulled hard enough to elicit the full firing response of the gun (threshold is reached). Squeezing the trigger harder does not produce a greater explosion. Just as it is not possible to fire a gun halfway, it is not possible to cause a halfway action potential.

The threshold phenomenon allows some discrimination between important and unimportant stimuli or other triggering events. Stimuli too weak to bring the membrane to threshold do not initiate action potentials and therefore do not clutter up the nervous system by transmitting insignificant signals.

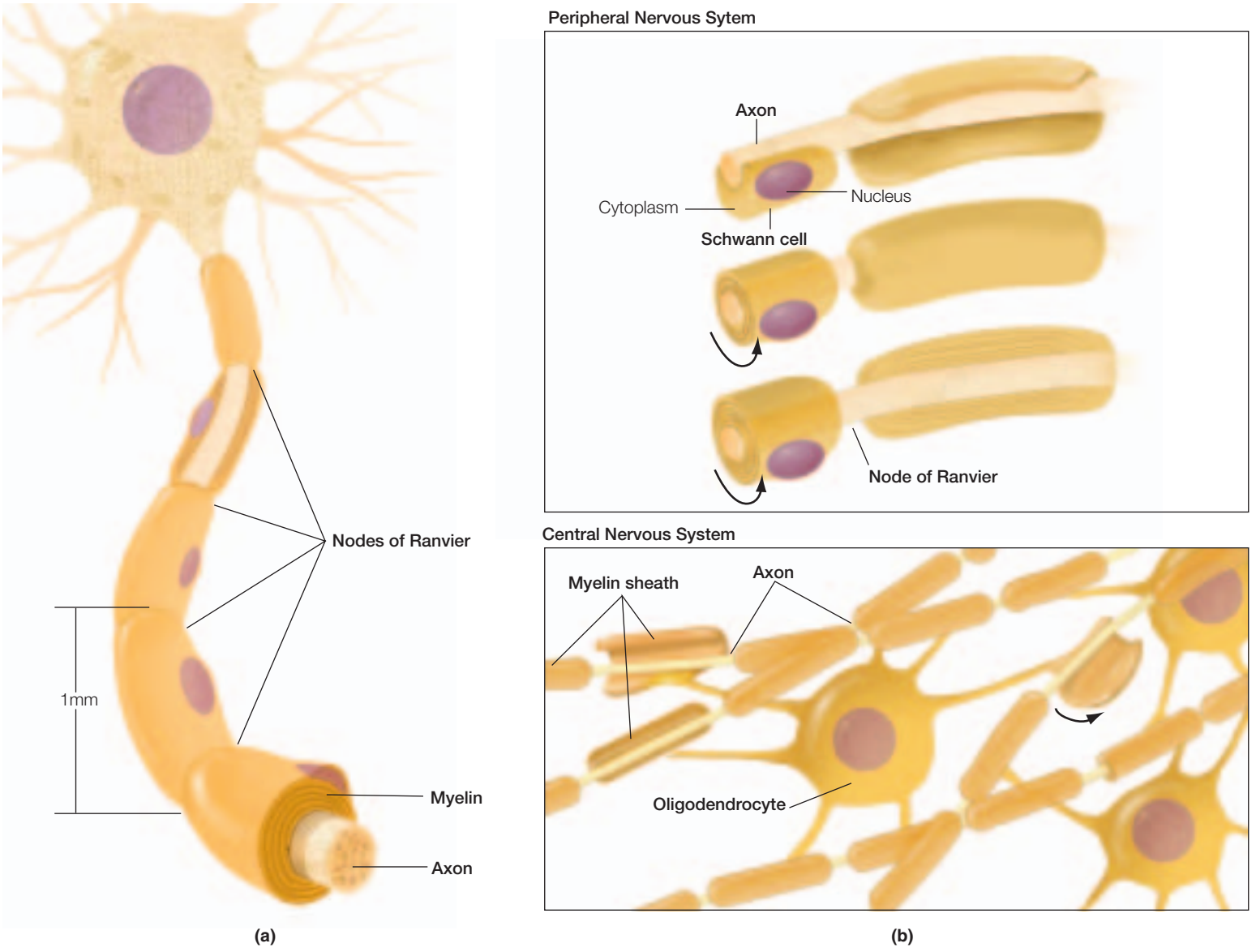
## The strength of a stimulus is coded by the frequency of action potentials.

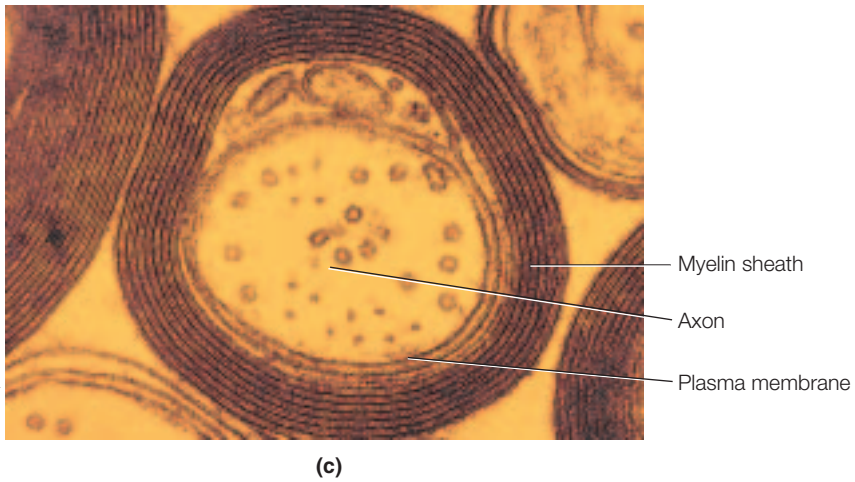
How is it possible to differentiate between two stimuli of varying strengths when both stimuli bring the membrane to threshold and generate action potentials of the same magnitude? For example, how can one distinguish between touching a warm object or touching a very hot object if both trigger identical action potentials in a nerve fiber relaying information about skin temperature to the central nervous system? The answer lies in the *frequency* with which the action potentials are generated. A stronger stimulus does not produce a larger action potential, but it does trigger a greater *number* of action potentials per second. In addition, a stronger stimulus in a region causes more neurons to reach threshold, increasing the total information sent to the central nervous system.

Once initiated, the velocity, or speed, with which an action potential travels down the axon depends on whether the fiber is myelinated. Contiguous conduction occurs in unmyelinated fibers. In this case, as you just learned, each individual action potential initiates an identical new action potential in the next contiguous (bordering) segment of the axon membrane so that every portion of the membrane undergoes an action potential as this electrical signal is conducted from the beginning to the end of the axon. A faster method of propagation, *saltatory conduction,* takes place in myelinated fibers. We are next going to see how a myelinated fiber compares with an unmyelinated fiber, then see how saltatory conduction compares with contiguous conduction.

## Myelination increases the speed of conduction of action potentials.

**Myelinated fibers,** as the name implies, are covered with myelin at regular intervals along the length of the axon (● Figure 4-13a). **Myelin** is composed primarily of lipids. Because the water-soluble ions responsible for carrying current across the membrane cannot permeate this thick lipid barrier, the myelin coating acts as an insulator, just like plastic around an electrical wire, to prevent current leakage across the myelinated portion of the membrane. Myelin is not actually a part of the nerve cell but consists of separate myelin-forming cells that wrap themselves around the axon in jelly-roll fashion




C. Raines/Visuals Unlimited

**● FIGURE 4-13**

**Myelinated fibers.** (a) A myelinated fiber is surrounded by myelin at regular intervals. The intervening unmyelinated regions are known as nodes of Ranvier. (b) In the peripheral nervous system, each patch of myelin is formed by a separate Schwann cell that wraps itself jelly-roll fashion around the nerve fiber. In the central nervous system, each of the several processes ("arms") of a myelin-forming oligodendrocyte forms a patch of myelin around a separate nerve fiber. (c) An electron micrograph of a myelinated fiber in cross section.

(● Figure 4-13b and c). These myelin-forming cells are **oligodendrocytes** in the central nervous system (the brain and spinal cord) and **Schwann cells** in the peripheral nervous system (the nerves running between the central nervous system and the various regions of the body). The lipid composition of myelin is due to the presence of layer on layer of the lipid

bilayer that composes the plasma membrane of these myelin-forming cells. Between the myelinated regions, at the **nodes of Ranvier**, the axonal membrane is bare and exposed to the ECF. Only at these bare spaces can current flow across the membrane to produce action potentials. Voltage-gated $Na^+$ channels are concentrated at the nodes, whereas the myelin-covered regions are almost devoid of these special passageways. By contrast, an unmyelinated fiber has a high density of voltage-gated $Na^+$ channels throughout its entire length. As you now know, action potentials can be generated only at portions of the membrane furnished with an abundance of these channels.

The nodes are usually about 1 mm apart, short enough that local current from an active node can reach an adjacent node before dying off. When an action potential occurs at one node, opposite charges attract from the adjacent inactive node, reducing its potential to threshold so that it undergoes an action potential, and so on. Consequently, in a myelinated fiber, the impulse "jumps" from node to node, skipping over the myelinated sections of the axon; this process is called *saltatory conduction* (*saltere* means "to jump or leap"). Saltatory conduction propagates action potentials more rapidly than does contiguous conduction, because the action potential does not have to be regenerated at myelinated sections but must be regenerated within every section of an unmyelinated axonal membrane from beginning to end. Myelinated fibers conduct impulses about 50 times faster than unmyelinated fibers of comparable size. Thus the most urgent types of information are transmitted via myelinated fibers, whereas nervous pathways carrying less urgent information are unmyelinated.


**Multiple sclerosis (MS)** is a pathophysiological condition in which nerve fibers in various locations throughout the nervous system become demyelinated (lose their myelin). MS is an autoimmune disease, in which the body's defense system erroneously attacks the myelin sheath surrounding myelinated nerve fibers (*auto* means "self"; *immune* means "defense against"). Loss of myelin slows transmission of impulses in the affected neurons. A hardened scar known as a *sclerosis* (meaning "hardness") forms at the multiple sites of myelin damage. These scars further interfere with and can eventually block action potential propagation in the underlying axons. The symptoms of MS vary considerably, depending on the extent and location of the myelin damage.

You have now seen how an action potential is propagated along the axon. But what happens when an action potential reaches the end of the axon? We are going to now turn our attention to this topic.


Click on the Media Exercises menu of the CD-ROM and work Media Exercises 4.1: Basics of a Neuron and 4.2: Graded Potentials and Action Potentials to test your understanding of the previous sections.

## SYNAPSES AND NEURONAL INTEGRATION

When the action potential reaches the axon terminals, they release a chemical messenger that alters the activity of the cells on which the neuron terminates. A neuron may terminate on one of three structures: a muscle, a gland, or another neuron. Therefore, depending on where a neuron terminates, it can cause a muscle cell to contract, a gland cell to secrete, another neuron to convey an electrical message along a nerve pathway, or some other function. When a neuron terminates on a muscle or a gland, the neuron is said to **innervate**, or supply, the structure. The junctions between nerves and the muscles and glands that they innervate will be described later. For now we will concentrate on the junction between two neurons—a **synapse.** (Sometimes the term *synapse* is used to describe a junction between any two excitable cells, but we will reserve this term for the junction between two neurons.)

### Synapses are junctions between presynaptic and postsynaptic neurons.

Typically, a synapse involves a junction between an axon terminal of one neuron, known as the *presynaptic neuron,* and the dendrites or cell body of a second neuron, known as the *postsynaptic neuron.* (*Pre* means "before" and *post* means "after"; the presynaptic neuron lies before the synapse and the postsynaptic neuron lies after the synapse.) The dendrites and to a lesser extent the cell body of most neurons receive thousands of synaptic inputs, which are axon terminals from many other neurons. It has been estimated that some neurons within the central nervous system receive as many as 100,000 synaptic inputs (● Figure 4-14).

The anatomy of one of these thousands of synapses is shown in ● Figure 4-15a. The axon terminal of the **presynaptic neuron**, which conducts its action potentials *toward* the synapse, ends in a slight swelling, the **synaptic knob.** The synaptic knob contains **synaptic vesicles**, which store a specific chemical messenger, a **neurotransmitter** that has been synthesized and packaged by the presynaptic neuron. The synaptic knob comes into close proximity to, but does not actually directly touch, the **postsynaptic neuron**, the neuron whose action potentials are propagated *away* from the synapse. The space between the presynaptic and postsynaptic neurons, the **synaptic cleft**, is too wide for the direct spread of current from one cell to the other and therefore prevents action potentials from electrically passing between the neurons. The portion of the postsynaptic membrane immediately underlying the synaptic knob is referred to as the **subsynaptic membrane** (*sub* means "under").

Synapses operate in one direction only; that is, the presynaptic neuron brings about changes in membrane potential of the postsynaptic neuron, but the postsynaptic neuron does not directly influence the potential of the presynaptic neuron. The reason for this becomes readily apparent when you examine the events that occur at a synapse.

### A neurotransmitter carries the signal across a synapse.

Here are the events that occur at a synapse (● Figure 4-15):

1. When an action potential in a presynaptic neuron has been propagated to the axon terminal (step 1 in ● Fig-

ure 4-15), this local change in potential triggers the opening of voltage-gated $Ca^{2+}$ channels in the synaptic knob.
2. Because $Ca^{2+}$ is much more highly concentrated in the ECF and its electrical gradient is inward, this ion flows into the synaptic knob through the opened channels (step 2).
3. $Ca^{2+}$ induces the release of a neurotransmitter from some of the synaptic vesicles into the synaptic cleft (step 3). The release is accomplished by exocytosis (see p. 24).
4. The released neurotransmitter diffuses across the cleft and binds with specific protein receptor sites on the subsynaptic membrane (step 4).
5. This binding triggers the opening of specific ion channels in the subsynaptic membrane, changing the ion permeability of the postsynaptic neuron (step 5). These are chemically gated channels, in contrast to the voltage-gated channels responsible for the action potential and for the $Ca^{2+}$ influx into the synaptic knob.

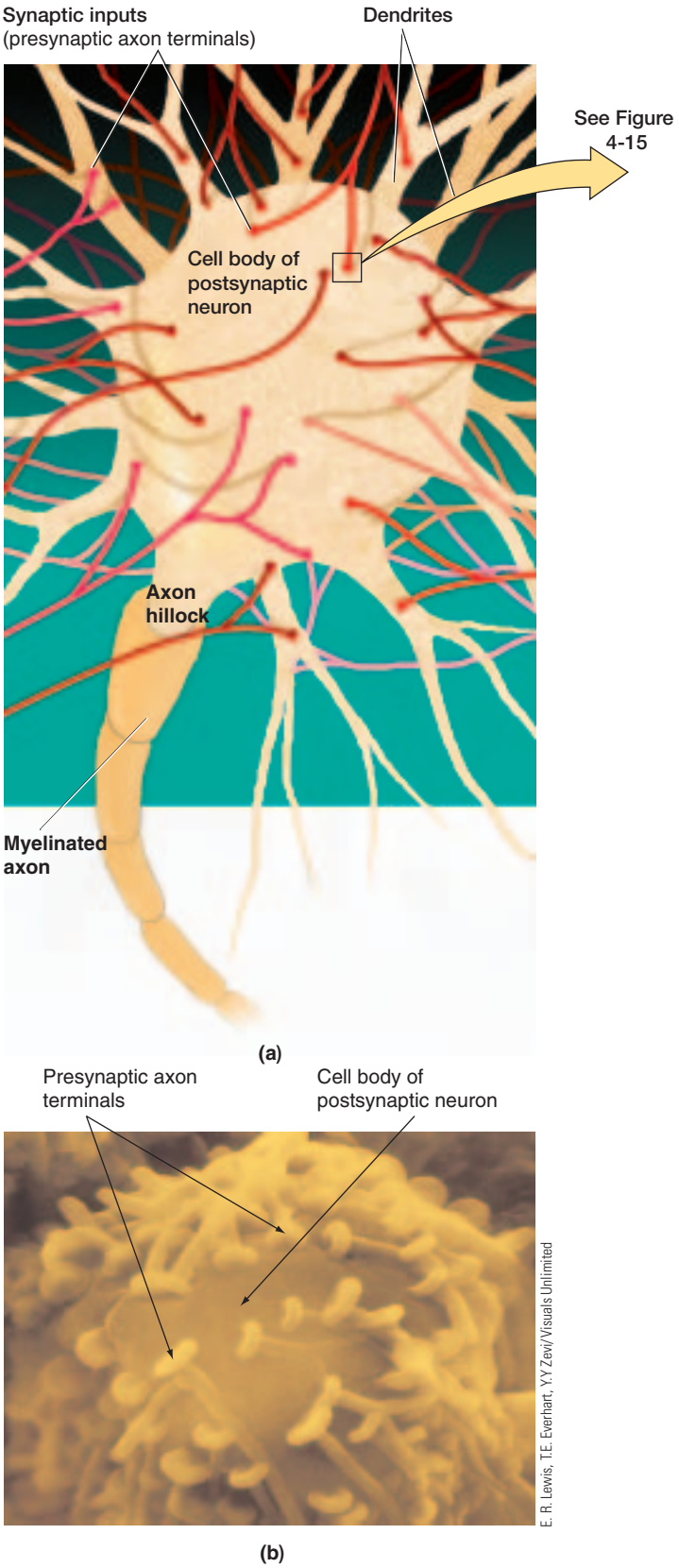
Because the presynaptic terminal releases the neurotransmitter and the subsynaptic membrane of the postsynaptic neuron has receptor sites for the neurotransmitter, the synapse can operate only in the direction from presynaptic to postsynaptic neuron.

## Some synapses excite whereas others inhibit the postsynaptic neuron.

Each presynaptic neuron typically releases only one neurotransmitter; however, different neurons vary in the neurotransmitter they release. On binding with their subsynaptic receptor sites, different neurotransmitters cause different ion permeability changes. There are two types of synapses, depending on the permeability changes induced in the postsynaptic neuron by the combination of a specific neurotransmitter with its receptor sites: *excitatory synapses* and *inhibitory synapses*.

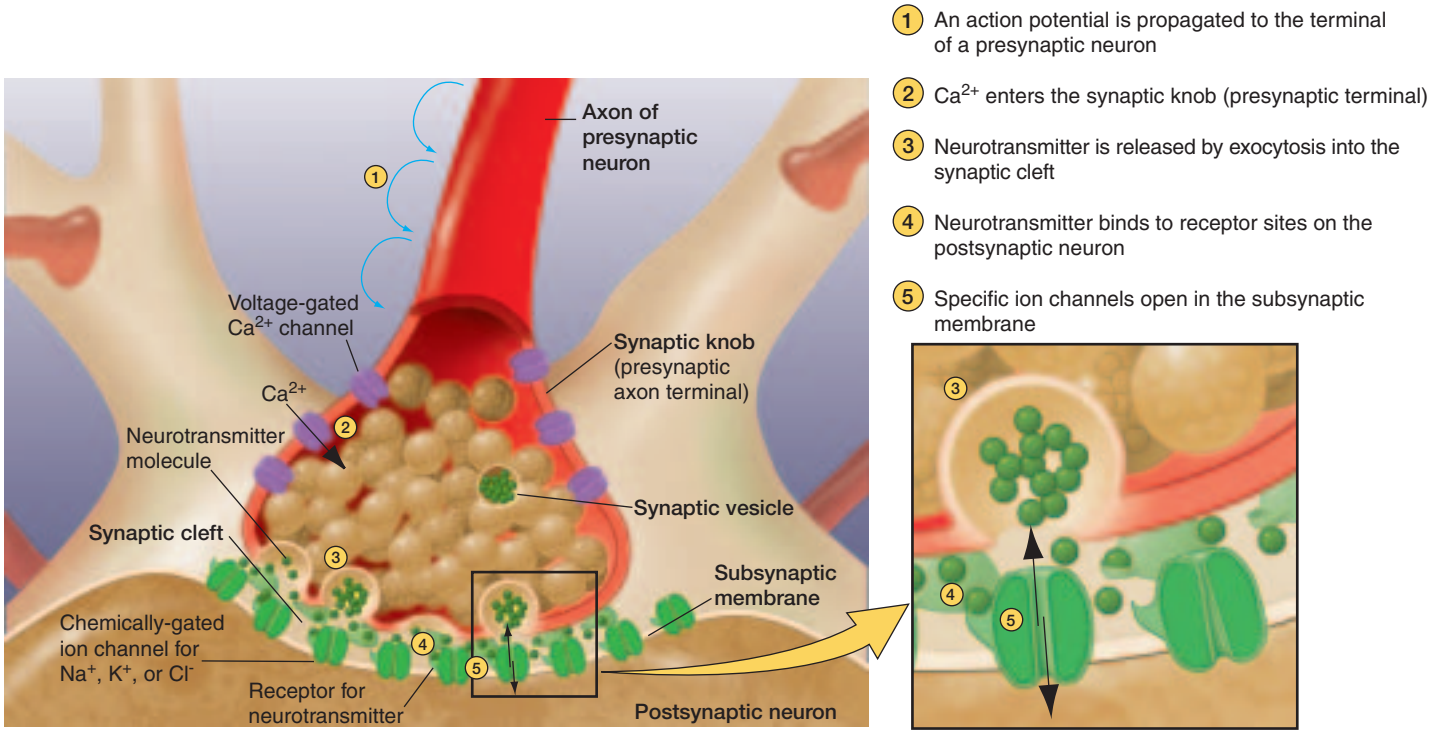
### EXCITATORY SYNAPSES

At an **excitatory synapse**, the response to the binding of a neurotransmitter to the receptor is the opening of nonspecific cation channels within the subsynaptic membrane that permit simultaneous passage of $Na^+$ and $K^+$ through them. (These are a different type of channel from those you have encountered before.) Thus permeability to both these ions is increased at the same time. How much of each ion diffuses through an open cation channel depends on their electrochemical gradients. At resting potential, both the concentration and electrical gradients for $Na^+$ favor its movement into the postsynaptic neuron, whereas only the concentration gradient for $K^+$ favors its movement outward. Therefore, the permeability change induced at an excitatory synapse results in the movement of a few $K^+$ ions out of the postsynaptic neuron, while a relatively larger number of $Na^+$ ions simultaneously enter this neuron. The result is a net movement of positive ions into the cell. This makes the inside of the membrane slightly less negative than at resting potential, thus producing a *small depolarization* of the postsynaptic neuron.




**● FIGURE 4-14**

**Synaptic inputs to a postsynaptic neuron.** (a) Schematic representation of synaptic inputs (presynaptic axon terminals) to the dendrites and cell body of a single postsynaptic neuron. (b) Electron micrograph showing multiple presynaptic axon terminals to a single postsynaptic cell body.




● **FIGURE 4-15**

**Synaptic structure and function.** (a) Schematic representation of the structure of a single synapse. The circled numbers designate the sequence of events that take place at a synapse. (b) A blow-up depicting the release by exocytosis of neurotransmitter from the presynaptic axon terminal and its subsequent binding with receptor sites specific for it on the subsynaptic membrane of the postsynaptic neuron.

PhysioEdge For an animation of this figure, click the Synapses and Neural Integration tab in the Neuronal Physiology and Hormonal Communication tutorial on the CD-ROM.

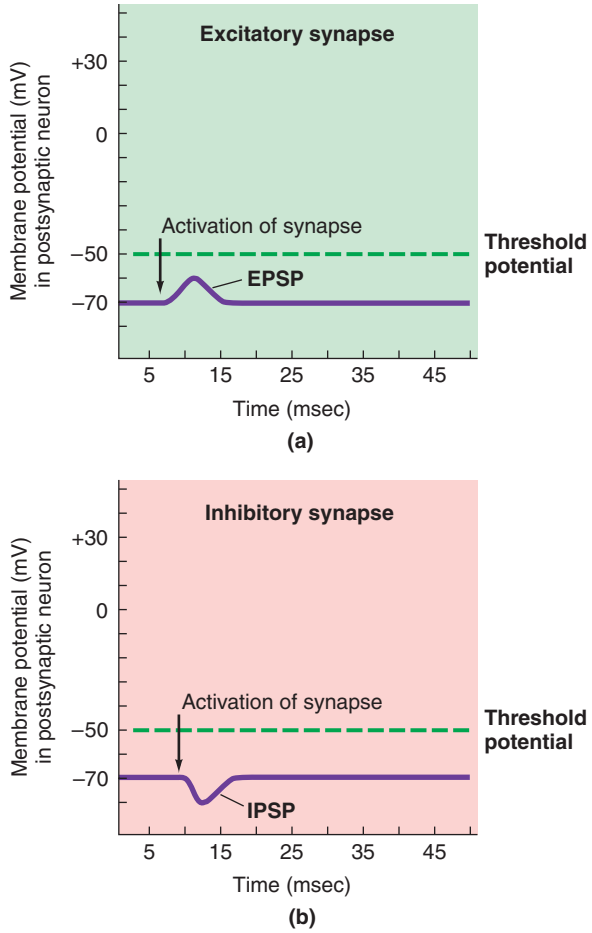
Activation of one excitatory synapse can rarely depolarize the postsynaptic neuron sufficiently to bring it to threshold. Too few channels are involved at a single subsynaptic membrane to permit adequate ion flow to reduce the potential to threshold. This small depolarization, however, does bring the membrane of the postsynaptic neuron closer to threshold, increasing the likelihood that threshold will be reached (in response to further excitatory input) and an action potential will occur. That is, the membrane is now more excitable (easier to bring to threshold) than when at rest. Accordingly, this postsynaptic potential change occurring at an excitatory synapse is called an **excitatory postsynaptic potential**, or **EPSP** (● Figure 4-16a).

## INHIBITORY SYNAPSES

At an **inhibitory synapse**, the binding of a different released neurotransmitter with its receptor sites increases the permeability of the subsynaptic membrane to either $K^+$ or $Cl^-$. In either case, the resulting ion movements bring about a *small hyperpolarization* of the postsynaptic neuron—that is, greater internal negativity. In the case of increased $P_{K^+}$, more positive charges leave the cell via $K^+$ efflux, leaving more negative charges behind on the inside; in the case of increased $P_{Cl^-}$, negative charges enter the cell in the form of $Cl^-$ ions, because $Cl^-$ concentration is higher outside the cell. This small hyperpolarization moves the membrane potential even farther away from threshold (● Figure 4-16b), lessening the likelihood that the postsynaptic neuron will reach threshold and undergo an action potential. That is, the membrane is now less excitable (harder to bring to threshold by excitatory input) than when it is at resting potential. The membrane is said to be inhibited under these circumstances, and the small hyperpolarization of the postsynaptic cell is called an **inhibitory postsynaptic potential**, or **IPSP**.

## SYNAPTIC DELAY

This conversion of the electrical signal in the presynaptic neuron (an action potential) to an electrical signal in the postsynaptic neuron (either an EPSP or IPSP) by chemical means (via the neurotransmitter–receptor combination) takes time. This **synaptic delay** is usually about 0.5 to 1 msec. In a neural pathway, chains of neurons often must be traversed. The more complex the pathway, the more synaptic delays, and the longer the *total reaction time* (the time required to respond to a particular event).




● **FIGURE 4-16**

**Postsynaptic potentials.** (a) Excitatory synapse. An excitatory postsynaptic potential (EPSP) brought about by activation of an excitatory presynaptic input brings the postsynaptic neuron closer to threshold potential. (b) Inhibitory synapse. An inhibitory postsynaptic potential (IPSP) brought about by activation of an inhibitory presynaptic input moves the postsynaptic neuron farther from threshold potential.

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For an animation of this figure, click the Synapses and Neural Integration tab in the Neuronal Physiology and Hormonal Communication tutorial on the CD-ROM.

## Each synapse is either always excitatory or always inhibitory.

Many different chemicals serve as neurotransmitters (▲ Table 4-2). Even though neurotransmitters vary from synapse to synapse, the same neurotransmitter is always released at a particular synapse. Furthermore, at a given synapse, binding of a neurotransmitter with its appropriate subsynaptic receptors always leads to the same change in permeability and resultant change in potential of the postsynaptic membrane. That is, the response to a given neurotransmitter–receptor combination is always constant. *Each synapse is either always excitatory or always inhibitory.* It does not give rise to an EPSP under one circumstance and produce an IPSP at another time. As examples, *glutamate* is a common excitatory neurotransmitter and *gamma-aminobutyric acid (GABA)* is a common inhibitory neurotransmitter in the central nervous system.

▲ **TABLE 4-2**

Some Common Neurotransmitters

| | |
|---|---|
| Acetylcholine | Histamine |
| Dopamine | Glycine |
| Norepinephrine | Glutamate |
| Epinephrine | Aspartate |
| Serotonin | Gamma-aminobutyric acid (GABA) |

## Neurotransmitters are quickly removed from the synaptic cleft.

As long as the neurotransmitter remains bound to the receptor sites, the alteration in membrane permeability responsible for the EPSP or IPSP continues. The neurotransmitter must be inactivated or removed after it has produced the appropriate response in the postsynaptic neuron, however, so that the postsynaptic "slate" is "wiped clean," leaving it ready to receive additional messages from the same or other presynaptic inputs. Thus, after combining with the postsynaptic receptor, chemical transmitters are removed and the response is terminated. Several mechanisms can remove the neurotransmitter: It may diffuse away from the synaptic cleft, be inactivated by specific enzymes within the subsynaptic membrane, or be actively taken back up into the axon terminal by transport mechanisms in the presynaptic membrane. The method employed depends on the particular synapse.

## The grand postsynaptic potential depends on the sum of the activities of all presynaptic inputs.

The events that occur at a single synapse result in either an EPSP or an IPSP at the postsynaptic neuron. But if a single EPSP is inadequate to bring the postsynaptic neuron to threshold and an IPSP moves it even farther from threshold, how can an action potential be initiated in the postsynaptic neuron? The answer lies in the thousands of presynaptic inputs that a typical neuronal cell body receives from many other neurons. Some of these presynaptic inputs may be carrying sensory information from the environment; some may be signaling internal changes in homeostatic balance; others may be transmitting signals from control centers in the brain; and still others may arrive carrying other bits of information. At any given time, any number of these presynaptic neurons (probably hundreds) may be firing and thus influencing the postsynaptic neuron's level of activity. The total potential in the post-

synaptic neuron, the **grand postsynaptic potential (GPSP)**, is a composite of all EPSPs and IPSPs occurring at approximately the same time.

The postsynaptic neuron can be brought to threshold in two ways: (1) *temporal summation* and (2) *spatial summation*. To illustrate these methods of summation, we will examine the possible interactions of three presynaptic inputs—two excitatory inputs (Ex1 and Ex2) and one inhibitory input (In1)—on a hypothetical postsynaptic neuron (● Figure 4-17). The recording shown in the figure represents the potential in the postsynaptic cell. Bear in mind during our discussion of this simplified version that many thousands of synapses are actually interacting in the same way on a single cell body and its dendrites.

## TEMPORAL SUMMATION

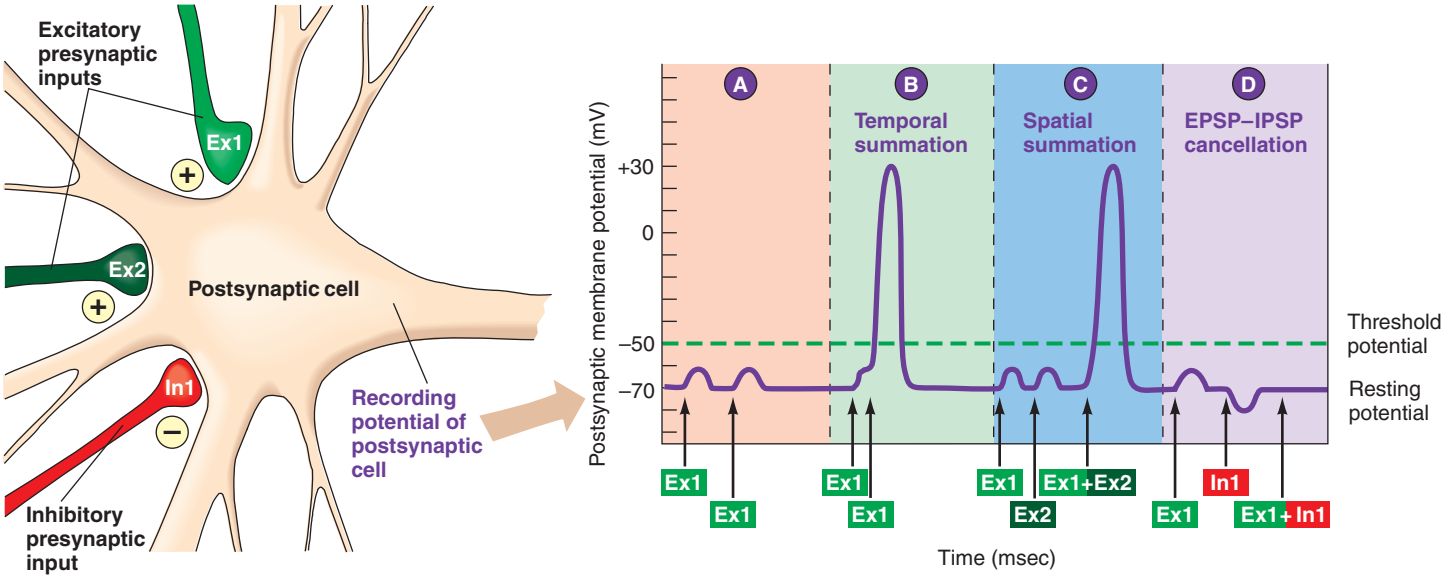
Suppose that Ex1 has an action potential that causes an EPSP in the postsynaptic neuron. If another action potential occurs later in Ex1, an EPSP of the same magnitude takes place (panel A in ● Figure 4-17). Next suppose that Ex1 has two action potentials in close succession (panel B). The first action potential in Ex1 produces an EPSP in the postsynaptic membrane. While the postsynaptic membrane is still partially depolarized from this first EPSP, the second action potential in Ex1 produces a second EPSP. The second EPSP adds on to the first EPSP, bringing the membrane to threshold, so an action potential occurs in the postsynaptic neuron. Graded potentials do not have a refractory period, so this additive effect is possible.

The summing of several EPSPs occurring very close together in time because of successive firing of a single presynaptic neuron is known as **temporal summation** (*tempus* means "time"). In reality, the situation is much more complex than just described. The sum of up to 50 EPSPs might be needed to bring the postsynaptic membrane to threshold. Each action potential in a single presynaptic neuron triggers the emptying of a certain number of synaptic vesicles. The amount of neurotransmitter released and the resultant magnitude of the change in postsynaptic potential are thus directly related to the frequency of presynaptic action potentials. One way, then,

● **FIGURE 4-17**

**Determination of the grand postsynaptic potential by the sum of activity in the presynaptic inputs.** Two excitatory (*Ex*1 and *Ex*2) and one inhibitory (*In*1) presynaptic inputs terminate on this hypothetical postsynaptic neuron. The potential of the postsynaptic neuron is being recorded.

PhysioEdge For an animation of this figure, click the Synapses and Neural Integration tab in the Neuronal Physiology and Hormonal Communication tutorial on the CD-ROM.




**Panel A** If an excitatory presynaptic input (Ex1) is stimulated a second time after the first EPSP in the postsynaptic cell has died off, a second EPSP of the same magnitude will occur.

**Panel B** If, however, Ex1 is stimulated a second time before the first EPSP has died off, the second EPSP will add onto, or sum with, the first EPSP, resulting in *temporal summation*, which may bring the postsynaptic cell to threshold.

**Panel C** The postsynaptic cell may also be brought to threshold by *spatial summation* of EPSPs that are initiated by simultaneous activation of two (Ex1 and Ex2) or more excitatory presynaptic inputs.

**Panel D** Simultaneous activation of an excitatory (Ex1) and inhibitory (In1) presynaptic input does not change the postsynaptic potential, because the resultant EPSP and IPSP cancel each other out.

in which the postsynaptic membrane can be brought to threshold is through rapid, repetitive excitation from a single persistent input.

### SPATIAL SUMMATION

Let us now see what happens in the postsynaptic neuron if both excitatory inputs are stimulated simultaneously (panel C). An action potential in either Ex1 or Ex2 will produce an EPSP in the postsynaptic neuron; however, neither of these alone brings the membrane to threshold to elicit a postsynaptic action potential. But simultaneous action potentials in Ex1 and Ex2 produce EPSPs that add to each other, bringing the postsynaptic membrane to threshold, so an action potential does occur. The summation of EPSPs originating simultaneously from several different presynaptic inputs (that is, from different points in "space") is known as **spatial summation.** A second way, therefore, to elicit an action potential in a postsynaptic cell is through concurrent activation of several excitatory inputs. Again, in reality up to 50 simultaneous EPSPs are required to bring the postsynaptic membrane to threshold.

Similarly, IPSPs can undergo temporal and spatial summation. As IPSPs add together, however, they progressively move the potential further from threshold.

### CANCELLATION OF CONCURRENT EPSPS AND IPSPS

If an excitatory and an inhibitory input are simultaneously activated, the concurrent EPSP and IPSP more or less cancel each other out. The extent of cancellation depends on their respective magnitudes. In most cases, the postsynaptic membrane potential remains close to resting (panel D).

### IMPORTANCE OF POSTSYNAPTIC NEURONAL INTEGRATION

The magnitude of the GPSP depends on the sum of activity in all the presynaptic inputs and in turn determines whether or not the neuron will undergo an action potential to pass information on to the cells on which the neuron terminates. The following oversimplified real-life example demonstrates the benefits of this neuronal integration. The explanation is not completely accurate technically, but the principles of summation are accurate.

Assume for simplicity's sake that urination is controlled by a postsynaptic neuron that innervates the urinary bladder. When this neuron fires, the bladder contracts. (Actually, voluntary control of urination is accomplished by postsynaptic integration at the neuron controlling the external urethral sphincter rather than the bladder itself.) As the bladder starts to fill with urine and becomes stretched, a reflex is initiated that ultimately produces EPSPs in the postsynaptic neuron responsible for causing bladder contraction. Partial filling of the bladder does not cause enough excitation to bring the neuron to threshold, so urination does not take place (panel A of ● Figure 4-17). As the bladder becomes progressively filled, the frequency of action potentials progressively increases in the presynaptic neuron that signals the postsynaptic neuron of the extent of bladder filling (Ex1 in panel B of ● Figure 4-17). When the frequency becomes great enough that the EPSPs are temporally summed to threshold, the postsynaptic neuron undergoes an action potential that stimulates bladder contraction.

What if the time is inopportune for urination to take place? IPSPs can be produced at the bladder postsynaptic neuron by presynaptic inputs originating in higher levels of the brain responsible for voluntary control (In1 panel D of ● Figure 4-17). These "voluntary" IPSPs in effect cancel out the "reflex" EPSPs triggered by stretching of the bladder. Thus the postsynaptic neuron remains at resting potential and does not have an action potential, so the bladder is prevented from contracting and emptying even though it is full.

What if a person's bladder is only partially filled, so that the presynaptic input originating from this source is insufficient to bring the postsynaptic neuron to threshold to cause bladder contraction, and yet he or she needs to supply a urine specimen for laboratory analysis? The person can voluntarily activate an excitatory presynaptic neuron (Ex2 in panel C of ● Figure 4-17). The EPSPs originating from this neuron and the EPSPs of the reflex-activated presynaptic neuron (Ex1) are spatially summed to bring the postsynaptic neuron to threshold. This achieves the action potential necessary to stimulate bladder contraction, even though the bladder is not full.

This example illustrates the importance of postsynaptic neuronal integration. Each postsynaptic neuron in a sense "computes" all the input it receives and makes a "decision" about whether to pass the information on (that is, whether threshold is reached and an action potential is transmitted down the axon). In this way, neurons serve as complex computational devices, or integrators. The dendrites function as the primary processors of incoming information. They receive and tally the signals coming in from all the presynaptic neurons. Each neuron's output in the form of frequency of action potentials to other cells (muscle cells, gland cells, or other neurons) reflects the balance of activity in the inputs it receives via EPSPs or IPSPs from the thousands of other neurons that terminate on it. Each postsynaptic neuron filters out and does not pass on information it receives that is not significant enough to bring it to threshold. If every action potential in every presynaptic neuron that impinges on a particular postsynaptic neuron were to cause an action potential in the postsynaptic neuron, the neuronal pathways would be overwhelmed with trivia. Only if an excitatory presynaptic signal is reinforced by other supporting signals through summation will the information be passed on. Furthermore, interaction of postsynaptic potentials provides a way for one set of signals to offset another set (IPSPs negating EPSPs). This allows a fine degree of discrimination and control in determining what information will be passed on.

Let us now see why action potentials are initiated at the axon hillock.

## Action potentials are initiated at the axon hillock because it has the lowest threshold.

Threshold potential is not uniform throughout the postsynaptic neuron. The lowest threshold is present at the axon

hillock, because this region has a much greater density of voltage-gated $Na^+$ channels than anywhere else in the neuron. This greater density of these voltage-sensitive channels makes the axon hillock considerably more responsive to changes in potential than the dendrites or remainder of the cell body. The latter regions have a significantly higher threshold than the axon hillock. Because of local current flow, changes in membrane potential (EPSPs or IPSPs) occurring anywhere on the dendrites or cell body spread throughout the dendrites, cell body, and axon hillock. When summation of EPSPs takes place, the lower threshold of the axon hillock is reached first, whereas the dendrites and cell body at the same potential are still considerably below their own, much higher thresholds. Therefore, an action potential originates in the axon hillock and is propagated from there to the end of the axon.

## Neuropeptides act primarily as neuromodulators.

Researchers recently discovered that in addition to the classical neurotransmitters just described, some neurons also release neuropeptides. **Neuropeptides** are larger than classical neurotransmitters and are cosecreted along with the neurotransmitter. Most neuropeptides function as neuromodulators. **Neuromodulators** are chemical messengers that do not cause the formation of EPSPs or IPSPs, but rather bring about long-term changes that subtly *modulate*—depress or enhance—the action of the synapse. They bind to neuronal receptors at nonsynaptic sites—that is, not at the subsynaptic membrane. Neuromodulators may act at either presynaptic or postsynaptic sites. For example, a neuromodulator may influence the level of an enzyme involved in the synthesis of a neurotransmitter by a presynaptic neuron, or it may alter the sensitivity of the postsynaptic neuron to a particular neurotransmitter by causing long-term changes in the number of subsynaptic receptor sites for the neurotransmitter. Thus neuromodulators delicately fine-tune the synaptic response. The effect may last for days or even months or years. Whereas neurotransmitters are involved in rapid communication between neurons, neuromodulators are involved with more long-lasting events, such as learning and motivation.

## Drugs and diseases can modify synaptic transmission.


The vast majority of drugs that influence the nervous system perform their function by altering synaptic mechanisms. Synaptic drugs may block an undesirable effect or enhance a desirable effect. Possible drug actions include (1) altering the synthesis, storage, or release of a neurotransmitter; (2) modifying neurotransmitter interaction with the postsynaptic receptor; (3) influencing neurotransmitter reuptake or destruction; and (4) replacing a deficient neurotransmitter with a substitute transmitter.

For example, the socially abused drug **cocaine** blocks the reuptake of the neurotransmitter *dopamine* at presynaptic terminals. It does so by binding competitively with the dopamine reuptake transporter, which is a protein molecule that picks up released dopamine from the synaptic cleft and shuttles it back to the axon terminal. With cocaine occupying the dopamine transporter, dopamine remains in the synaptic cleft longer than usual and continues to interact with its postsynaptic receptor sites. The result is prolonged activation of neural pathways that use this chemical as a neurotransmitter. Among these pathways are those that play a role in emotional responses, especially feelings of pleasure. In essence, when cocaine is present the neural switches in the pleasure pathway are locked in the "on" position.

Cocaine is addictive because it causes long-term molecular adaptations of the involved neurons such that they cannot transmit normally across synapses without increasingly higher doses of the drug. Because the postsynaptic cells are incessantly stimulated for an extended time, they become accustomed or adapt to "expecting" this high level of stimulation; that is, they are "hooked" on the drug. The term **tolerance** refers to this *desensitization* to an addictive drug so that the user needs greater quantities of the drug to achieve the same effect. Specifically, with prolonged use of cocaine, the number of dopamine receptors in the brain is reduced in response to the glut of the abused substance. As a result of this desensitization, the user must steadily increase the dosage of the drug to get the same "high," or sensation of pleasure. When the cocaine molecules diffuse away, the sense of pleasure evaporates, because the normal level of dopamine activity does not sufficiently "satisfy" the overly needy demands of the postsynaptic cells for stimulation. Cocaine users reaching this low become frantic and profoundly depressed. Only more cocaine makes them feel good again. But repeated use of cocaine modifies responsiveness to the drug. Over the course of abuse, the user often no longer can derive pleasure from the drug but suffers unpleasant *withdrawal symptoms* once the effect of the drug has worn off. Furthermore, the amount of cocaine needed to overcome the devastating crashes progressively increases. The user typically becomes **addicted** to the drug, compulsively seeking out and taking the drug at all costs, first to experience the pleasurable sensations and later to avoid the negative withdrawal symptoms, even when the drug no longer provides pleasure. Cocaine is abused by millions who have become addicted to its mind-altering properties, with devastating social and economic effects.

Whereas cocaine abuse leads to excessive dopamine activity, **Parkinson's disease** is attributable to a deficiency of dopamine in the *basal nuclei,* a region of the brain involved in controlling complex movements. This movement disorder is characterized by muscle rigidity and involuntary tremors at rest. The standard treatment for Parkinson's disease is the administration of *levodopa* (L-dopa), a precursor of dopamine. Dopamine itself cannot be administered because it is unable to cross the blood–brain barrier (discussed in the following chapter), but L-dopa can enter the brain from the blood. Once inside the brain, L-dopa is converted into dopamine, thus substituting for the deficient neurotransmitter. This therapy greatly alleviates the symptoms associated with the deficit in most patients. You will learn more about this condition when we discuss the basal nuclei.

Synaptic transmission is also vulnerable to neural toxins, which may cause nervous system disorders by acting at either presynaptic or postsynaptic sites. For example, **tetanus toxin** prevents the release of the neurotransmitter GABA from inhibitory presynaptic inputs terminating at neurons that supply skeletal muscles. Unchecked excitatory inputs to these neurons result in uncontrolled muscle spasms. These spasms occur especially in the jaw muscles early in the disease, giving rise to the common name of *lockjaw* for this condition. Later they progress to the muscles responsible for breathing, at which point death occurs.

Other drugs and diseases that influence synaptic transmission are too numerous to mention, but as these examples illustrate, any site along the synaptic pathway is vulnerable to interference.

## Neurons are linked through complex converging and diverging pathways.

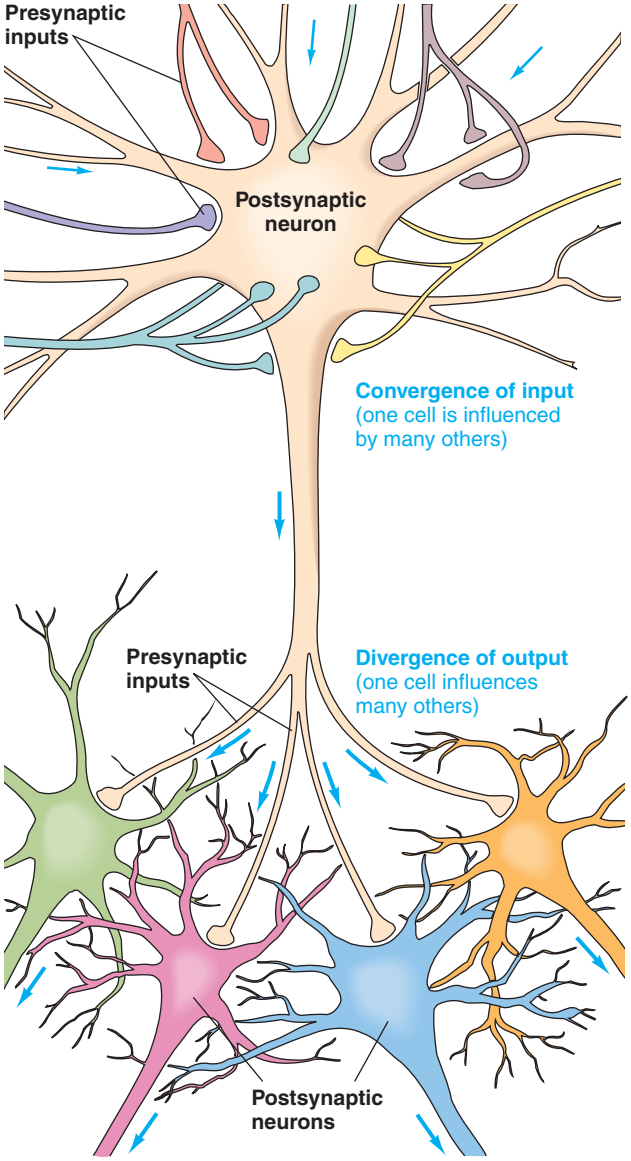
Two important relationships exist between neurons: convergence and divergence. A given neuron may have many other neurons synapsing on it. Such a relationship is known as **convergence** (● Figure 4-18). Through this converging input, a single cell is influenced by thousands of other cells. This single cell, in turn, influences the level of activity in many other cells by divergence of output. The term **divergence** refers to the branching of axon terminals so that a single cell synapses with and influences many other cells.

Note that a particular neuron is postsynaptic to the neurons converging on it but presynaptic to the other cells at which it terminates. Thus the terms *presynaptic* and *postsynaptic* refer only to a single synapse. Most neurons are presynaptic to one group of neurons and postsynaptic to another group.

There are an estimated 100 billion neurons and $10^{14}$ (100 quadrillion) synapses in the brain alone! When you consider the vast and intricate interconnections possible between these neurons through converging and diverging pathways, you can begin to imagine how complex the wiring mechanism of our nervous system really is. Even the most sophisticated computers are far less complex than the human brain. The "language" of the nervous system—that is, all communication between neurons—is in the form of graded potentials, action potentials, neurotransmitter signaling across synapses, and other nonsynaptic forms of chemical chatter. All activities for which the nervous system is responsible—every sensation you feel, every command to move a muscle, every thought, every emotion, every memory, every spark of creativity—all depend on the patterns of electrical and chemical signaling between neurons along these complexly wired neural pathways.

A neuron communicates with the cells it influences by releasing a neurotransmitter, but this is only one means of intercellular ("between cell") communication. We will now consider all the ways by which cells can "talk with each other."

PhysioEdge Click on the Media Exercises menu of the CD-ROM and work Media Exercise 4.3: Synapses and Neuronal Integration to test your understanding of the previous section.




● **FIGURE 4-18**

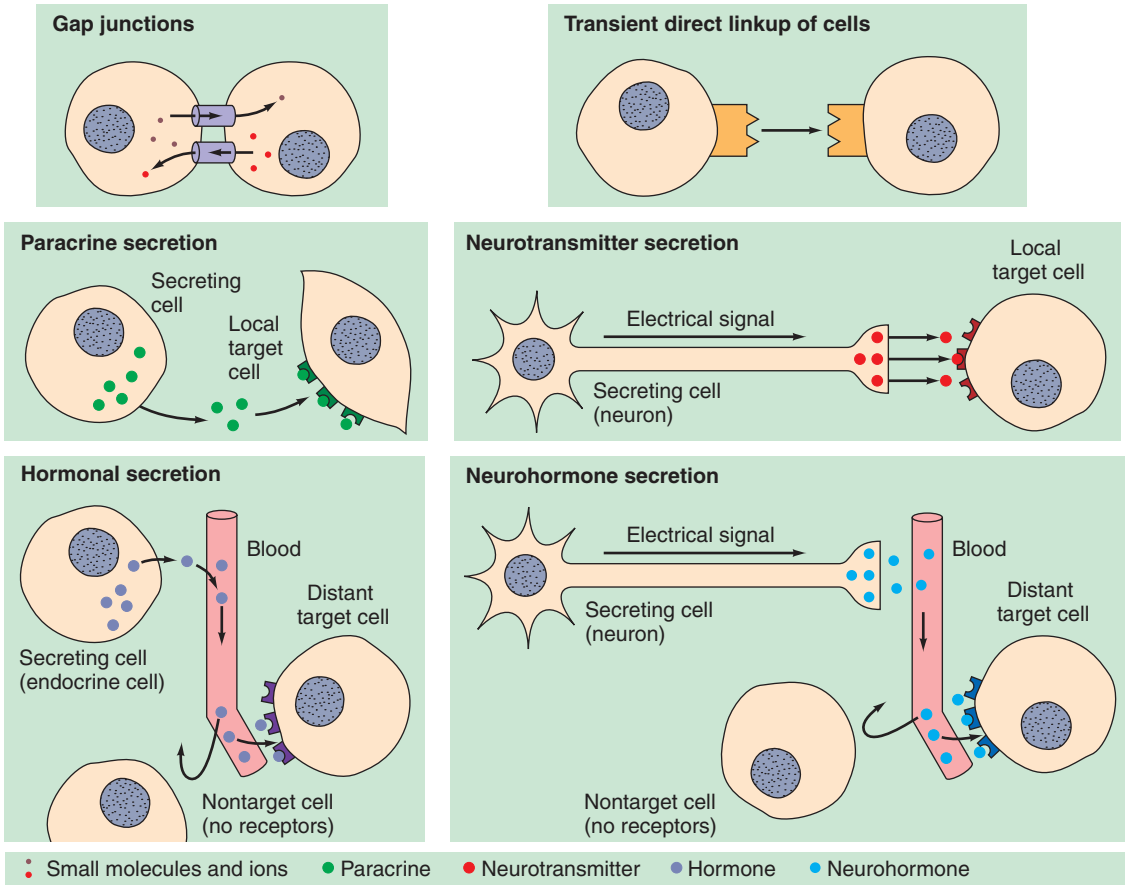
**Convergence and divergence**

# INTERCELLULAR COMMUNICATION AND SIGNAL TRANSDUCTION

Coordination of the diverse activities of cells throughout the body to accomplish life-sustaining and other desired activities depends on the ability of cells to communicate with each other.

## Communication between cells is largely orchestrated by extracellular chemical messengers.

There are three types of intercellular ("between cell") communication (● Figure 4-19):




**● FIGURE 4-19**

**Types of intercellular communication.** Gap junctions and transient direct linkup of cells are both means of direct communication between cells. Paracrines, neurotransmitters, hormones, and neurohormones are all extracellular chemical messengers that accomplish indirect communication between cells. These chemical messengers differ in their source and the distance they travel to reach their target cells.

1. The most intimate means of intercellular communication is through gap junctions, which are minute tunnels that bridge the cytoplasm of neighboring cells in some types of tissues. Through these specialized anatomic arrangements, small ions and molecules are directly exchanged between interacting cells without ever entering the extracellular fluid (see p. 49).
2. The presence of identifying markers on the surface membrane of some cells permits them to directly link up transiently and interact with certain other cells in a specialized way. This is the means by which the phagocytes of the body's defense system specifically recognize and selectively destroy only undesirable cells, such as cancer cells, while leaving the body's own healthy cells alone.
3. The most common means by which cells communicate with each other is through **extracellular chemical messengers**, of which there are four types: *paracrines, neurotransmitters, hormones,* and *neurohormones.* In each case, a specific chemical messenger is synthesized by specialized cells to serve a designated purpose. On being released into the ECF by appropriate stimulation, these signaling agents act on other particular cells, the messenger's **target cells**, in a prescribed manner. To exert its effect, an extracellular chemical messenger must bind with target cell receptors specific for it.

The four types of chemical messengers differ in their source and the distance and means by which they get to their site of action as follows:

- **Paracrines** are local chemical messengers whose effect is exerted only on neighboring cells in the immediate environment of their site of secretion. Because paracrines are distributed by simple diffusion, their action is restricted to short distances. They do not gain entry to the blood in any significant quantity because they are rapidly inactivated by locally existing enzymes. One example of a paracrine is *histamine,* which is released from a specific type of connective tissue cell during an inflammatory response within an invaded or injured tissue (see p. •••). Among other things, histamine dilates (opens more widely) the blood vessels in the vicinity to increase blood flow to the tissue. This action brings additional blood-borne combat supplies into the affected area.

Paracrines must be distinguished from chemicals that influence neighboring cells after being nonspecifically released during the course of cellular activity. For example, an

increased local concentration of $CO_2$ in an exercising muscle is among the factors that promote local dilation of the blood vessels supplying the muscle. The resultant increased blood flow helps to meet the more active tissue's increased metabolic demands. However, $CO_2$ is produced by all cells and is not specifically released to accomplish this particular response, so it and similar nonspecifically released chemicals are not considered paracrines.

- As you just learned, neurons communicate directly with the cells they innervate (their target cells) by releasing **neurotransmitters**, which are very short-range chemical messengers, in response to electrical signals (action potentials). Like paracrines, neurotransmitters diffuse from their site of release across a narrow extracellular space to act locally on only an adjoining target cell, which may be another neuron, a muscle, or a gland.
- **Hormones** are long-range chemical messengers that are specifically secreted into the blood by endocrine glands in response to an appropriate signal. The blood carries the messengers to other sites in the body, where they exert their effects on their target cells some distance away from their site of release. Only the target cells of a particular hormone have membrane receptors for binding with this hormone. Nontarget cells are not influenced by any blood-borne hormones that reach them.
- **Neurohormones** are hormones released into the blood by *neurosecretory neurons*. Like ordinary neurons, neurosecretory neurons can respond to and conduct electrical signals. Instead of directly innervating target cells, however, a neurosecretory neuron releases its chemical messenger, a neurohormone, into the blood on appropriate stimulation. The neurohormone is then distributed through the blood to distant target cells. Thus, like endocrine cells, neurosecretory neurons release blood-borne chemical messengers, whereas ordinary neurons secrete short-range neurotransmitters into a confined space. In the future, the general term "hormone" will tacitly include both blood-borne hormonal and neurohormonal messengers.

In every case, extracellular chemical messengers are released from one cell type and interact with other target cells to bring about a desired effect in the target cells. We now turn our attention to how these chemical messengers bring about the desired cell response.

## Extracellular chemical messengers bring about cell responses primarily by signal transduction.

The term **signal transduction** refers to the process by which incoming signals (instructions from extracellular chemical messengers) are conveyed to the target cell's interior for execution. (A *transducer* is a device that receives energy from one system and transmits it in a different form to another system. For example, your radio receives radio waves sent out from the broadcast station and transmits these signals in the form of sound waves that can be detected by your ears.) Lipid-soluble extracellular chemical messengers, such as cholesterol-derived steroid hormones, can gain entry into the cell by dissolving in and passing through the lipid bilayer of the target cell's plasma membrane. Thus these extracellular chemical messengers bind to receptors inside the target cell to initiate the desired intracellular response themselves. By contrast, extracellular chemical messengers that are water soluble cannot gain entry to the target cell because they are poorly soluble in lipid and cannot dissolve in the plasma membrane. Protein hormones delivered by the blood and neurotransmitters released from nerve endings are the major water-soluble extracellular messengers. These messengers signal the cell to perform a given response by first binding with surface membrane receptors specific for that given messenger. These receptors are specialized proteins within the plasma membrane (see p. 46). The combination of extracellular messenger with a surface membrane receptor triggers a sequence of intracellular events that ultimately controls a particular cellular activity, such as membrane transport, secretion, metabolism, or contraction.

Despite the wide range of possible responses, binding the receptor with an extracellular messenger (the **first messenger**) brings about the desired intracellular response by only two general means: (1) by opening or closing channels or (2) by activating second-messenger systems. Because of the universal nature of these events, let's examine each more closely.

## Some extracellular chemical messengers open chemically gated channels.

Some extracellular messengers accomplish the desired intracellular response by opening or closing specific chemically gated channels in the membrane to regulate the movement of particular ions into or out of the cell. An example is the opening of chemically gated channels in the subsynaptic membrane in response to neurotransmitter binding. The resultant small, short-lived movement of given charge-carrying ions across the membrane through these open channels generates electrical signals, in this example EPSPs and IPSPs.

Stimulation of muscle cells to bring about contraction likewise occurs when chemically gated channels in the muscle cells open in response to binding of neurotransmitter released from the neurons supplying the muscle. You will learn more about this mechanism in the muscle chapter (Chapter 8). Thus control of chemically gated channels by extracellular messengers is an important regulatory mechanism in both nerve and muscle physiology.

On completion of the response, the extracellular messenger is removed from the receptor site, and the chemically gated channels close once again. The ions that moved across the membrane through opened channels to trigger the response are returned to their original location by special membrane carriers.

## Many extracellular chemical messengers activate second-messenger pathways.

Many extracellular chemical messengers that cannot actually enter their target cells bring about the desired intracellular

response by another means than opening chemically gated channels. These first messengers issue their orders by triggering a "Psst, pass it on" process. Binding of the first messenger to a membrane receptor serves as a signal for activating an intracellular **second messenger.** The second messenger ultimately relays the orders through a series of biochemical intermediaries to particular intracellular proteins that carry out the dictated response, such as changes in cellular metabolism or secretory activity. The intracellular pathways activated by a second messenger in response to binding of the first messenger to a surface receptor are remarkably similar among different cells despite the diversity of ultimate responses to that signal. The variability in response depends on the specialization of the cell, not on the mechanism used.

Second-messenger systems are widely used throughout the body, including being one of the key means by which most water-soluble hormones ultimately bring about their effects. Let's now turn our attention to hormonal communication, where we will examine second-messenger systems in more detail.

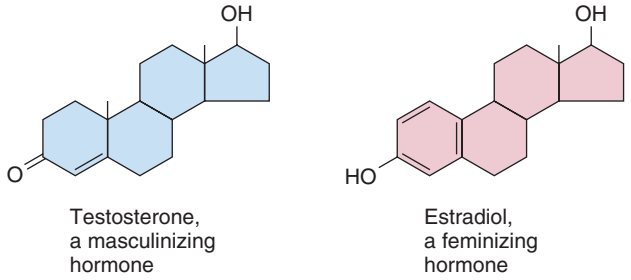
## PRINCIPLES OF HORMONAL COMMUNICATION

**Endocrinology** is the study of homeostatic chemical adjustments and other activities accomplished by hormones, which are secreted into the blood by endocrine glands. The nervous system and the endocrine system are the body's two major regulatory systems. The first part of this chapter described the underlying molecular and cellular mechanisms that serve as the basis for how the whole nervous system operates—electrical signaling within neurons and chemical transmission of signals between neurons. We are now going to focus on the molecular and cellular features of hormonal action and will compare the similarities and differences in how nerve cells and endocrine cells communicate with other cells in carrying out their regulatory actions. Finally, building on the different modes of action at the molecular and cellular level, the last section of the chapter will compare in a general way how the nervous and endocrine systems differ as regulatory systems.

### Hormones are chemically classified as being hydrophilic or lipophilic.

Hormones are not all similar chemically but instead fall into two distinct groups based on their solubility properties: hydrophilic or lipophilic hormones. Hormones within each group are further classified according to their biochemical structure and/or source as follows:

1. **Hydrophilic** ("water loving") **hormones** are highly water soluble and have low lipid solubility. Most hydrophilic hormones are peptide or protein hormones consisting of specific amino acids arranged in a chain of varying length. The shorter chains are peptides and the longer ones are proteins. For convenience, in the future we will refer to this entire category as *peptides*. An example is insulin from the pancreas. Another group of hydrophilic hormones are the *catecholamines*, which are derived from the amino acid tyrosine and are specifically secreted by the adrenal medulla. The adrenal gland consists of an inner adrenal medulla surrounded by an outer adrenal cortex. (You will learn more about the location and structure of the endocrine glands in later chapters.) Epinephrine is the major catecholamine.
2. **Lipophilic** ("lipid-loving") **hormones** have high lipid solubility and are poorly soluble in water. Lipophilic hormones include *thyroid hormone* and the *steroid hormones*. Steroids are neutral lipids derived from cholesterol. The hormones secreted by the adrenal cortex, such as cortisol, and the sex hormones (testosterone in males and estrogen in females) secreted by the reproductive organs are all steroids.




● **FIGURE 4-20**

**Comparison of two steroid hormones, testosterone and estradiol**

Minor differences in chemical structure between hormones within each category often result in profound differences in biologic response. Comparing two steroid hormones in ● Figure 4-20, for example, note the subtle difference between testosterone, the male sex hormone responsible for inducing the development of masculine characteristics, and estradiol, a form of estrogen, which is the feminizing female sex hormone.

The solubility properties of a hormone determine the means by which (1) the hormone is processed by the endocrine cell, (2) the way the hormone is transported in the blood, and (3) the mechanism by which the hormone exerts its effects at the target cell. We are first going to consider the different ways in which these hormone types are processed at their site of origin, the endocrine cell, before comparing their means of transport and their mechanisms of action.

### The mechanisms of synthesis, storage, and secretion of hormones vary according to their chemical differences.

Because of their chemical differences, the means by which the various types of hormones are synthesized, stored, and secreted differ as follows:

#### PROCESSING OF HYDROPHILIC PEPTIDE HORMONES

Peptide hormones are synthesized and secreted by the same steps used for manufacturing any protein that is exported

from the cell (see ● Figure 2-3, p. 23). From the time peptide hormones are synthesized until they are secreted, they are always segregated from intracellular proteins by being contained within membrane-enclosed compartments. Here is a brief overview of these steps:

1. Large precursor proteins, or **preprohormones**, are synthesized by ribosomes on the rough endoplasmic reticulum (ER). They then migrate to the Golgi complex in membrane-enclosed vesicles that pinch off from the smooth ER.
2. During their journey through the ER and Golgi complex, the large preprohormone precursor molecules are pruned to active hormones.
3. The Golgi complex then packages the finished hormones into secretory vesicles that are pinched off and stored in the cytoplasm until an appropriate signal triggers their secretion.
4. On appropriate stimulation, the secretory vesicles fuse with the plasma membrane and release their contents to the outside by exocytosis (see p. 24). Such secretion usually does not go on continuously; it is triggered only by specific stimuli. The blood then picks up the secreted hormone for distribution.

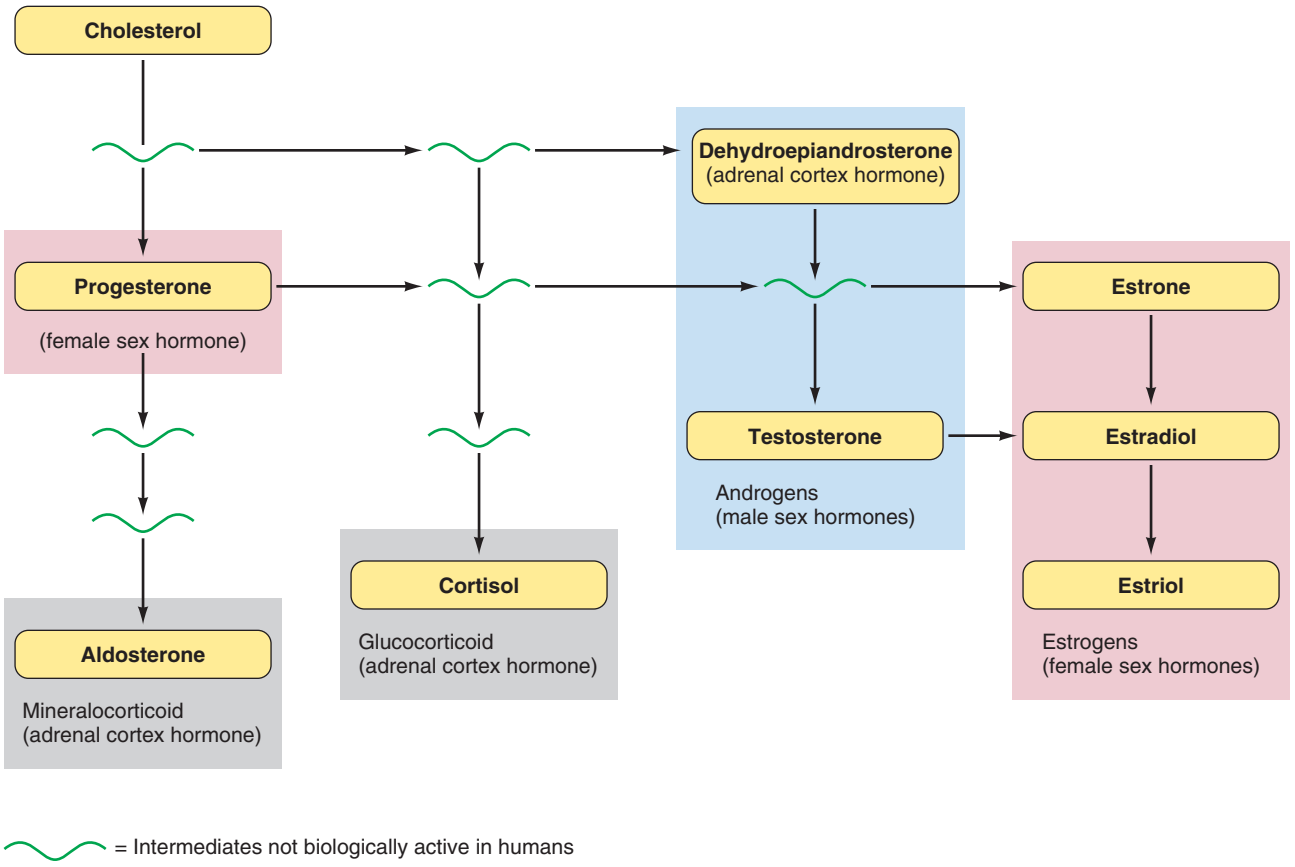
## PROCESSING OF LIPOPHILIC STEROID HORMONES

All steroidogenic (steroid-producing) cells perform the following steps to produce and release their hormonal product:

1. Cholesterol is the common precursor for all steroid hormones.
2. Synthesis of the various steroid hormones from cholesterol requires a series of enzymatic reactions that modify the basic cholesterol molecule—for example, by varying the type and position of side groups attached to the cholesterol framework (● Figure 4-21). Each conversion from cholesterol to a specific steroid hormone requires the help of a number of enzymes that are limited to certain steroidogenic organs. Accordingly, each steroidogenic organ can produce only the steroid hormone or hormones for which it has a complete set of appropriate enzymes. For example, a key enzyme

● **FIGURE 4-21**

**Steroidogenic pathways for the major steroid hormones.** All steroid hormones are produced through a series of enzymatic reactions that modify cholesterol molecules, such as by varying the side groups attached to them. Each steroidogenic organ can produce only those steroid hormones for which it has a complete set of the enzymes needed to appropriately modify cholesterol. For example, the testes have the enzymes necessary to convert cholesterol into testosterone (male sex hormone), whereas the ovaries have the enzymes needed to yield progesterone and the various estrogens (female sex hormones).



necessary for producing cortisol is found only in the adrenal cortex, so no other steroidogenic organ can produce this hormone.
3. Unlike peptide hormones, steroid hormones are not stored. Once formed, the lipid-soluble steroid hormones immediately diffuse through the steroidogenic cell's lipid plasma membrane to enter the blood. Only the hormone precursor cholesterol is stored in significant quantities within steroidogenic cells. Accordingly, the rate of steroid hormone secretion is controlled entirely by the rate of hormone synthesis. In contrast, peptide hormone secretion is controlled primarily by regulating the release of presynthesized stored hormone.

The adrenomedullary catecholamines and thyroid hormone have unique synthetic and secretory pathways that will be described when addressing each of these hormones specifically in the endocrine chapter, Chapter 17.

## Hydrophilic hormones dissolve in the plasma; lipophilic hormones are transported by plasma proteins.

All hormones are carried by the blood, but they are not all transported in the same manner:

- The hydrophilic peptide hormones are transported simply dissolved in the plasma.
- Lipophilic steroids and thyroid hormone, which are poorly soluble in water, cannot dissolve to any extent in the watery plasma. Instead, the majority of the lipophilic hormones circulate in the blood to their target cells reversibly bound to plasma proteins. Some are bound to specific plasma proteins designed to carry only one type of hormone, whereas other plasma proteins, such as albumin, indiscriminately pick up any "hitchhiking" hormone.

Only the small, unbound, freely dissolved fraction of a lipophilic hormone is biologically active (that is, free to cross capillary walls and bind with target cell receptors to exert an effect). The bound form of steroid and thyroid hormones provides a large reserve of these lipophilic hormones that can be called on to replenish the active free pool. To maintain normal endocrine function, the magnitude of the small free, effective pool, rather than the total plasma concentration of a particular lipophilic hormone, is monitored and adjusted.


The chemical properties of a hormone dictate not only the means by which blood transports it but also how it can be artificially introduced into the blood for therapeutic purposes. Because the digestive system does not secrete enzymes that can digest steroid and thyroid hormones, when taken orally these hormones, such as the sex steroids contained in birth control pills, can be absorbed intact from the digestive tract into the blood. No other type of hormones can be taken orally, because protein-digesting enzymes would attack and convert them into inactive fragments. Therefore, these hormones must be administered by nonoral routes; for example, insulin deficiency is treated with daily injections of insulin.

We will now examine how the hydrophilic and lipophilic hormones vary in their mechanisms of action at their target cells.

## Hormones generally produce their effect by altering intracellular proteins.

To induce their effect, hormones must bind with target cell receptors specific for them. Each interaction between a particular hormone and a target cell receptor produces a highly characteristic response that differs among hormones and among different target cells influenced by the same hormone. Both the location of the receptors within the target cell, and the mechanism by which binding of the hormone with the receptors induces a response, vary depending on the hormone's solubility characteristics.

### LOCATION OF RECEPTORS FOR HYDROPHILIC AND LIPOPHILIC HORMONES

Hormones can be grouped into two categories based on the location of their receptors:

1. The hydrophilic peptides and catecholamines, which are poorly soluble in lipid, cannot pass through the lipid membrane barriers of their target cells. Instead, they bind with specific receptors located on the *outer plasma membrane surface* of the target cell.
2. The lipophilic steroids and thyroid hormone easily pass through the surface membrane to bind with specific receptors located inside the target cell.

### GENERAL MEANS OF HYDROPHILIC AND LIPOPHILIC HORMONE ACTION

Even though hormones elicit a wide variety of biologic responses, all hormones ultimately influence their target cells by altering the cell's proteins through three general means:

1. A few hydrophilic hormones, on binding with a target cell's surface receptors change the cell's permeability (either opening or closing channels to one or more ions) by *altering the conformation (shape) of adjacent channel-forming proteins already in the membrane.*
2. Most surface-binding hydrophilic hormones function by activating second-messenger systems within the target cell. This activation directly *alters the activity of pre-existing intracellular proteins, usually enzymes, to produce the desired effect.*
3. All lipophilic hormones function by *activating specific genes in the target cell to cause formation of new intracellular proteins,* which in turn produce the desired effect. The new proteins may be enzymatic or structural.

Let us examine the two major mechanisms of hormonal action (activation of second-messenger systems and activation of genes) in more detail.

## Hydrophilic hormones alter pre-existing proteins via second-messenger systems.

Most hydrophilic hormones (peptides and catecholamines) bind to surface membrane receptors and produce their effects in their target cells by acting through a second-messenger system to alter the activity of pre-existing proteins. There are two major second-messenger pathways: One uses **cyclic adenosine monophosphate** (**cyclic AMP**, or **cAMP**) as a second messenger, and the other employs $Ca^{2+}$ in this role. Let's examine the cAMP pathway in more detail to illustrate how second-messenger systems function.

### CYCLIC AMP SECOND-MESSENGER PATHWAY

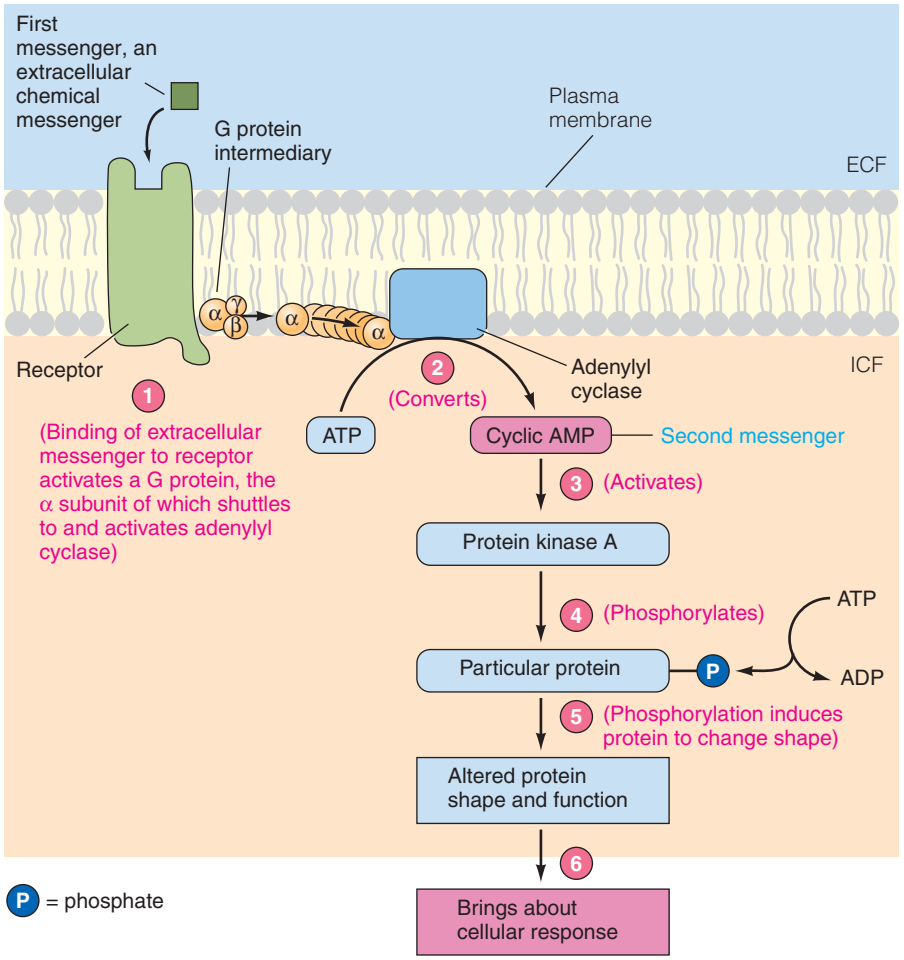
In the following description of the cAMP pathway, the numbered steps correlate to the numbered steps in ● Figure 4-22.

1. Binding of an appropriate extracellular messenger (a first messenger) to its surface membrane receptor eventually activates the enzyme **adenylyl cyclase** (step 1), which is located on the cytoplasmic side of the plasma membrane. A membrane-bound "middleman," a **G protein**, acts as an intermediary between the receptor and adenylyl cyclase. G proteins are found on the inner surface of the plasma membrane. An unactivated G protein consists of a complex of alpha (α), beta (β), and gamma (γ) subunits. A number of different G proteins with varying α subunits have been identified. The different G proteins are activated in response to binding of various first messengers to surface receptors. When a first messenger binds with its receptor, the receptor attaches to the appropriate G protein, resulting in activation of the α subunit. Once activated, the α subunit breaks away from the G protein complex and moves along the inner surface of the plasma membrane until it reaches an effector protein. An effector protein is either an ion channel or an enzyme within the membrane. The α subunit links up with the effector protein and alters its activity. In the cAMP pathway, adenylyl cyclase is the effector protein activated. Researchers have identified more than 300 different receptors that convey instructions of extracellular

● **FIGURE 4-22**

**Mechanism of action of hydrophilic hormones via activation of the cyclic AMP second-messenger system**

PhysioEdge For an animation of this figure, click the Intercellular Communication and Signal Transduction tab in the Membrane Potential tutorial on the CD-ROM.




1. Binding of an extracellular messenger, the *first messenger*, to a surface membrane receptor activates by means of a G protein intermediary the membrane-bound enzyme adenylyl cyclase.
2. Adenylyl cyclase converts intracellular ATP into cyclic AMP.
3. Cyclic AMP acts as an intracellular *second messenger*, triggering the desired cellular response by activating protein kinase A.
4. Protein kinase A in turn phosphorylates a particular intracellular protein.
5. Phosphorylation induces a change in the shape and function of the protein.
6. The altered protein then accomplishes the cellular response dictated by the extracellular messenger.

messengers through the membrane to effector proteins by means of G proteins.

2. Adenylyl cyclase induces the conversion of intracellular ATP to cAMP by cleaving off two of the phosphates (step 2). (This is the same ATP used as the common energy currency in the body.)

3. Acting as the intracellular second messenger, cAMP triggers a preprogrammed series of biochemical steps within the cell to bring about the response dictated by the first messenger. To begin, cyclic AMP activates a specific intracellular enzyme, **protein kinase A** (step 3).

4. Protein kinase A in turn phosphorylates (attaches a phosphate group from ATP to) a specific pre-existing intracellular protein (step 4), such as an enzyme important in a particular metabolic pathway.

5. Phosphorylation causes the protein to change its shape and function (either activating or inhibiting it) (step 5).

6. This altered protein brings about a change in cell function (step 6). The resultant change is the target cell's ultimate physiologic response to the first messenger. For example, the activity of a particular enzymatic protein that regulates a specific metabolic event may be increased or decreased.

After the response is accomplished and the first messenger is removed, the $\alpha$ subunit rejoins the $\alpha$ and $\gamma$ subunits to restore the inactive G-protein complex. Cyclic AMP and the other participating chemicals are inactivated so that the intracellular message is "erased" and the response can be terminated. Otherwise, once triggered the response would go on indefinitely until the cell ran out of necessary supplies.

Note that in this signal transduction pathway, the steps involving the extracellular first messenger, the receptor, the G protein complex, and the effector protein occur *in the plasma membrane* and lead to activation of the second messenger. The extracellular messenger cannot gain entry into the cell to "personally" deliver its message to the proteins that carry out the desired response. Instead, it initiates membrane events that activate an intracellular messenger, cAMP. The second messenger then triggers a chain reaction of biochemical events *inside the cell* that leads to the cellular response.

Different types of cells have different pre-existing proteins available for phosphorylation and modification by protein kinase A. Therefore, a *common second messenger, cAMP, can induce widely differing responses in different cells,* depending on what proteins are modified. Cyclic AMP can be thought of as a commonly used molecular "switch" that can "turn on" (or "turn off") different cell events, depending on the kinds of protein activity ultimately modified in the various target cells. The type of proteins altered by a second messenger depends on the unique specialization of a particular cell type. This can be likened to being able to either illuminate or cool off a room depending on whether the wall switch you flip on is wired to a device specialized to light up (a chandelier) or one specialized to create air movement (a ceiling fan). In the body, the variable responsiveness once the switch is turned on is due to the genetically programmed differences in the sets of proteins within different cells. For example, activating the cAMP system brings about modification of heart rate in the heart, stimulation of the formation of female sex hormones in the ovaries, breakdown of stored glucose in the liver, control of water conservation during urine formation in the kidneys, creation of some simple memory traces in the brain, and perception of a sweet taste by a taste bud. (See the accompanying boxed feature, ◗ Beyond the Basics, for a description of a surprising signal-transduction pathway—one that causes a cell to kill itself.)

Many hydrophilic hormones use cAMP as their second messenger. A few use intracellular $Ca^{2+}$ in this role; for others, the second messenger is still unknown.

Recognize that activation of second messengers is a universal mechanism employed by a variety of extracellular messengers in addition to hydrophilic hormones. Other chemical messengers that use the cAMP second-messenger system to accomplish their effects include neuromodulators and molecules that give rise to a number of different taste or smell sensations.

## AMPLIFICATION BY A SECOND-MESSENGER PATHWAY

Several remaining points about receptor activation and the ensuing events merit attention. First, considering the number of steps involved in a second-messenger relay chain, you might wonder why so many cell types use the same complex system to accomplish such a wide range of functions. The multiple steps of a second-messenger pathway are actually advantageous, because a **cascading** (multiplying) **effect** of these pathways greatly amplifies the initial signal. Amplification means that the magnitude of the output of a system is much greater than the input. Binding of one extracellular chemical-messenger molecule to a receptor activates a number of adenyl cyclase molecules (let us arbitrarily say 10), each of which activates many (in our hypothetical example, let's say 100) cAMP molecules. Each cAMP molecule then acts on a single protein kinase A, which phosphorylates and thereby influences many (again, let us say 100) specific proteins, such as enzymes. Each enzyme, in turn, is responsible for producing many (perhaps 100) molecules of a particular product, such as a secretory product. The result of this cascade of events, with one event triggering the next event in sequence, is a tremendous amplification of the initial signal. In our hypothetical example, one chemical-messenger molecule has been responsible for inducing a yield of 10 million molecules of a secretory product. In this way, very low concentrations of hormones and other chemical messengers can trigger pronounced cell responses.

## MODIFICATIONS OF SECOND-MESSENGER PATHWAYS

Although membrane receptors serve as links between extracellular first messengers and intracellular second messengers in the regulation of specific cellular activities, the receptors themselves are also frequently subject to regulation. In many instances, the number and affinity (attraction of a receptor for its chemical messenger) can be altered, depending on the circumstances.

Many disease processes can be linked to malfunctioning receptors or defects in signal transduction pathways. For ex-

Beyond the Basics

## Programmed Cell Suicide: A Surprising Example of a Signal Transduction Pathway

In the vast majority of cases, the signal transduction pathways triggered by the binding of an extracellular chemical messenger to a cell's surface membrane receptor are aimed at promoting proper functioning, growth, survival, or reproduction of the cell. By contrast, every cell has an unusual built-in pathway that, if triggered, causes the cell to commit suicide by activating intracellular protein-snipping enzymes, which slice the cell into small, disposable pieces. Such intentional programmed cell death is called **apoptosis.** (This term means "dropping off," in reference to the dropping off of cells that are no longer useful, much as autumn leaves drop off trees.) Apoptosis is a normal part of life: Individual cells that have become superfluous or disordered are triggered to self-destruct for the greater good of maintaining the whole body's health.

### Roles of Apoptosis

Here are examples of the vital roles played by this intrinsic sacrificial program:

- *Predictable self-elimination of selected cells is a normal part of development.* Certain unwanted cells produced during development are programmed to kill themselves as the body is sculpted into its final form. During the development of a female, for example, apoptosis deliberately prunes the embryonic ducts capable of forming a male reproductive tract Likewise, apoptosis carves fingers from a mitten-shaped developing hand by eliminating the weblike membranes between them.
- *Apoptosis is important in tissue turnover in the adult body.* Optimal functioning of most tissues depends on a balance between controlled production of new cells and regulated cell self-destruction. This balance maintains the proper number of cells in a given tissue while ensuring a controlled supply of fresh cells that are at their peak of performance.
- *Programmed cell death plays an important role in the immune system.* Apoptosis provides a means to remove cells infected with harmful viruses. Furthermore, infection-fighting white blood cells that have finished their prescribed function and are no longer needed, execute themselves.
- *Undesirable cells that threaten homeostasis are typically culled from the body by apoptosis.* Included in this hit list are aged cells, cells that have suffered irreparable damage by exposure to radiation or other poisons, and cells that have somehow gone awry. Many mutated cells are eliminated by this means before they become fully cancerous.

### Comparison of Apoptosis and Necrosis

Apoptosis is not the only means by which a cell can die, but it is the neatest way. Apoptosis is a controlled, intentional, tidy way of removing individual cells that are no longer needed or that pose a threat to the body. The other form of cell death, **necrosis** (meaning "making dead"), is uncontrolled, accidental, messy murder of useful cells that have been severely injured by an agent external to the cell, as by a physical blow, $O_2$ deprivation, or disease. For example, heart muscle cells deprived of their $O_2$ supply by complete blockage of the blood vessels supplying them during a heart attack die as a result of necrosis (see p. •••).

Even though necrosis and apoptosis both result in cell death, the steps involved are very different. In necrosis the dying cells are passive victims, whereas in apoptosis the cells actively participate in their own deaths. In necrosis, the injured cell cannot pump out $Na^+$ as usual. As a result, water streams in by osmosis, causing the cell to swell and rupture. Typically, in necrosis the insult that prompted cell death injures many cells in the vicinity, so many neighboring cells swell and rupture together. Release of intracellular contents into the surrounding tissues initiates an inflammatory response at the damaged site (see p. •••). Unfortunately, the inflammatory response can potentially harm healthy neighboring cells.

By contrast, apoptosis targets individual cells for destruction, leaving the surrounding cells intact. A cell signaled to commit suicide detaches itself from its neighbors, then shrinks instead of swelling and bursting. As its lethal weapon, the suicidal cell activates a cascade of normally inactive intracellular protein-cutting enzymes, the **caspases,** which kill the cell from

Clinical Note

ample, in Laron dwarfism, the person is abnormally short despite having normal levels of growth hormone because the tissues cannot respond normally to growth-promoting factors. This is in contrast to the more usual type of dwarfism in which the person is abnormally short because of growth hormone deficiency.

PhysioEdge

Click on the Media Exercises menu of the CD-ROM and work Media Exercise 3.3: Signaling at Cell Membranes and Membrane Potential to test your understanding of the previous section.

### By stimulating genes, lipophilic hormones promote synthesis of new proteins.

All lipophilic hormones (steroids and thyroid hormone) bind with intracellular receptors and produce their effects in their target cells by activating specific genes to cause the synthesis of new enzymatic or structural proteins. The following steps in this process correlate with those numbered in ● Figure 4-23:

1. Free lipophilic hormone (hormone not bound with its carrier) diffuses through the plasma membrane of the target cell and binds with its specific receptor inside the cell (step 1). Most lipophilic hormone receptors are located in the nucleus.
2. Each receptor has a specific region for binding with its hormone and another region for binding with DNA. The receptor cannot bind with DNA unless it first binds with the hormone. Once the hormone is bound to the receptor, the hormone receptor complex binds with DNA at a specific attachment site on DNA known as the **hormone response element (HRE)** (step 2). Different steroid hormones and thyroid hormone, once bound with their respective receptors, attach at different HREs on DNA. For example, the estrogen receptor complex binds at DNA's estrogen response element.

● **FIGURE 4-23**

**Mechanism of action of lipophilic hormones via activation of genes**

(*Source:* Adapted with permission from George A. Hedge, Howard D. Colby, and Robert L. Goodman, *Clinical Endocrine Physiology.* Philadelphia: W.B. Saunders Company, 1987, Figure 1-9, p. 20.)

within. Once unleashed, the caspases act like molecular scissors to systematically dismantle the cell. Snipping protein after protein, they chop up the nucleus, disassembling its life-essential DNA, then break down the internal shape-holding cytoskeleton, and finally fragment the cell itself into disposable membrane-enclosed packets. Importantly, the contents of the dying cell remain wrapped by plasma membrane throughout the entire self-execution process, thus avoiding the spewing of potentially harmful intracellular contents characteristic of necrosis. No inflammatory response is triggered, so no neighboring cells are harmed. Instead, cells in the vicinity swiftly engulf and destroy the apoptotic cell fragments by phagocytosis. The breakdown products are recycled for other purposes as needed. Meanwhile, the tissue as a whole has continued to function normally, while the targeted cell has unobtrusively killed itself.

**Control of Apoptosis**

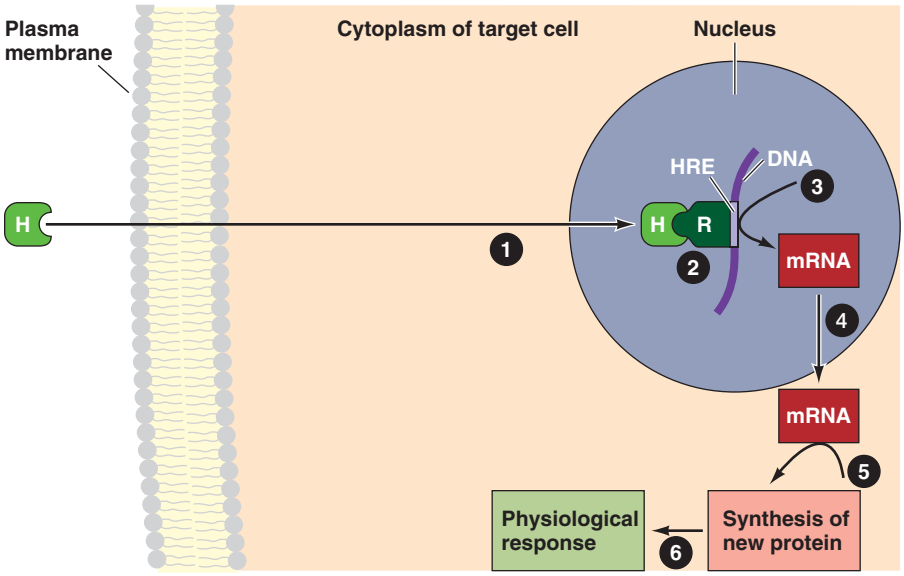
If every cell contains the potent self-destructive caspases, what normally keeps these powerful enzymes under control (that is, in inactive form) in cells that are useful to the body and deserve to live? Likewise, what activates the death-wielding caspase cascade in unwanted cells destined to eliminate themselves? Given the importance of these life-or-death decisions, it is not surprising that multiple pathways tightly control whether a cell is "to be or not to be."

A cell normally receives a constant stream of "survival signals," which reassure the cell that it is useful to the body, that all is right in the internal environment surrounding the cell, and that everything is in good working order within the cell. These signals include tissue-specific growth factors, certain hormones, and appropriate contact with neighboring cells and the extracellular matrix. These extracellular survival signals trigger intracellular pathways that block activation of the caspase cascade, thus restraining the cell's death machinery. Most cells are programmed to commit suicide if they do not receive their normal reassuring survival signals. The usual safeguards are removed, and the lethal protein-snipping enzymes are unleashed. For example, withdrawal of growth factors or detachment from the extracellular matrix causes a cell to promptly execute itself.

Furthermore, cells display "death receptors" in their plasma membrane that receive specific extracellular "death signals," such as a particular hormone or a specific chemical messenger from white blood cells. Activation of death pathways by these signals can override the life-saving pathways triggered by the survival signals. The death-signal transduction pathway swiftly ignites the internal apoptotic machinery, driving the cell to its own demise. Likewise, the self-execution machinery is set in motion when a cell suffers irreparable intracellular damage. Thus some signals block apoptosis, whereas others promote it. Whether a cell lives or dies depends on which of these competing signals dominates at any given time. Although all cells have the same death machinery, they vary in the specific signals that induce them to commit suicide.

Considering that every cell's life hangs in delicate balance at all times, it is not surprising that faulty control of apoptosis—resulting in either too much or too little cell suicide—appears to participate in many major diseases. Excessive apoptotic activity is believed to contribute to the brain cell death associated with Alzheimer's disease, Parkinson's disease, and stroke as well as to the premature demise of important infection-fighting cells in AIDS. Conversely, too little apoptosis most likely plays a role in cancer. Evidence suggests that cancer cells fail to respond to the normal extracellular signals that promote cell death. Because these cells neglect to die on cue, they grow in unchecked fashion, forming a chaotic, out-of-control mass.

Apoptosis is currently one of the hottest topics of investigation. Researchers are scrambling to sort out the multiple factors involved in the signal transduction pathways controlling this process. Their hope is to find ways to tinker with the apoptotic machinery to find badly needed new therapies to treat a variety of big killers.




1. A lipophilic hormone diffuses through the plasma and nuclear membranes of its target cells and binds with a nuclear receptor specific for it.
2. The hormone receptor complex in turn binds with the hormone response element, a segment of DNA specific for the hormone receptor complex.
3. DNA binding activates specific genes, which produce complementary messenger RNA.
4. Messenger RNA leaves the nucleus.
5. In the cytoplasm, messenger RNA directs the synthesis of new proteins.
6. These new proteins, either enzymatic or structural, accomplish the target cell's ultimate physiologic response to the hormone.

H = Free lipophilic hormone
R = Lipophilic hormone receptor
HRE = Hormone response element
mRNA = Messenger RNA

3. Binding of the hormone receptor complex with DNA ultimately "turns on" a specific gene within the target cell. This gene contains a code for synthesizing a given protein. The code of the activated gene is transcribed into complementary messenger RNA (step 3).
4. The new messenger RNA leaves the nucleus and enters the cytoplasm (step 4).
5. In the cytoplasm, messenger RNA binds to a ribosome, the "workbench" that mediates the assembly of new proteins (p. A-••). Here, messenger RNA directs the synthesis of the designated new proteins according to the DNA code in the activated genes (step 5).
6. The newly synthesized protein, either enzymatic or structural, produces the target cell's ultimate physiologic response to the hormone (step 6).

By means of this mechanism, different genes are activated by different lipophilic hormones, resulting in different biologic effects.

### Hormonal responses are slower and longer than neural responses.

Compared to neural responses that are brought about within milliseconds, hormone action is relatively slow and prolonged, taking minutes to hours after the hormone binds to its receptor, for the response to take place. The variability in time of onset for hormonal responses depends on the mechanism employed. Hormones that act through a second-messenger system to alter a pre-existing enzyme's activity elicit full action within a few minutes. In contrast, hormonal responses that require the synthesis of new protein may take up to several hours before any action is initiated.

Also in contrast to neural responses that are quickly terminated once the triggering signal ceases, hormonal responses persist for a period of time after the hormone is no longer bound to its receptor. Once an enzyme is activated in response to hydrophilic hormonal input, it no longer depends on the presence of the hormone. Thus the response lasts until the enzyme is inactivated. Likewise, once a new protein is synthesized in response to lipophilic hormonal input, it continues to function until it is degraded. As a result, a hormone's effect usually lasts for some time after its withdrawal. Predictably, the responses that depend on protein synthesis last longer than do those stemming from enzyme activation.

Let's now compare further the similarities and differences between neural and hormonal responses at the system level.

## COMPARISON OF THE NERVOUS AND ENDOCRINE SYSTEMS

As you know, the nervous and endocrine systems are the two main regulatory systems of the body. The **nervous system** swiftly transmits electrical impulses to the skeletal muscles and the exocrine glands that it innervates. The **endocrine system** secretes hormones into the blood for delivery to distant sites of action. Although these two systems differ in many respects, they have much in common (▲ Table 4-3). They both ultimately alter their target cells (their sites of action) by releasing chemical messengers (neurotransmitters in the case of nerve cells, hormones in the case of endocrine cells), which interact in particular ways with specific receptors of the target cells. Let's examine the anatomic distinctions between these two systems and the different ways in which they accomplish specificity of action.

▲ **TABLE 4-3**
Comparison of the Nervous System and the Endocrine System

| PROPERTY | NERVOUS SYSTEM | ENDOCRINE SYSTEM |
|---|---|---|
| **Anatomic Arrangement** | A "wired" system; specific structural arrangement between neurons and their target cells; structural continuity in the system | A "wireless" system; endocrine glands widely dispersed and not structurally related to one another or to their target cells |
| **Type of Chemical Messenger** | Neurotransmitters released into synaptic cleft | Hormones released into blood |
| **Distance of Action of Chemical Messenger** | Very short distance (diffuses across synaptic cleft) | Long distance (carried by blood) |
| **Means of Specificity of Action on Target Cell** | Dependent on close anatomic relationship between nerve cells and their target cells | Dependent on specificity of target cell binding and responsiveness to a particular hormone |
| **Speed of Response** | Rapid (milliseconds) | Slow (minutes to hours) |
| **Duration of Action** | Brief (milliseconds) | Long (minutes to days or longer) |
| **Major Functions** | Coordinates rapid, precise responses | Controls activities that require long duration rather than speed |

## The nervous system is "wired" and the endocrine system is "wireless."

Anatomically, the nervous and endocrine systems are quite different. In the nervous system, each nerve cell terminates directly on its specific target cells; that is, the nervous system is "wired" in a very specific way into highly organized, distinct anatomic pathways for transmission of signals from one part of the body to another. Information is carried along chains of neurons to the desired destination through action potential propagation coupled with synaptic transmission. In contrast, the endocrine system is a "wireless" system in that the endocrine glands are not anatomically linked with their target cells. Instead, the endocrine chemical messengers are secreted into the blood and delivered to distant target sites. In fact, the components of the endocrine system itself are not anatomically interconnected; the endocrine glands are scattered throughout the body (see ● Figure 17-1, p. •••). These glands constitute a system in a functional sense, however, because they all secrete hormones and many interactions take place between various endocrine glands.

## Neural specificity is due to anatomic proximity and endocrine specificity to receptor specialization.

As a result of their anatomic differences, the nervous and endocrine systems accomplish specificity of action by distinctly different means. Specificity of neural communication depends on nerve cells having a close anatomic relationship with their target cells, so that each neuron has a very narrow range of influence. A neurotransmitter is released for restricted distribution only to specific adjacent target cells, then is swiftly inactivated or removed before it can gain access to the blood. The target cells for a particular neuron have receptors for the neurotransmitter, but so do many other cells in other locations, and they could respond to this same mediator if it were delivered to them. For example, the entire system of nerve cells supplying all your body's skeletal muscles (motor neurons) use the same neurotransmitter, *acetylcholine (ACh),* and all your skeletal muscles bear complementary ACh receptors (Chapter 7). Yet you can specifically wiggle your big toe without influencing any of your other muscles, because ACh can be discretely released from the motor neurons that are specifically wired to the muscles controlling your toe. If ACh were indiscriminately released into the blood, as are the hormones of the wireless endocrine system, all the skeletal muscles would simultaneously respond by contracting, because they all have identical receptors for ACh. This does not happen, of course, because of the precise wiring patterns that provide direct lines of communication between motor neurons and their target cells.

This specificity sharply contrasts to the way specificity of communication is built into the endocrine system. Because hormones travel in the blood, they can reach virtually all tissues. Yet despite this ubiquitous distribution, only specific target cells can respond to each hormone. Specificity of hormonal action depends on specialization of target cell receptors. For a hormone to exert its effect, the hormone must first bind with receptors specific for it that are located only on or in the hormone's target cells. Target cell receptors are highly discerning in their binding function. They will recognize and bind only a certain hormone, even though they are exposed simultaneously to many other blood-borne hormones, some of which are structurally very similar to the one that they discriminately bind. A receptor recognizes a specific hormone because the conformation of a portion of the receptor molecule matches a unique portion of its binding hormone in "lock-and-key" fashion. Binding of a hormone with target cell receptors initiates a reaction that culminates in the hormone's final effect. The hormone cannot influence any other cells, because they lack the right binding receptors.

## The nervous and endocrine systems have their own realms of authority but interact functionally.

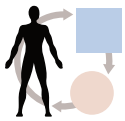
The nervous and endocrine systems are specialized for controlling different types of activities. In general, the nervous system governs the coordination of rapid, precise responses. It is especially important in the body's interactions with the external environment. Neural signals in the form of action potentials are rapidly propagated along nerve cell fibers, resulting in the release at the nerve terminal of a neurotransmitter that has to diffuse only a microscopic distance to its target cell before a response is effected. A neurally mediated response is not only rapid but brief; the action is quickly halted as the neurotransmitter is swiftly removed from the target site. This permits either ending the response, almost immediately repeating the response, or rapidly initiating an alternate response, as circumstances demand (for example, the swift changes in commands to muscle groups needed to coordinate walking). This mode of action makes neural communication extremely rapid and precise. The target tissues of the nervous system are the muscles and glands, especially exocrine glands, of the body.

The endocrine system, in contrast, is specialized to control activities that require duration rather than speed, such as regulating organic metabolism and water and electrolyte balance; promoting smooth, sequential growth and development; and controlling reproduction. The endocrine system responds more slowly to its triggering stimuli than does the nervous system for several reasons. First, the endocrine system must depend on blood flow to convey its hormonal messengers over long distances. Second, hormones' mechanism of action at their target cells is more complex than that of neurotransmitters and thus requires more time before a response occurs. The ultimate effect of some hormones cannot be detected until a few hours after they bind with target cell receptors. Also, because of the receptors' high affinity for their respective hormone, hormones often remain bound to receptors for some time, thus prolonging their biological effectiveness. Furthermore, unlike the brief, neurally induced responses that stop almost immediately after the neurotransmitter is removed, endocrine effects usually last for some time after the

hormone's withdrawal. Neural responses to a single burst of neurotransmitter release usually last only milliseconds to seconds, whereas the alterations that hormones induce in target cells range from minutes to days or, in the case of growth-promoting effects, even a lifetime. Thus hormonal action is relatively slow and prolonged, making endocrine control particularly suitable for regulating metabolic activities that require long-term stability.

Although the endocrine and nervous systems have their own areas of specialization, they are intimately interconnected functionally. Some nerve cells do not release neurotransmitters at synapses but instead end at blood vessels and release their chemical messengers (neurohormones) into the blood, where these chemicals act as hormones. A given messenger may even be a neurotransmitter when released from a nerve ending and a hormone when secreted by an endocrine cell (see p. •••). The nervous system directly or indirectly controls the secretion of many hormones (see Chapter 17). At the same time, many hormones act as neuromodulators, altering synaptic effectiveness and thereby influencing the excitability of the nervous system. The presence of certain key hormones is even essential for the proper development and maturation of the brain during fetal life. Furthermore, in many instances the nervous and endocrine systems both influence the same target cells in supplementary fashion. For example, these two major regulatory systems both help regulate the circulatory and digestive systems. Thus many important regulatory interfaces exist between the nervous and endocrine systems.

In the next three chapters, we will concentrate on the nervous system and will examine the endocrine system in more detail in later chapters. Throughout the text we will continue to point out the numerous ways these two regulatory systems interact, so that the body is a coordinated whole, even though each system has its own realm of authority.



## CHAPTER IN PERSPECTIVE: FOCUS ON HOMEOSTASIS

To maintain homeostasis, cells must communicate so that they work together to accomplish life-sustaining activities. To bring about desired responses, the two major regulatory systems of the body, the nervous system and the endocrine system, in particular must communicate with the target cells they are controlling. Neural and hormonal communication are therefore critical in maintaining a stable internal environment as well as in coordinating nonhomeostatic activities.

Nerve cells are specialized to receive, process, encode, and rapidly transmit information from one part of the body to another. The information is transmitted over intricate nerve pathways by propagation of action potentials along the nerve cell's length as well as by chemical transmission of the signal from neuron to neuron at synapses and from neuron to muscles and glands through other neurotransmitter–receptor interactions at these junctions.

Collectively, the nerve cells make up the nervous system. Many of the activities controlled by the nervous system are geared toward maintaining homeostasis. Some neuronal electrical signals convey information about changes to which the body must rapidly respond in order to maintain homeostasis—for example, information about a fall in blood pressure. Other neuronal electrical signals swiftly convey messages to muscles and glands to stimulate appropriate responses to counteract these changes—for example, adjustments in heart and blood vessel activity to restore blood pressure to normal when it starts to fall.

The endocrine system secretes hormones into the blood, which carries these chemical messengers to distant target cells where they bring about their effect by changing the activity of enzymatic or structural proteins within these cells. Water-soluble hormones largely alter pre-existing intracellular proteins by activating second-messenger systems. Lipid-soluble hormones activate genes to promote the synthesis of new intracellular proteins. The resultant changes in activity of specific intracellular proteins accomplish the physiologic response directed by the hormonal messenger. Through its relatively slow acting hormonal messengers, the endocrine system generally regulates activities that require duration rather than speed. Most of these activities are directed toward maintaining homeostasis. For example, hormones help maintain the proper concentration of nutrients in the internal environment by directing chemical reactions involved in the cellular uptake, storage, release and use of these molecules. Also, hormones help maintain the proper water and electrolyte balance in the internal environment. Unrelated to homeostasis, hormones direct growth and control most aspects of the reproductive system.

Together the nervous and endocrine systems orchestrate a wide range of adjustments that help the body maintain homeostasis in response to stress. Likewise, these systems work in concert to control the circulatory and digestive systems, which in turn carry out important homeostatic activities.

## CHAPTER SUMMARY

**Introduction to Neural Communication (pp. 71–73)**

- Nerve and muscle cells are known as *excitable tissues* because they can rapidly alter their membrane permeabilities and thus undergo transient membrane potential changes when excited. These rapid changes in potential serve as electrical signals.
- Compared to resting potential, a membrane becomes depolarized when its potential is reduced (becomes less negative) and hyperpolarized when its potential is increased (becomes more negative). *(Review Figure 4-1.)*
- Changes in potential are brought about by triggering events that alter membrane permeability, in turn leading to changes in ion movement across the membrane.
- There are two kinds of potential change: (1) graded potentials, which serve as short-distance signals, and (2) action potentials, the long-distance signals. *(Review Table 4-1, p. 82.)*

**Graded Potentials (pp. 73–75)**

- Graded potentials occur in a small, specialized region of an excitable cell membrane. *(Review Figure 4-2.)*
- The magnitude of a graded potential varies directly with the magnitude of the triggering event.
- Graded potentials passively spread decrementally by local current flow and die out over a short distance. *(Review Figures 4-3 and 4-4.)*

**Action Potentials (pp. 75–85)**

- During an action potential, depolarization of the membrane to threshold potential triggers sequential changes in permeability caused by conformational changes in voltage-gated $Na^+$ and $K^+$ channels. *(Review Figures 4-5 and 4-6.)*
- These permeability changes bring about a brief reversal of membrane potential, with $Na^+$ influx causing the rising phase (from $-70$ mV to $+30$ mV), followed by $K^+$ efflux causing the falling phase (from peak back to resting potential). *(Review Figure 4-8.)*
- Before an action potential returns to resting, it regenerates an identical new action potential in the area next to it by means of current flow that brings the previously inactive area to threshold. This self-perpetuating cycle continues until the action potential has spread throughout the cell membrane in undiminished fashion.
- There are two types of action potential propagation: (1) contiguous conduction in unmyelinated fibers, in which the action potential spreads along every portion of the membrane; and (2) the more rapid, saltatory conduction in myelinated fibers, where the impulse jumps over the sections of the fiber covered with insulating myelin. *(Review Figures 4-10 and 4-13.)*
- The $Na^+$–$K^+$ pump gradually restores the ions that moved during propagation of the action potential to their original location, to maintain the concentration gradients.
- It is impossible to restimulate the portion of the membrane where the impulse has just passed until it has recovered from its refractory period. The refractory period ensures the one-way propagation of action potentials away from the original site of activation. *(Review Figures 4-11 and 4-12.)*
- Action potentials occur either maximally in response to stimulation or not at all.
- Variable strengths of stimuli are coded by varying the frequency of action potentials, not their magnitude.

**Synapses and Neuronal Integration (pp. 85–92)**

- The primary means by which one neuron directly interacts with another neuron is through a synapse. *(Review Figure 4-14.)*
- Most neurons have four different functional parts:
  1. The dendrite/cell body region is specialized to serve as the postsynaptic component that binds with and responds to neurotransmitters released from other neurons.
  2. The axon hillock is specialized for initiation of action potentials in response to graded potential changes induced by binding of a neurotransmitter with receptors on the dendrite/cell body region
  3. The axon, or nerve fiber, is specialized to conduct action potentials in undiminished fashion from the axon hillock to the axon terminals.
  4. The axon terminal is specialized to serve as the presynaptic component, which releases a neurotransmitter that influences other postsynaptic cells in response to action potential propagation down the axon. *(Review Figure 4-9.)*
- Released neurotransmitter combines with receptor sites on the postsynaptic neuron with which the presynaptic axon terminal interacts. This combination opens chemically gated channels in the postsynaptic neuron. *(Review Figure 4-15.)*
  1. If nonspecific cation channels that permit passage of both $Na^+$ and $K^+$ are opened, the resultant ionic fluxes cause an EPSP, a small depolarization that brings the postsynaptic cell closer to threshold. *(Review Figure 4-16.)*
  2. However, the likelihood that the postsynaptic neuron will reach threshold is diminished when an IPSP, a small hyperpolarization, is produced as a result of the opening of either $K^+$ or $Cl^-$ channels, or both. *(Review Figure 4-16.)*
- Even though there are a number of different neurotransmitters, each synapse always releases the same neurotransmitter to produce a given response when combined with a particular receptor.
- The interconnecting synaptic pathways between various neurons are incredibly complex, due to convergence of neuronal input and divergence of its output. Usually, many presynaptic inputs converge on a single neuron and jointly control its level of excitability. This same neuron, in turn, diverges to synapse with and influence the excitability of many other cells. Each neuron thus has the task of computing an output to numerous other cells from a complex set of inputs to itself. *(Review Figure 4-18.)*
- If the dominant activity is in its excitatory inputs, the postsynaptic cell is likely to be brought to threshold and have an action potential. This can be accomplished by either (1) temporal summation (EPSPs from a single, repetitively firing, presynaptic input occurring so close together in time that they add together) or (2) spatial summation (adding of EPSPs occurring simultaneously from several different presynaptic inputs). *(Review Figure 4-17.)*
- If inhibitory inputs dominate, the postsynaptic potential is brought farther than usual away from threshold.
- If excitatory and inhibitory activity to the postsynaptic neuron is balanced, the membrane remains close to resting.

**Intercellular Communication and Signal Transduction (pp. 92–95)**

- Intercellular communication is accomplished by (1) gap junctions, (2) transient direct link up and interaction between cells, and (3) extracellular chemical messengers. *(Review Figure 4-19.)*
- Cells communicate with each other to carry out various coordinated activities largely by dispatching extracellular chemical messengers, which act on particular target cells to bring about the desired response.
- There are four types of extracellular chemical messengers, depending on their source and the distance and means by which they get to their site of action: (1) paracrines (local chemical messengers); (2) neurotransmitters (very short-range chemical messengers released by neurons); (3) hormones (long-range chemical messengers secreted into the blood by endocrine glands; and (4) neurohormones (long-range chemical messengers secreted into the blood by neurosecretory neurons). *(Review Figure 4-19.)*
- Transfer of the signal carried by the extracellular messenger into the cell for execution is known as *signal transduction.*
- Attachment of an extracellular chemical messenger that cannot gain entry to the cell such as a protein hormone (the first messenger) to a membrane triggers cellular responses by two major methods: (1) opening or closing specific channels or (2) activating an intracellular messenger (the second messenger). *(Review Figure 4-22.)*

**Principles of Hormonal Communication (pp. 95–102)**

- Hormones are long-distance chemical messengers secreted by the endocrine glands into the blood, which transports the hormones to specific target sites where they control a particular function by altering protein activity within the target cells.

- Hormones are grouped into two categories based on their solubility differences: (1) hydrophilic (water-soluble) hormones, which include peptides (the majority of hormones) and catecholamines (secreted by the adrenal medulla) and (2) lipophilic (lipid-soluble) hormones, which include thyroid hormone and steroid hormones (the sex hormones and those secreted by the adrenal cortex).
- Hydrophilic peptide hormones are synthesized and packaged for export by the endoplasmic reticulum/Golgi complex, stored in secretory vesicles, and released by exocytosis on appropriate stimulation.
- Hydrophilic hormones dissolve freely in the plasma for transport to their target cells.
- At their target cells, hydrophilic hormones bind with surface membrane receptors. On binding, a hydrophilic hormone triggers a chain of intracellular events by means of a second-messenger system that ultimately alters pre-existing cell proteins, usually enzymes, which exert the effect leading to the target cell's response to the hormone. *(Review Figure 4-22.)*
- Steroids are synthesized by modifications of stored cholesterol by means of enzymes specific for each steroidogenic tissue. *(Review Figure 4-21.)*
- Steroids are not stored in the endocrine cells. Being lipophilic, they diffuse out through the lipid membrane barrier as soon as they are synthesized. Control of steroids is directed at their synthesis.
- Lipophilic steroids and thyroid hormone are both transported in the blood largely bound to carrier plasma proteins, with only free, unbound hormone being biologically active.
- Lipophilic hormones readily enter through the lipid membrane barriers of their target cells and bind with nuclear receptors. Hormonal binding activates the synthesis of new enzymatic or structural intracellular proteins that carry out the hormone's effect on the target cell. *(Review Figure 4-23.)*

**Comparison of the Nervous and Endocrine Systems (pp. 102–104)**

- The nervous and endocrine systems are the two main regulatory systems of the body. *(Review Table 4-3.)*
- The nervous system is anatomically "wired" to its target organs, whereas the "wireless" endocrine system secretes blood-borne hormones that reach distant target organs.
- Specificity of neural action depends on the anatomic proximity of the neurotransmitter-releasing neuronal terminal to its target organ. Specificity of endocrine action depends on specialization of target-cell receptors for a specific circulating hormone.
- In general, the nervous system coordinates rapid responses, whereas the endocrine system regulates activities that require duration rather than speed.

## REVIEW EXERCISES

**Objective Questions (Answers on p. A-••)**

1. Conformational changes in channel proteins brought about by voltage changes are responsible for opening and closing $Na^+$ and $K^+$ gates during the generation of an action potential. *(True or false?)*
2. The $Na^+$–$K^+$ pump restores the membrane to resting potential after it reaches the peak of an action potential. *(True or false?)*
3. Following an action potential, there is more $K^+$ outside the cell than inside because of the efflux of $K^+$ during the falling phase. *(True or false?)*
4. Postsynaptic neurons can either excite or inhibit presynaptic neurons. *(True or false?)*
5. Second-messenger systems ultimately bring about the desired cell response by inducing a change in the shape and function of particular intracellular proteins. *(True or false?)*
6. Each steroidogenic organ has all the enzymes necessary to produce any steroid hormone. *(True or false?)*
7. The one-way propagation of action potentials away from the original site of activation is ensured by the _____.
8. The _____ is the site of action potential initiation in most neurons because it has the lowest threshold.
9. A junction in which electrical activity in one neuron influences the electrical activity in another neuron by means of a neurotransmitter is called a _____.
10. Summing of EPSPs occurring very close together in time as a result of repetitive firing of a single presynaptic input is known as _____.
11. Summing of EPSPs occurring simultaneously from several different presynaptic inputs is known as _____.
12. The neuronal relationship where synapses from many presynaptic inputs act on a single postsynaptic cell is called _____, whereas the relationship in which a single presynaptic neuron synapses with and thereby influences the activity of many postsynaptic cells is known as _____.
13. A common membrane-bound intermediary between the receptor and the effector protein within the plasma membrane is the _____.
14. Using the following answer code, indicate which potential is being described:

    (a) graded potential
    (b) action potential

    ____ 1. behaves in all-or-none fashion
    ____ 2. magnitude of the potential change varies with the magnitude of the triggering response
    ____ 3. decremental spread away from the original site
    ____ 4. spreads throughout the membrane in nondiminishing fashion
    ____ 5. serves as a long-distance signal
    ____ 6. serves as a short-distance signal
15. Using the following answer code, indicate which characteristics apply to peptide and steroid hormones:

    (a) peptide hormones
    (b) steroid hormones
    (c) both peptide and steroid hormones
    (d) neither peptide or steroid hormones

    ____ 1. are hydrophilic
    ____ 2. are lipophilic
    ____ 3. are synthesized by the ER
    ____ 4. are synthesized by modifying cholesterol
    ____ 5. includes epinephrine from the adrenal medulla
    ____ 6. includes cortisol from the adrenal cortex
    ____ 7. bind to plasma proteins
    ____ 8. bind to nuclear receptors
    ____ 9. bind to surface membrane receptors
    ____ 10. activate genes to promote synthesis of new proteins
    ____ 11. act via second-messenger to alter pre-existing proteins
    ____ 12. are secreted into blood by endocrine glands and carried to distant target sites

**Essay Questions**

1. What are the two types of excitable tissue?
2. Define the following terms: *polarization, depolarization, hyperpolarization, repolarization, resting membrane potential, threshold potential, action potential, refractory period, all-or-none law.*
3. Describe the permeability changes and ion fluxes that occur during an action potential.
4. Compare contiguous conduction and saltatory conduction.
5. Compare the events that occur at excitatory and inhibitory synapses.
6. Compare the four kinds of gated channels in terms of the factor that opens or closes them.
7. List and describe the types of intercellular communication.
8. Discuss the sequence of events in the cAMP second-messenger pathway.
9. Compare the nervous and endocrine systems.

## POINTS TO PONDER

**(Explanations on p. A-••)**

1. Which of the following would occur if a neuron were experimentally stimulated simultaneously at both ends?
   a. The action potentials would pass in the middle and travel to the opposite ends.
   b. The action potentials would meet in the middle and then be propagated back to their starting positions.
   c. The action potentials would stop as they met in the middle.
   d. The stronger action potential would override the weaker action potential.
   e. Summation would occur when the action potentials met in the middle, resulting in a larger action potential.
2. Compare the expected changes in membrane potential of a neuron stimulated with a *subthreshold stimulus* (a stimulus not sufficient to bring a membrane to threshold), a *threshold stimulus* (a stimulus just sufficient to bring the membrane to threshold), and a *suprathreshold stimulus* (a stimulus larger than that necessary to bring the membrane to threshold).
3. Assume you touched a hot stove with your finger. Contraction of the biceps muscle causes flexion (bending) of the elbow, whereas contraction of the triceps muscle causes extension (straightening) of the elbow. What pattern of postsynaptic potentials (EPSPs and IPSPs) would you expect to be initiated as a reflex in the cell bodies of the neurons controlling these muscles to pull your hand away from the painful stimulus?

   Now assume your finger is being pricked to obtain a blood sample. The same *withdrawal reflex* would be initiated. What pattern of postsynaptic potentials would you voluntarily produce in the neurons controlling the biceps and triceps to keep your arm extended in spite of the painful stimulus?
4. Researchers believe *schizophrenia* is caused by excessive dopamine activity in a particular region of the brain. Explain why symptoms of schizophrenia sometimes occur as a side effect in patients being treated for Parkinson's disease.
5. Assume presynaptic excitatory neuron A terminates on a postsynaptic cell near the axon hillock and presynaptic excitatory neuron B terminates on the same postsynaptic cell on a dendrite located on the side of the cell body opposite the axon hillock. Explain why rapid firing of presynaptic neuron A could bring the postsynaptic neuron to threshold through temporal summation, thus initiating an action potential, whereas firing of presynaptic neuron B at the same frequency and the same magnitude of EPSPs may not bring the postsynaptic neuron to threshold.

## CLINICAL CONSIDERATION

Becky N. was apprehensive as she sat in the dentist's chair awaiting the placement of her first silver amalgam (the "filling" in a cavity in a tooth). Before preparing the tooth for the amalgam by drilling away the decayed portion of the tooth, the dentist injected a local anesthetic in the nerve pathway supplying the region. As a result, Becky, much to her relief, did not feel any pain during the drilling and filling procedure. Local anesthetics block $Na^+$ channels. Explain how this action prevents the transmission of pain impulses to the brain.

## PHYSIOEDGE RESOURCES


**PhysioEdge CD-ROM**

PhysioEdge, the CD-ROM packaged with your text, focuses on the concepts students find most difficult to learn. Figures marked with this icon have associated activities on the CD. For a visual review of concepts in this chapter, check out the following:

Tutorial: Neuronal Physiology and Hormonal Communication

Media Exercise 4.1: Basics of a Neuron

Media Exercise 4.2: Graded Potentials and Action Potentials

Media Exercise 4.3: Synapses and Neural Integration

Media Exercise 3.3: Signaling at Cell Membranes and Membrane Potential

**PhysioEdge Website**

The website for this book contains a wealth of helpful study aids, as well as many ideas for further reading and research. Log on to: **http://www.brookscole.com/hpfundamentals3**

Select Chapter 4 from the drop-down menu, or click on one of the many resource areas, including **Case Histories,** which introduce clinical aspects of human physiology. For this chapter check out: Case History 15: A Stiff Baby, and Case History 16: And a Limp Baby.

For Suggested Readings, consult **InfoTrac College Edition/ Research** on the PhysioEdge website or go directly to InfoTrac College Edition, your online research library, at: **http://infotrac.thomsonlearning.com**