48

Neurons, Synapses, and Signaling

▲ **Figure 48.1 What makes this snail such a deadly predator?**

KEY CONCEPTS

OVERVIEW

Lines of Communication

The tropical cone snail (*Conus geographus*) in **Figure 48.1** is both beautiful and dangerous. A carnivore, this marine snail hunts, kills, and dines on fish. Injecting venom with a hollow, harpoon-like part of its mouth, the cone snail paralyzes its free-swimming prey in seconds. The venom is so deadly that unlucky scuba divers have died from just a single injection. What makes cone snail venom so fast acting and lethal? As Baldomero Olivera discusses in the interview opening the unit (pp. 850–851), the answer is a mixture of molecules that disable **neurons**, the nerve cells that transfer information within the body. Because the venom almost instantaneously disrupts neuronal control of locomotion and respiration, an animal attacked by the cone snail can neither defend itself nor escape.

Communication by neurons largely consists of long-distance electrical signals and short-distance chemical signals. The specialized structure of neurons allows them to use pulses of electrical current to receive, transmit, and regulate the flow of information over long distances within the body. In transferring information from one cell to another, neurons often rely on chemical signals that act over very short distances. The cone snail's venom is particularly potent because it interferes with both electrical and chemical signaling by neurons.

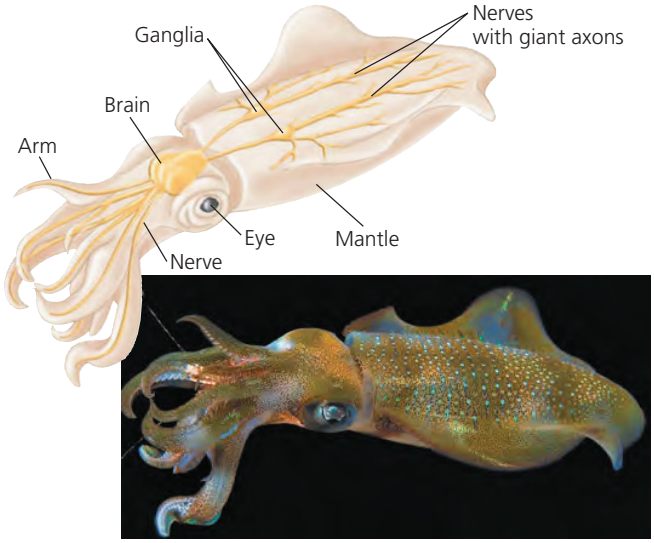
Neurons transmit sensory information, control heart rate, coordinate hand and eye movement, record memories, generate dreams, and much more. All of this information is transmitted within neurons as an electrical signal. The identity of the type of information being transmitted is encoded by the connections made by the active neuron. Interpreting signals in the nervous system therefore involves sorting a complex set of neuronal paths and connections. In more complex animals, this higher-order processing is carried out largely in groups of neurons organized into a **brain** or into simpler clusters called **ganglia**.

In this chapter, we examine the structure of a neuron and explore the molecules and physical principles that govern signaling by neurons. In Chapter 49, we will look at the organization of nervous systems and at higher-order information processing in vertebrates. In Chapter 50, we will investigate systems that detect environmental stimuli and systems that carry out the body's responses to those stimuli. Finally, in Chapter 51, we will consider how these nervous system functions are integrated into the activities and interactions that make up animal behavior.

CONCEPT 48.1

Neuron organization and structure reflect function in information transfer

Before delving into the activity of an individual neuron, let's take an overall look at how neurons function in the flow of information through the animal body. We'll use as our example the squid, an organism that has some extraordinarily large nerve cells that played a crucial role in the discovery of how neurons transmit signals.



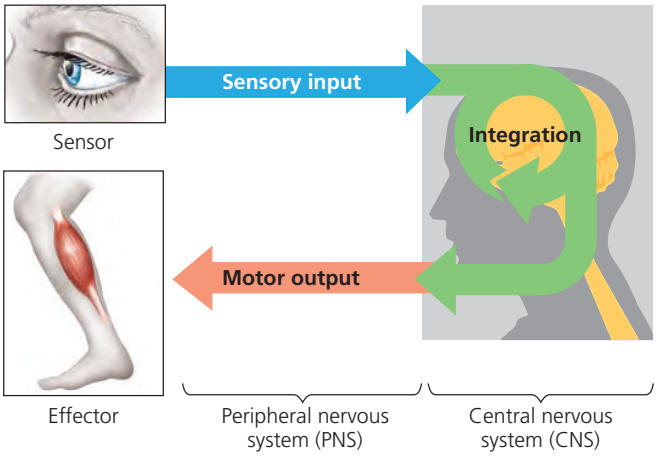
▲ Figure 48.2 Overview of the squid nervous system. Signals travel from the brain to the muscular mantle along *giant axons*, nerve cell extensions of unusually large diameter.

Introduction to Information Processing

Like the cone snail in Figure 48.1, the squid in **Figure 48.2** is an active predator. Using its brain to process information captured by its image-forming eyes, the squid surveys its environment. When the squid spots prey, signals travel from its brain to neurons in its mantle, causing muscle contractions that propel the squid forward.

Information processing by a nervous system occurs in three stages: sensory input, integration, and motor output **(Figure 48.3)**. In many animals, the neurons that carry out integration are organized in a **central nervous system (CNS)**, which includes the brain and a longitudinal nerve cord. The neurons that carry information into and out of the CNS constitute the **peripheral nervous system (PNS)**. When bundled together, such neurons form **nerves**.

In all but the simplest animals, specialized populations of neurons handle each stage of information processing. **Sensory neurons** transmit information from eyes and other sensors that detect external stimuli (light, sound, touch, heat, smell, and taste) or internal conditions (such as blood pressure, blood carbon dioxide level, and muscle tension). This information is sent to processing centers in the brain or ganglia. Neurons in the brain or ganglia integrate (analyze and interpret) the sensory input, taking into account the immediate context and the animal's experience. The vast majority of neurons in the brain are **interneurons**, which form the local circuits connecting neurons in the brain. Motor output relies on neurons that extend out of the processing centers and trigger muscle or gland activity. For example, **motor neurons** transmit signals to muscle cells, causing them to contract. In exploring how this transmission of information flows within the nervous system, we'll begin with the unique structure of neurons.



▲ Figure 48.3 Summary of information processing.

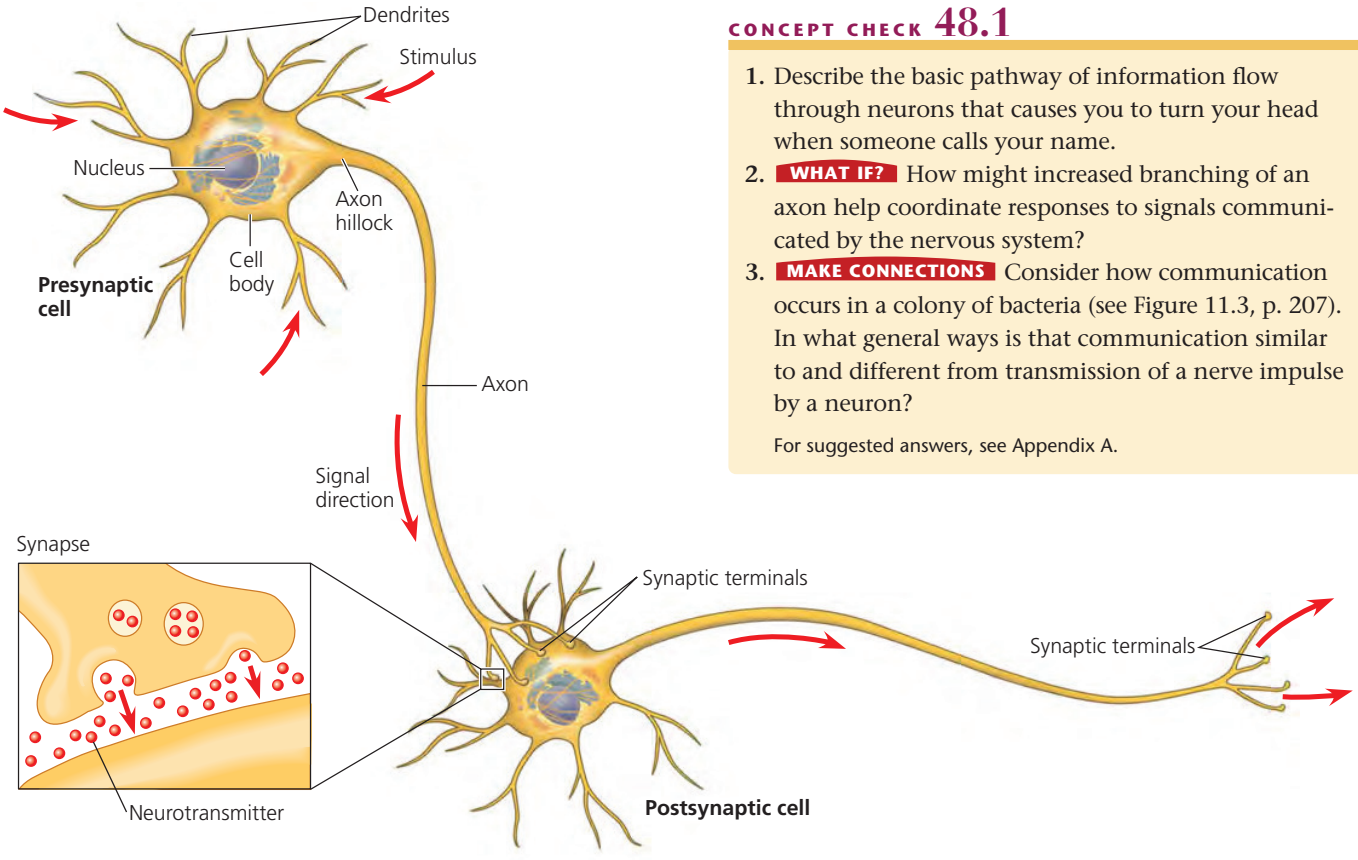
Neuron Structure and Function

The ability of a neuron to receive and transmit information is based on a highly specialized cellular organization **(Figure 48.4)**. Most of a neuron's organelles, including its nucleus, are located in the **cell body**. A typical neuron has numerous highly branched extensions called **dendrites** (from the Greek *dendron*, tree). Together with the cell body, the dendrites *receive* signals from other neurons. A neuron also has a single **axon**, an extension that *transmits* signals to other cells. Axons are often much longer than dendrites, and some, such as those that reach from the spinal cord of a giraffe to the muscle cells in its feet, are over a meter long. The cone-shaped base of an axon, the *axon hillock*, is typically where signals that travel down the axon are generated. Near its other end, an axon usually divides into many branches.

Each branched end of an axon transmits information to another cell at a junction called a **synapse** (see Figure 48.4). The part of each axon branch that forms this specialized junction is a *synaptic terminal*. At most synapses, chemical messengers called **neurotransmitters** pass information from the transmitting neuron to the receiving cell. In describing a synapse, we refer to the transmitting neuron as the *presynaptic cell* and the neuron, muscle, or gland cell that receives the signal as the *postsynaptic cell*.

Depending on the number of synapses a neuron has with other cells, its shape can vary from simple to quite complex **(Figure 48.5)**. Highly branched axons can transmit information to many target cells. Similarly, neurons with highly branched dendrites can receive input through large numbers of synapses, as many as 100,000 in the case of some interneurons.

The neurons of vertebrates and most invertebrates require supporting cells called **glial cells**, or **glia** (from a Greek word meaning "glue") **(Figure 48.6)**. Glia nourish neurons, insulate the axons of neurons, and regulate the extracellular fluid surrounding neurons. Overall, glia outnumber neurons in the mammalian brain 10- to 50-fold. We will examine the functions of specific glia later in this chapter and in Chapter 49.

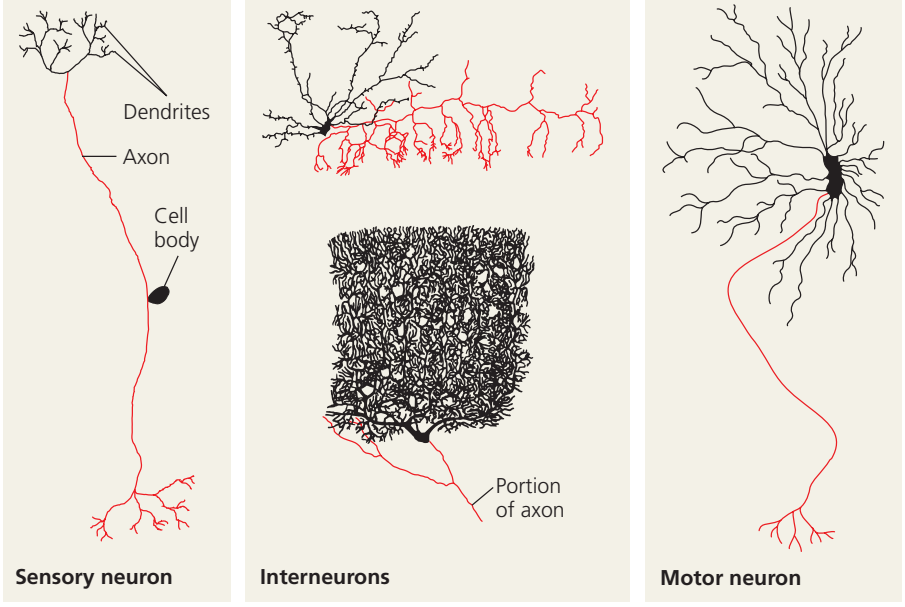


▲ **Figure 48.4 Neuron structure and organization.**

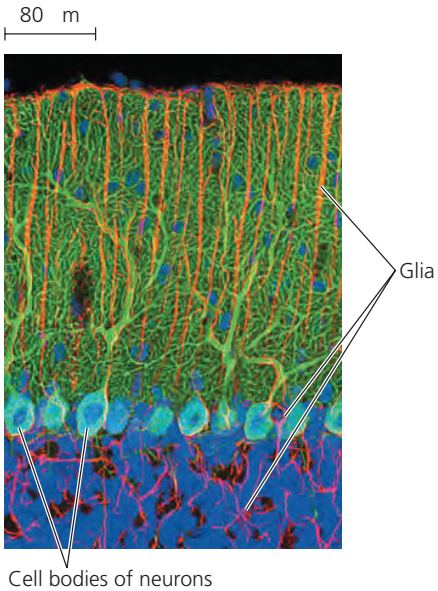
CONCEPT CHECK 48.1

1. Describe the basic pathway of information flow through neurons that causes you to turn your head when someone calls your name.
2. **WHAT IF?** How might increased branching of an axon help coordinate responses to signals communicated by the nervous system?
3. **MAKE CONNECTIONS** Consider how communication occurs in a colony of bacteria (see Figure 11.3, p. 207). In what general ways is that communication similar to and different from transmission of a nerve impulse by a neuron?

For suggested answers, see Appendix A.



▲ **Figure 48.5 Structural diversity of neurons.** Cell bodies and dendrites are black in these diagrams; axons are red. In the sensory neuron, unlike the other neurons here, the cell body is located partway along the axon that conveys signals from the dendrites to the axon's terminal branches.



▲ **Figure 48.6 Glia in the mammalian brain.** This micrograph (a fluorescently labeled laser confocal image) shows a region of the rat brain packed with glia and interneurons. The glia are labeled red, the DNA in nuclei is labeled blue, and the dendrites of neurons are labeled green.

CONCEPT 48.2

Ion pumps and ion channels establish the resting potential of a neuron

As you read in Chapter 7, ions are unequally distributed between the interior of cells and the fluid that surrounds them. As a result, the inside of a cell is negatively charged relative to the outside. Because the attraction of opposite charges across the plasma membrane is a source of potential energy, this charge difference, or voltage, is called the **membrane potential**. The membrane potential of a resting neuron—one that is not sending a signal—is its **resting potential** and is typically between −60 and −80 mV (millivolts).

Inputs from other neurons or specific stimuli cause changes in the neuron's membrane potential that act as signals, transmitting and processing information. Rapid changes in membrane potential are what enable us to see a flower, read a book, or climb a tree. Thus, to understand how neurons function, we first need to examine how chemical and electrical forces form, maintain, and alter membrane potentials.

Formation of the Resting Potential

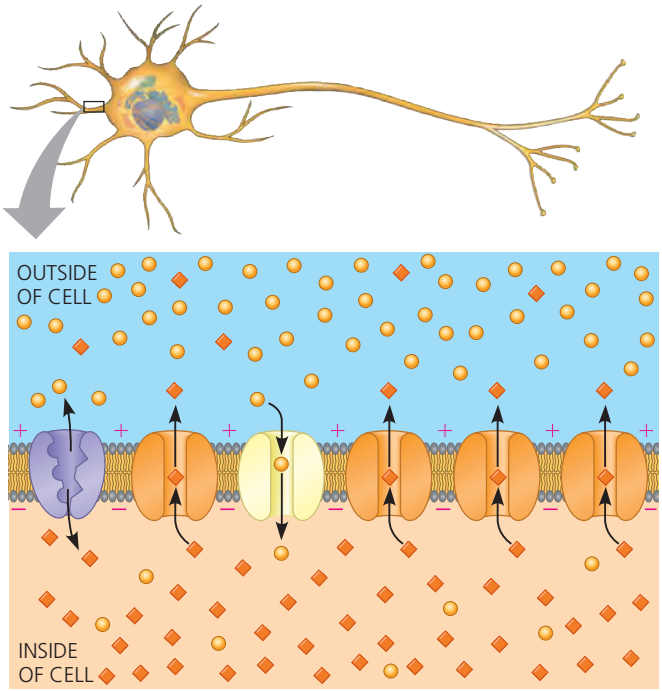
Potassium ions (K^+) and sodium ions (Na^+) play an essential role in the formation of the resting potential. Each type of ion has a concentration gradient across the plasma membrane of a neuron **(Table 48.1)**. In the case of mammalian neurons, the concentration of K^+ is highest inside the cell, while the concentration of Na^+ is highest outside. These Na^+ and K^+ gradients are maintained by *sodium-potassium pumps* in the plasma membrane. As discussed in Chapter 7, these ion pumps use the energy of ATP hydrolysis to actively transport Na^+ out of the cell and K^+ into the cell **(Figure 48.7)**. There are also concentration gradients for chloride ions (Cl^-) and other anions, as shown in Table 48.1, but we will ignore these for the moment.

A sodium-potassium pump transports three sodium ions out of the cell for every two potassium ions that it transports in. Although this pumping generates a net export of positive charge, the resulting voltage difference is only a few millivolts. Why, then, is there a voltage difference of 60–80 mV in a resting neuron? The answer lies in ion movement through **ion channels**, pores formed by clusters of specialized proteins that span the membrane. Ion channels allow ions to diffuse back and forth across the membrane. As ions diffuse through channels, they carry with them units of electrical charge. Any resulting *net* movement of positive or negative charge will generate a membrane potential, or voltage across the membrane.

The concentration gradients of K^+ and Na^+ across the plasma membrane represent a chemical form of potential energy. The ion channels that convert this chemical potential energy to electrical potential energy can do so because they have *selective permeability*, allowing only certain ions to pass. For example, a potassium channel allows K^+ to diffuse freely across the membrane, but not other ions, such as Na^+.

Table 48.1 Ion Concentrations Inside and Outside of Mammalian Neurons

Ion	Intracellular Concentration (m*M*)	Extracellular Concentration (m*M*)
Potassium (K^+)	140	5
Sodium (Na^+)	15	150
Chloride (Cl^-)	10	120
Large anions (A^-) inside cell, such as proteins	100	(not applicable)



▲ **Figure 48.7 The basis of the membrane potential.** The sodium-potassium pump generates and maintains the ionic gradients of Na^+ and K^+ shown in Table 48.1. The pump uses ATP to actively transport Na^+ out of the cell and K^+ into the cell. Although there is a substantial concentration gradient of sodium across the membrane, very little net diffusion of Na^+ occurs because there are very few open sodium channels. In contrast, the large number of open potassium channels allow a significant net outflow of K^+. Because the membrane is only weakly permeable to chloride and other anions, this outflow of K^+ results in a net negative charge inside the cell.

Diffusion of K^+ through open potassium channels is critical for formation of the resting potential. The K^+ concentration is 140 m*M* inside the cell, but only 5 m*M* outside. The chemical concentration gradient thus favors a net outflow of K^+. Furthermore, a resting neuron has many open potassium channels, but very few open sodium channels (see Figure 48.7). Because Na^+ and other ions can't readily cross the membrane, K^+ outflow leads to a net negative charge inside the cell. This buildup of negative charge within the neuron is the major source of the membrane potential.

What stops the buildup of negative charge? The excess negative charges inside the cell exert an attractive force that opposes the flow of additional positively charged potassium ions out of the cell. The separation of charge (voltage) thus results in an electrical gradient that counterbalances the chemical concentration gradient of K^+.

Modeling the Resting Potential

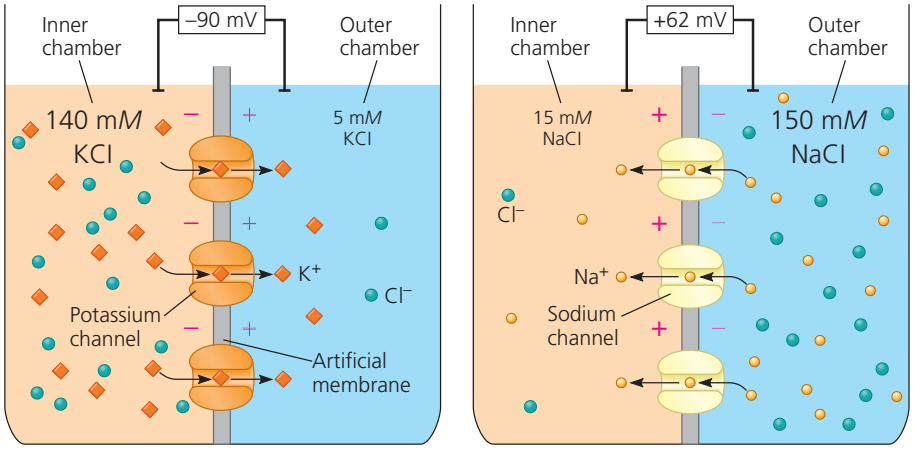
The net flow of K^+ out of a neuron proceeds until the chemical and electrical forces are in balance. How well do these two forces account for the resting potential in a mammalian neuron? To answer this question, let's consider a simple model consisting of two chambers separated by an artificial membrane **(Figure 48.8a)**. To begin, imagine that the membrane contains many open ion channels, all of which allow only K^+ to diffuse across. To produce a K^+ concentration gradient like that of a mammalian neuron, we place a solution of 140 m*M* potassium chloride (KCl) in the inner chamber and 5 m*M* KCl in the outer chamber. The K^+ will diffuse down its concentration gradient into the outer chamber. But because the chloride ions (Cl^-) lack a means of crossing the membrane, there will be an excess of negative charge in the inner chamber.

When our model neuron reaches equilibrium, the electrical gradient will exactly balance the chemical gradient, so that no further net diffusion of K^+ occurs across the membrane. The magnitude of the membrane voltage at equilibrium for a particular ion is called that ion's **equilibrium potential (E_{ion})**. For a membrane permeable to a single type of ion, E_{ion} can be calculated using a formula called the Nernst equation. At human body temperature (37°C) and for an ion with a net charge of 1+, such as K^+ or Na^+, the Nernst equation is

$$E_{ion} = 62 \text{ mV} \left(\log \frac{[\text{ion}]_{outside}}{[\text{ion}]_{inside}} \right)$$

Plugging in the K^+ concentrations reveals that the equilibrium potential for K^+ (E_K) is −90 mV (see Figure 48.8a). The minus sign indicates that K^+ is at equilibrium when the inside of the membrane is 90 mV more negative than the outside.

Although the equilibrium potential for K^+ is −90 mV, the resting potential of a mammalian neuron is somewhat less negative. This difference reflects the small but steady movement of Na^+ across the few open sodium channels in a resting neuron. The concentration gradient of Na^+ has a direction opposite to that of K^+ (see Table 48.1). Na^+ therefore diffuses into the cell, making the inside of the cell less negative. If we model a membrane in which the only open channels are selectively permeable to Na^+, we find that a tenfold higher concentration of Na^+ in the outer chamber results in an equilibrium potential (E_{Na}) of +62 mV **(Figure 48.8b)**. In an actual neuron, the resting potential (−60 to −80 mV) is much closer to E_K than to E_{Na} because there are many open potassium channels but only a small number of open sodium channels.



(a) Membrane selectively permeable to K^+

Nernst equation for K^+ equilibrium potential at 37°C:

$$E_K = 62 \text{ mV} \left(\log \frac{5 \text{ mM}}{140 \text{ mM}} \right) = -90 \text{ mV}$$

(b) Membrane selectively permeable to Na^+

Nernst equation for Na^+ equilibrium potential at 37°C:

$$E_{Na} = 62 \text{ mV} \left(\log \frac{150 \text{ mM}}{15 \text{ mM}} \right) = +62 \text{ mV}$$

◀ Figure 48.8 Modeling a mammalian neuron. Each container is divided into two chambers by an artificial membrane. Ion channels allow free diffusion for particular ions, resulting in the net ion flow represented by arrows. **(a)** The presence of open potassium channels makes the membrane selectively permeable to K^+, and the inner chamber contains a 28-fold higher concentration of K^+ than the outer chamber; at equilibrium, the inside of the membrane is −90 mV relative to the outside. **(b)** The membrane is selectively permeable to Na^+, and the inner chamber contains a tenfold lower concentration of Na^+ than the outer chamber; at equilibrium, the inside of the membrane is +62 mV relative to the outside.

WHAT IF? *Adding channels specific for one type of ion to the membrane in (b) would alter the membrane potential. Which ion would pass through these channels, and in what direction would the membrane potential change?*

Because neither K^+ nor Na^+ is at equilibrium in a resting neuron, each ion has a net flow (a current) across the membrane. The resting potential remains steady, which means that the K^+ and Na^+ currents are equal and opposite. Ion concentrations on either side of the membrane also remain steady. Keep in mind that the extent of ion movement required to generate the resting potential is extremely small (about 10^{-12} mole/cm^2 of membrane), far less than would be required to alter the chemical concentration gradient.

Under conditions that allow Na^+ to cross the membrane more readily, the membrane potential will move toward E_{Na} and away from E_K. As we will see in the next section, this is precisely what happens during the generation of a nerve impulse.

CONCEPT CHECK 48.2

1. Under what circumstances could ions flow through ion channels from regions of low ion concentration to regions of high ion concentration?
2. **WHAT IF?** Suppose a cell's membrane potential shifts from −70 mV to −50 mV. What changes in the cell's permeability to K^+ or Na^+ could cause such a shift?
3. **WHAT IF?** Ouabain, a plant substance used in some cultures to poison hunting arrows, disables the sodium-potassium pump. What change in the resting potential would you expect to see if you treated a neuron with ouabain? Explain.
4. **MAKE CONNECTIONS** Figure 7.13, on page 132, illustrates diffusion by dye molecules. Could diffusion eliminate the concentration gradient of a dye that has a net charge? Explain.

For suggested answers, see Appendix A.

CONCEPT 48.3

Action potentials are the signals conducted by axons

The membrane potential of a neuron changes in response to a variety of stimuli. Using the technique of intracellular recording, researchers can record and graph these changes as a function of time **(Figure 48.9)**. Changes in the membrane potential occur because neurons contain **gated ion channels**, ion channels that open or close in response to stimuli. The opening or closing of gated ion channels alters the membrane's permeability to particular ions, which in turn alters the membrane potential.

Hyperpolarization and Depolarization

To explore how the membrane potential changes, let's consider what happens when gated potassium channels that are closed in a resting neuron are stimulated to open. Opening these potassium channels increases the membrane's permeability to K^+. Net diffusion of K^+ out of the neuron increases, shifting the membrane potential toward E_K (−90 mV at 37°C). This increase in the magnitude of the membrane potential, called a **hyperpolarization**, makes the inside of the membrane more negative **(Figure 48.10a)**. In a resting neuron, hyperpolarization results from any stimulus that increases the outflow of positive ions or the inflow of negative ions.

Although opening potassium channels in a resting neuron causes hyperpolarization, opening some other types of ion channels has an opposite effect, making the inside of the membrane less negative **(Figure 48.10b)**. A reduction in the magnitude of the membrane potential is called a **depolarization**. Depolarization in neurons often involves gated sodium channels. If a stimulus causes the gated sodium channels in a resting neuron to open, the membrane's permeability to Na^+ increases. Na^+ diffuses into the cell along its concentration gradient, causing a depolarization as the membrane potential shifts toward E_{Na} (+62 mV at 37°C).

Graded Potentials and Action Potentials

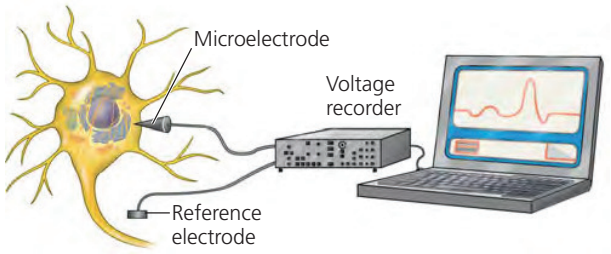
Sometimes, the response to hyperpolarization or depolarization is simply a shift in the membrane potential. This shift, called a **graded potential**, has a magnitude that varies with the strength of the stimulus, with a larger stimulus causing a greater change in the membrane potential. Graded potentials induce a small electrical current that leaks out of the neuron as it flows along the membrane. Graded potentials

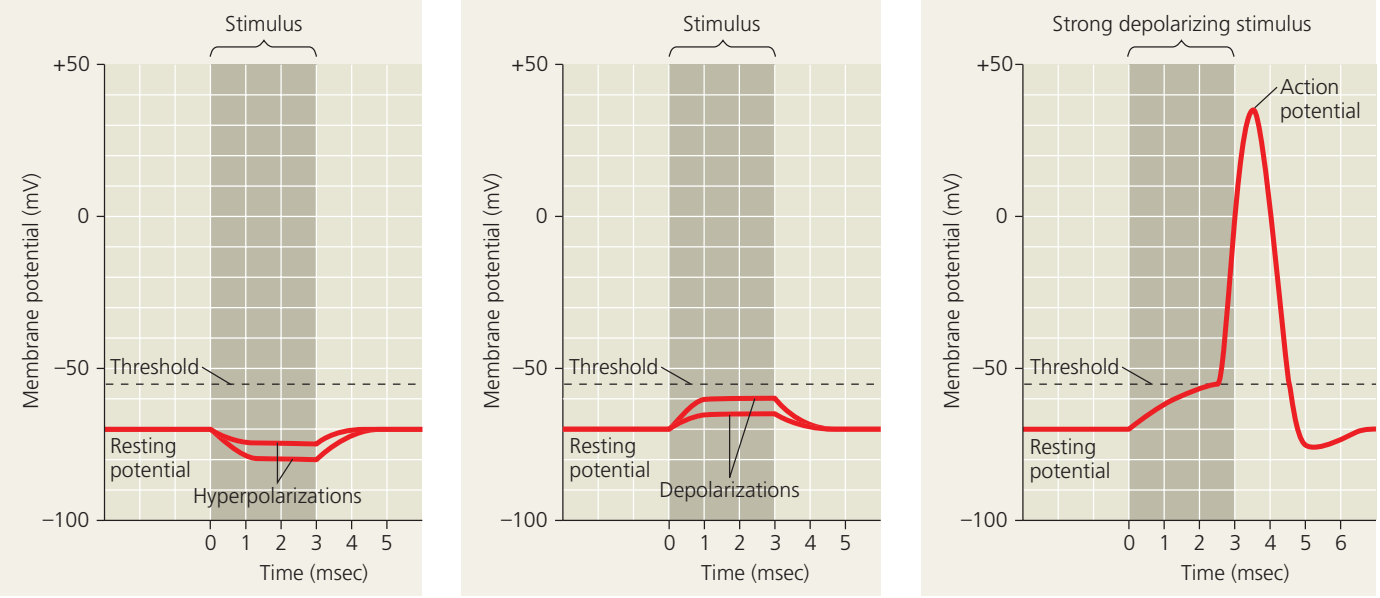
▼ Figure 48.9 RESEARCH METHOD

Intracellular Recording

APPLICATION Electrophysiologists use intracellular recording to measure the membrane potential of neurons and other cells.

TECHNIQUE A microelectrode is made from a glass capillary tube filled with an electrically conductive salt solution. One end of the tube tapers to an extremely fine tip (diameter < 1 μm). While looking through a microscope, the experimenter uses a micropositioner to insert the tip of the microelectrode into a cell. A voltage recorder (usually an oscilloscope or a computer-based system) measures the voltage between the microelectrode tip inside the cell and a reference electrode placed in the solution outside the cell.





(a) Graded hyperpolarizations produced by two stimuli that increase membrane permeability to K^+. The larger stimulus produces a larger hyperpolarization.

(b) Graded depolarizations produced by two stimuli that increase membrane permeability to Na^+. The larger stimulus produces a larger depolarization.

(c) Action potential triggered by a depolarization that reaches the threshold.

▲ Figure 48.10 Graded potentials and an action potential in a neuron.

DRAW IT *Redraw the graph in part (c), extending the y-axis. Then label the positions of E_K and E_{Na}.*

thus decay with distance from their source. Although graded potentials are not the nerve signals that travel along axons, they have a major effect on the generation of nerve signals.

If a depolarization shifts the membrane potential sufficiently, the result is a massive change in membrane voltage called an **action potential**. Unlike graded potentials, action potentials have a constant magnitude and can regenerate in adjacent regions of the membrane. Action potentials can therefore spread along axons, making them well suited for transmitting a signal over long distances.

Action potentials arise because some of the ion channels in neurons are **voltage-gated ion channels**, opening or closing when the membrane potential passes a particular level. If a depolarization opens voltage-gated sodium channels, the resulting flow of Na^+ into the neuron results in further depolarization. Because the sodium channels are voltage gated, an increased depolarization causes more sodium channels to open, leading to an even greater flow of current. The result is a process of *positive feedback* (see Figure 1.13) that triggers a very rapid opening of all voltage-gated sodium channels and the marked change in membrane potential that defines an action potential **(Figure 48.10c)**.

Action potentials occur whenever a depolarization increases the membrane voltage to a particular value, called the **threshold**. For mammalian neurons, the threshold is a membrane potential of about −55 mV. Once initiated, the action potential has a magnitude that is independent of the strength of the triggering stimulus. Because action potentials occur fully or not at all, they represent an *all-or-none* response to stimuli. This all-or-none property reflects the fact that depolarization opens voltage-gated sodium channels, and the opening of sodium channels causes further depolarization. The positive-feedback loop of depolarization and channel opening triggers an action potential whenever the membrane potential reaches the threshold.

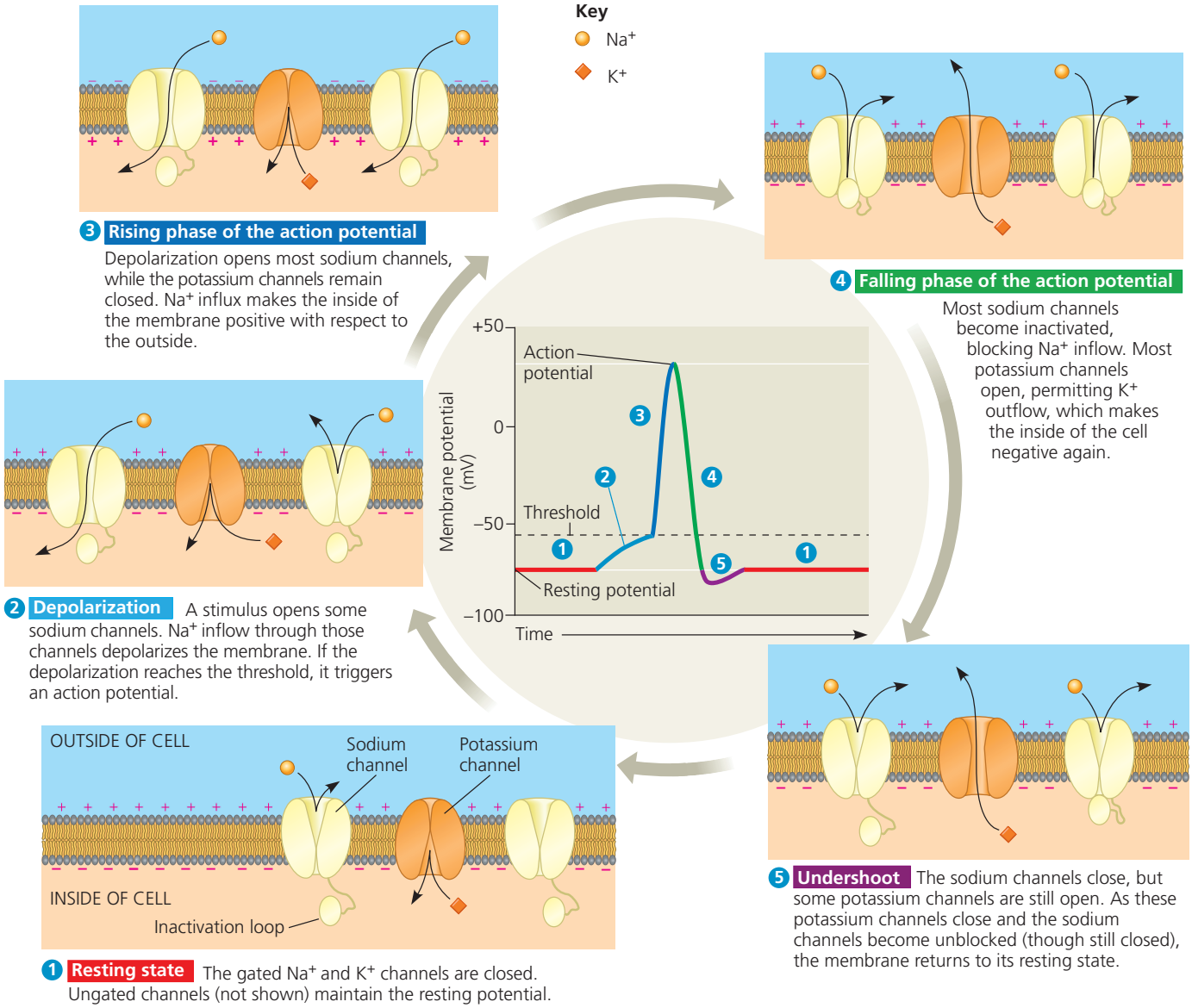
The discovery of how action potentials are generated dates to the 1940s and 1950s, with the work of British scientists Andrew Huxley and Alan Hodgkin. Because no techniques were available for studying electrical events in small cells, they took electrical recordings from the giant neurons of the squid (see Figure 48.2). Their experiments led to a model, presented in the next section, that earned them a Nobel Prize in 1963.

Generation of Action Potentials: *A Closer Look*

The characteristic shape of the graph of an action potential (see Figure 48.10c) reflects the large change in membrane potential resulting from ion movement through voltage-gated sodium and potassium channels. Membrane depolarization opens both types of channels, but they respond independently and sequentially. Sodium channels open first, initiating the action potential. As the action potential proceeds, the sodium channels become inactivated: A loop of the channel protein moves, blocking ion flow through the opening. Sodium channels remain inactivated until after the membrane returns to the resting potential and the channels close. Potassium channels open

more slowly than sodium channels, but remain open and functional until the end of the action potential.

To understand further how voltage-gated channels shape the action potential, we'll consider the process as a series of stages (**Figure 48.11**). 1 When the membrane of the axon is at the resting potential, most voltage-gated sodium channels are closed. Some potassium channels are open, but most voltage-gated potassium channels are closed. 2 When a stimulus depolarizes the membrane, some gated sodium channels open, allowing more Na^+ to diffuse into the cell. The Na^+ inflow causes further depolarization, which opens still more gated sodium channels, allowing even more Na^+ to diffuse into the cell. 3 Once the threshold is crossed, the positive-feedback cycle rapidly brings the membrane potential close to E_{Na}. This stage of the action potential is called the *rising phase*. 4 Two events prevent the membrane potential from actually reaching E_{Na}: Voltage-gated sodium channels inactivate soon after opening, halting Na^+ inflow; and most voltage-gated potassium channels open, causing a rapid outflow of K^+. Both events quickly bring the membrane potential back toward E_K. This stage is called the *falling phase*. 5 In the final phase of an action potential, called the *undershoot*, the membrane's permeability to K^+ is higher than at rest, so the membrane potential is closer to E_K than it is at the resting potential. The gated potassium channels eventually close, and the membrane potential returns to the resting potential.



▲ Figure 48.11 The role of voltage-gated ion channels in the generation of an action potential. The circled numbers on the graph in the center and the colors of the action potential phases correspond to the five diagrams showing voltage-gated sodium and potassium channels in a neuron's plasma membrane. (Ungated ion channels are not illustrated.)

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The sodium channels remain inactivated during the falling phase and the early part of the undershoot. As a result, if a second depolarizing stimulus occurs during this period, it will be unable to trigger an action potential. The "downtime" when a second action potential cannot be initiated is called the **refractory period**. This interval sets a limit on the maximum frequency at which action potentials can be generated. As we will discuss shortly, the refractory period also ensures that all signals in an axon travel in one direction, from the cell body to the axon terminals.

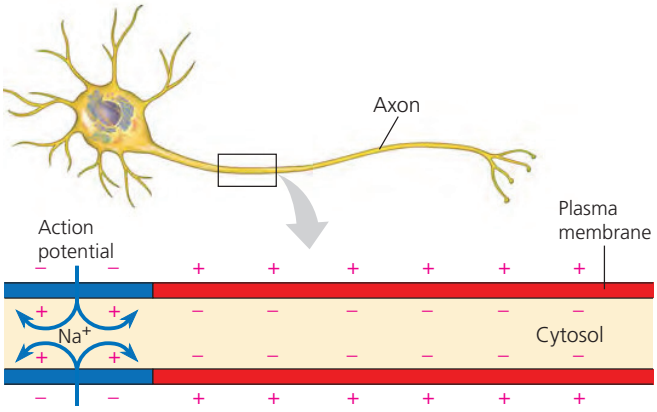
Note that the refractory period is due to the inactivation of sodium channels, not to a change in the ion gradients across the plasma membrane. The flow of charged particles during an action potential involves far too few ions to change the concentration on either side of the membrane significantly.

For most neurons, the interval between the onset of an action potential and the end of the refractory period is only 1–2 milliseconds (msec). Because action potentials are so brief, a neuron can produce hundreds per second. Furthermore, the frequency with which a neuron generates action potentials varies in response to input. Such differences in action potential frequency convey information about signal strength. In hearing, for example, louder sounds result in more frequent action potentials in neurons connecting the ear to the brain. Differences in the time interval between action potentials are in fact the only variable in transmission of information by an axon.

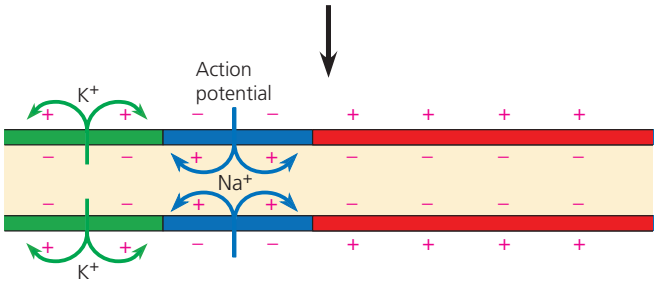
Gated ion channels and action potentials have a central role in all nervous system function. As a consequence, mutations in genes that encode ion channel proteins can cause disorders affecting the nerves, muscles, brain, or heart. The type of disorder depends largely on where in the body the gene for the ion channel protein is expressed. For example, mutations affecting voltage-gated sodium channels in skeletal muscle cells can cause myotonia, a periodic spasming of those muscles; and mutations affecting sodium channels in the brain can cause epilepsy, in which excessive synchronized firing of groups of nerve cells causes seizures.

Conduction of Action Potentials

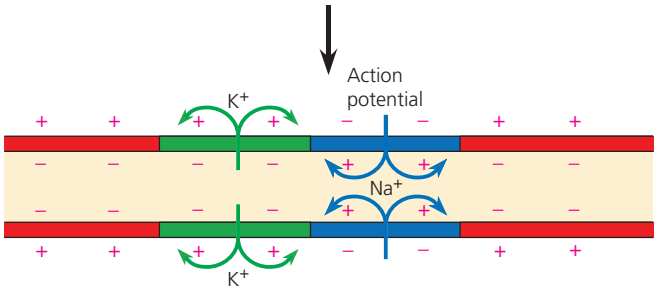
At the site where an action potential is initiated (usually the axon hillock), Na^+ inflow during the rising phase creates an electrical current that depolarizes the neighboring region of the axon membrane **(Figure 48.12)**. The depolarization in the neighboring region is large enough to reach the threshold, causing the action potential to be reinitiated there. This process is repeated many times along the length of the axon. Because an action potential is an all-or-none event, the magnitude and duration of the action potential remain constant at each position along the axon. The result is the movement of a nerve impulse from the cell body to the synaptic terminals, much like the cascade of events triggered by knocking over the first domino in a line.



1 An action potential is generated as Na^+ flows inward across the membrane at one location.



2 The depolarization of the action potential spreads to the neighboring region of the membrane, reinitiating the action potential there. To the left of this region, the membrane is repolarizing as K^+ flows outward.



3 The depolarization-repolarization process is repeated in the next region of the membrane. In this way, local currents of ions *across* the plasma membrane cause the action potential to be propagated *along* the length of the axon.

▲ **Figure 48.12 Conduction of an action potential.** This figure shows events at three successive times as an action potential passes from left to right. At each point along the axon, voltage-gated ion channels go through the sequence of changes in Figure 48.10. Membrane colors correspond to the action potential phases in Figure 48.10.

An action potential that starts at the axon hillock moves along the axon only toward the synaptic terminals. Why? Immediately behind the traveling zone of depolarization caused by Na^+ inflow is a zone of repolarization caused by K^+ outflow. In the repolarized zone, the sodium channels remain inactivated. Consequently, the inward current that depolarizes the axon membrane *ahead* of the action potential cannot produce another action potential *behind* it. This prevents action potentials from traveling back toward the cell body.

Evolutionary Adaptations of Axon Structure

EVOLUTION Axon diameter is a major factor affecting the speed at which action potentials are conducted. One adaptation that increases conductance speed is an increased axon width. Resistance to electrical current flow is inversely proportional to the cross-sectional area of a conductor (such as a wire or an axon). In the same way that a wide hose offers less resistance to the flow of water than does a narrow hose, a wide axon provides less resistance to the current associated with an action potential than does a narrow axon.

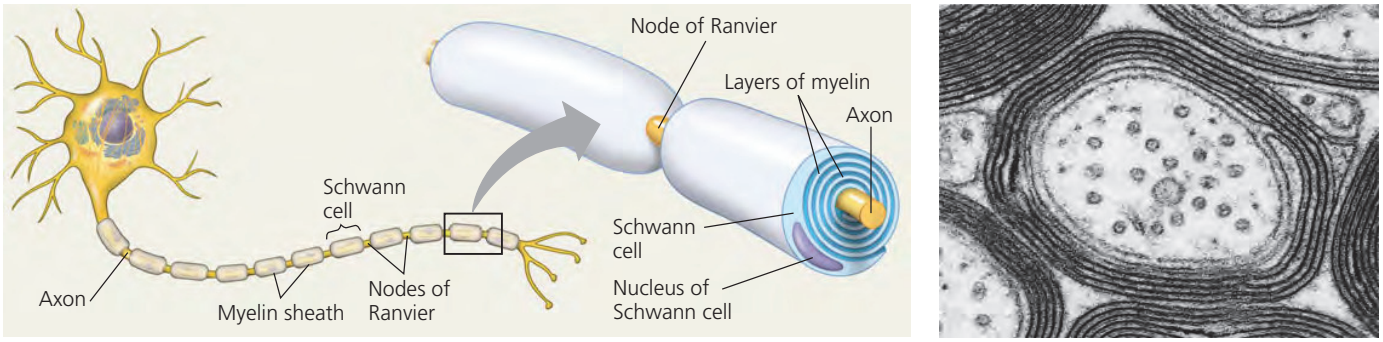
In invertebrates, conduction speed varies from several centimeters per second in very narrow axons to about 30 m/sec in the giant axons of some arthropods and molluscs (see Figure 48.2). These giant axons (up to 1 mm wide) function in rapid behavioral responses, such as the muscle contraction that propels a squid toward its prey.

Vertebrate axons have narrow diameters but can still conduct action potentials at high speed. How is this possible? The evolutionary adaptation that enables fast conduction in vertebrate axons is electrical insulation, analogous to the plastic insulation that covers many electrical wires. Insulation causes the depolarizing current associated with an action potential to spread farther along the axon interior, bringing more distant regions to the threshold sooner.

The electrical insulation that surrounds vertebrate axons is called a **myelin sheath** (Figure 48.13). Myelin sheaths are produced by two types of glia—**oligodendrocytes** in the CNS and **Schwann cells** in the PNS. During development, these specialized glia wrap axons in many layers of membrane. The membranes forming these layers are mostly lipid, which is a poor conductor of electrical current.

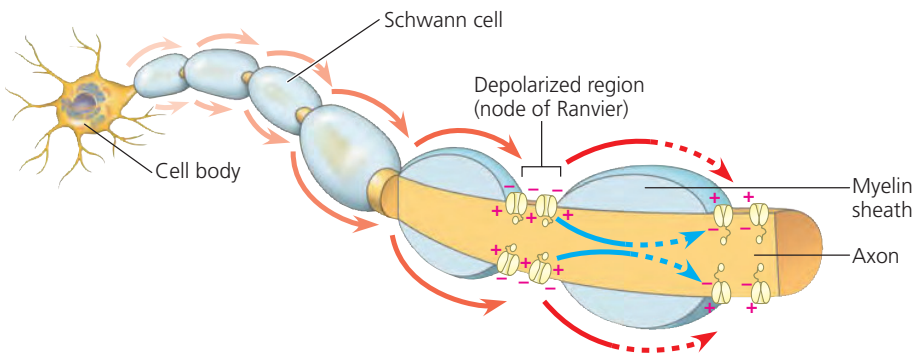
In myelinated axons, voltage-gated sodium channels are restricted to gaps in the myelin sheath called **nodes of Ranvier** (see Figure 48.13). The extracellular fluid is in contact with the axon membrane only at the nodes. As a result, action potentials are not generated in the regions between the nodes. Rather, the inward current produced during the rising phase of the action potential at a node travels all the way to the next node, where it depolarizes the membrane and regenerates the action potential (Figure 48.14). Thus, the time-consuming process of opening and closing of ion channels occurs at only a limited number of positions along the axon. This mechanism for action potential propagation is called **saltatory conduction** (from the Latin *saltare*, to leap) because the action potential appears to jump along the axon from node to node.

The major selective advantage of myelination is its space efficiency. A myelinated axon 20 µm in diameter has a conduction speed faster than that of a squid giant axon with a diameter 40 times greater. Furthermore, more than 2,000 of those myelinated axons can be packed into the space occupied by just one giant axon.



▲ **Figure 48.13 Schwann cells and the myelin sheath.** In the PNS, glia called Schwann cells wrap themselves around axons, forming layers of myelin. Gaps between adjacent Schwann cells are called nodes of Ranvier. The TEM shows a cross section through a myelinated axon.

▶ **Figure 48.14 Saltatory conduction.** In a myelinated axon, the depolarizing current during an action potential at one node of Ranvier spreads along the interior of the axon to the next node (blue arrows), where voltage-gated sodium channels enable reinitiation. Thus, the action potential jumps from node to node as it travels along the axon (red arrows).



CONCEPT CHECK 48.3

1. How do action potentials and graded potentials differ?
2. In multiple sclerosis (from the Greek *skleros*, hard), myelin sheaths harden and deteriorate. How would this affect nervous system function?
3. **WHAT IF?** Suppose a mutation caused gated sodium channels to remain inactivated longer after an action potential. How would this affect the frequency at which action potentials could be generated? Explain.

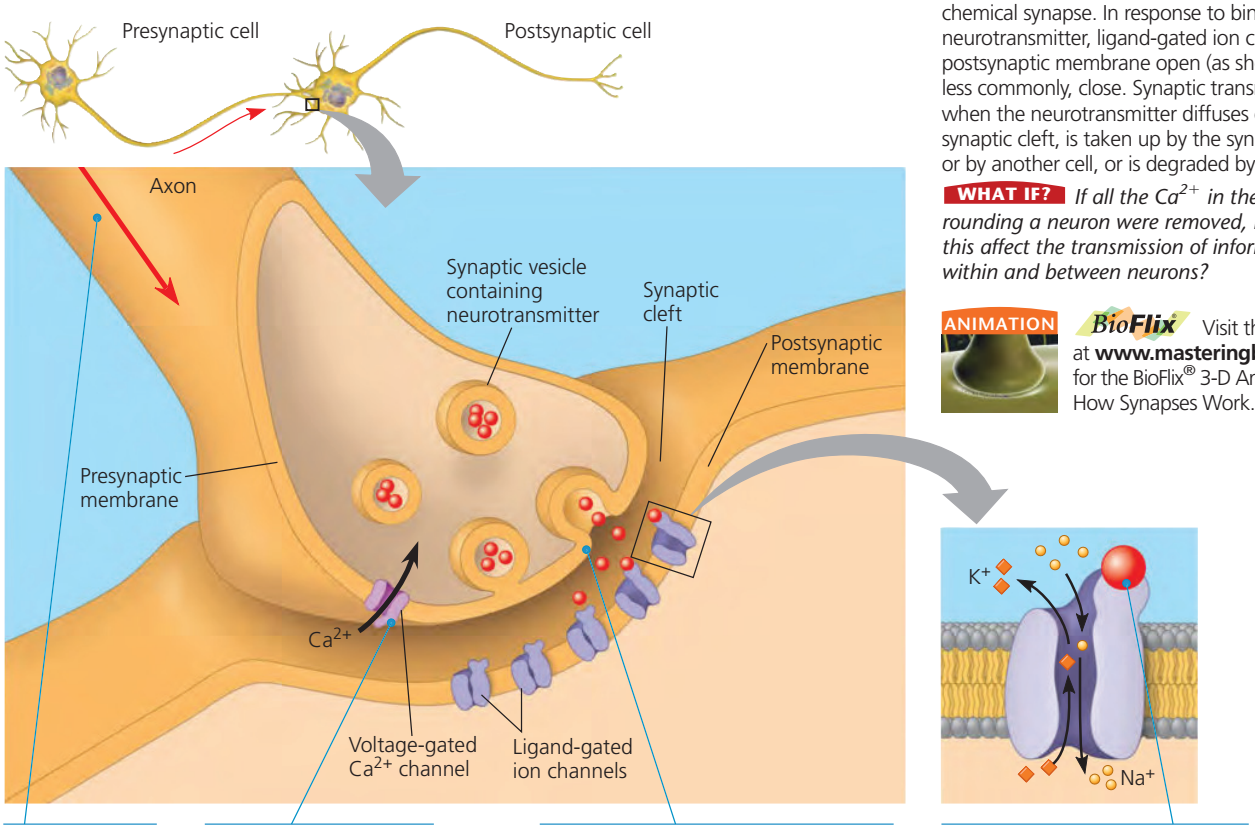
For suggested answers, see Appendix A.

CONCEPT 48.4

Neurons communicate with other cells at synapses

In most cases, action potentials are not transmitted from neurons to other cells. However, information is transmitted, and this transmission occurs at the synapses. Some synapses, called *electrical synapses*, contain gap junctions (see Figure 6.32), which *do* allow electrical current to flow directly from one neuron to another. In both vertebrates and invertebrates, electrical synapses synchronize the activity of neurons responsible for certain rapid, unvarying behaviors. For example, electrical synapses associated with the giant axons of squids and lobsters facilitate the swift execution of escape responses. There are also many electrical synapses in the vertebrate brain.

The majority of synapses are *chemical synapses*, which involve the release of a chemical neurotransmitter by the presynaptic neuron. At each terminal, the presynaptic neuron synthesizes the neurotransmitter and packages it in multiple membrane-bounded compartments called *synaptic vesicles*. The arrival of an action potential at a synaptic terminal depolarizes the plasma membrane, opening voltage-gated channels that allow Ca^{2+} to diffuse into the terminal **(Figure 48.15)**. The resulting rise in Ca^{2+} concentration in the terminal causes some of the synaptic vesicles to fuse with the terminal membrane, releasing the neurotransmitter.



◀ Figure 48.15 A chemical synapse. This figure illustrates the sequence of events that transmits a nerve impulse across a chemical synapse. In response to binding of neurotransmitter, ligand-gated ion channels in the postsynaptic membrane open (as shown here) or, less commonly, close. Synaptic transmission ends when the neurotransmitter diffuses out of the synaptic cleft, is taken up by the synaptic terminal or by another cell, or is degraded by an enzyme.

WHAT IF? *If all the Ca^{2+} in the fluid surrounding a neuron were removed, how would this affect the transmission of information within and between neurons?*

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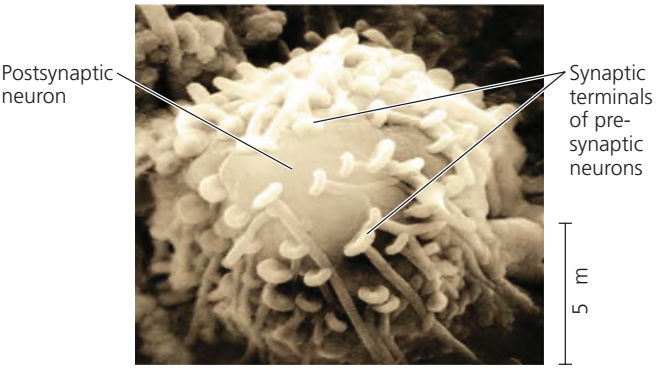
Once released, the neurotransmitter diffuses across the *synaptic cleft*, the gap that separates the presynaptic neuron from the postsynaptic cell. Diffusion time is very short because the gap is less than 50 nm across. Upon reaching the postsynaptic membrane, the neurotransmitter binds to and activates a specific receptor in the membrane.

Information transfer is much more readily modified at chemical synapses than at electrical synapses. A variety of factors can affect the amount of neurotransmitter that is released or the responsiveness of the postsynaptic cell. Such modifications underlie an animal's ability to alter its behavior in response to change and form the basis for learning and memory, as you will learn in Chapter 49.



▲ **Figure 48.16 Synaptic terminals on the cell body of a postsynaptic neuron** (colorized SEM).

Generation of Postsynaptic Potentials

At many chemical synapses, the receptor protein that binds and responds to neurotransmitters is a **ligand-gated ion channel**, often called an *ionotropic receptor*. These receptors are clustered in the membrane of the postsynaptic cell, directly opposite the synaptic terminal. Binding of the neurotransmitter (the receptor's ligand) to a particular part of the receptor opens the channel and allows specific ions to diffuse across the postsynaptic membrane. The result is a *postsynaptic potential*, a graded potential in the postsynaptic cell.

At some synapses, the ligand-gated ion channel is permeable to both K^+ and Na^+ (see Figure 48.15). When this channel opens, the membrane potential depolarizes toward a value roughly midway between E_K and E_{Na}. Because such a depolarization brings the membrane potential toward threshold, it is called an **excitatory postsynaptic potential (EPSP)**.

At other synapses, the ligand-gated ion channel is selectively permeable for only K^+ or Cl^-. When such a channel opens, the postsynaptic membrane hyperpolarizes. A hyperpolarization produced in this manner is an **inhibitory postsynaptic potential (IPSP)** because it moves the membrane potential further from threshold.

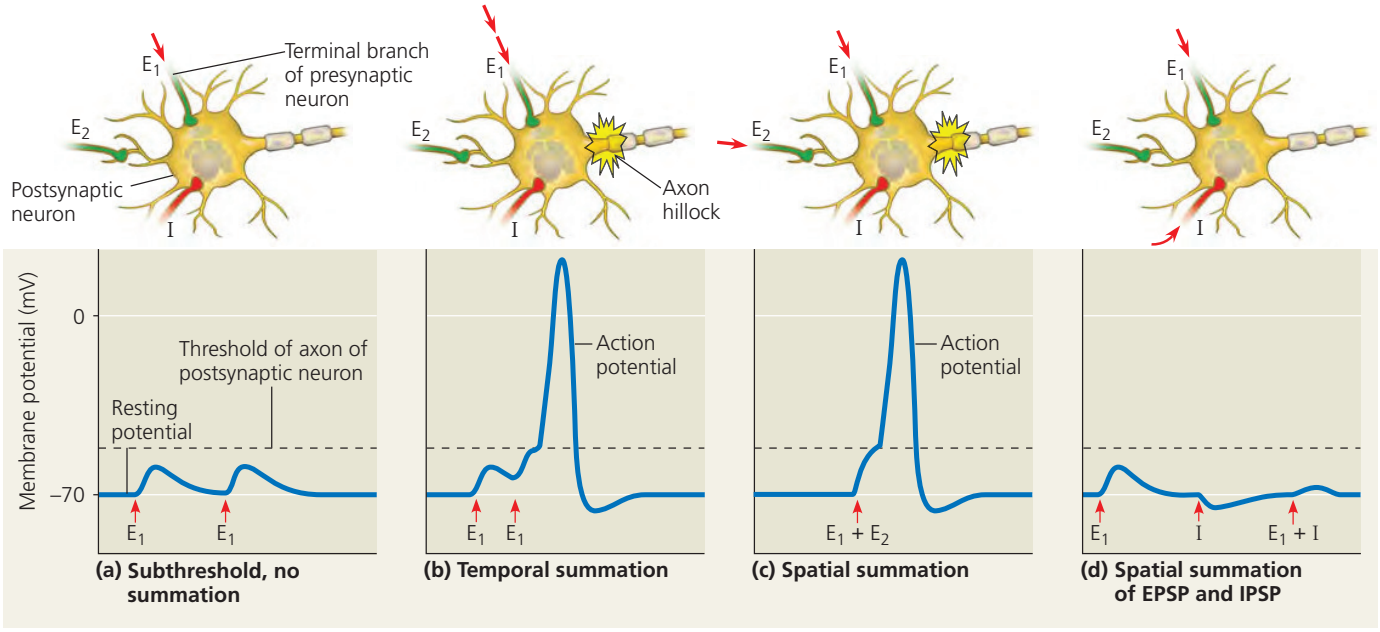
Various mechanisms that rapidly clear neurotransmitter molecules from the synaptic cleft limit the duration of postsynaptic potentials. Some neurotransmitters are actively transported back into the presynaptic neuron, to be repackaged into synaptic vesicles, or they are transported into glia, to be metabolized as fuel. Other neurotransmitters are removed from the synaptic cleft by simple diffusion or by an enzyme that catalyzes hydrolysis of the neurotransmitter.

Summation of Postsynaptic Potentials

The cell body and dendrites of one postsynaptic neuron may receive inputs from chemical synapses with hundreds or even thousands of synaptic terminals **(Figure 48.16)**. The magnitude of the postsynaptic potential at any one synapse varies with a number of factors, including the amount of neurotransmitter released by the presynaptic neuron. As a graded potential, a postsynaptic potential becomes smaller with distance from the synapse. Therefore, by the time a single EPSP reaches the axon hillock, it is usually too small to trigger an action potential in a postsynaptic neuron **(Figure 48.17a)**.

On some occasions, two EPSPs occur at a single synapse in such rapid succession that the postsynaptic neuron's membrane potential has not returned to the resting potential before the arrival of the second EPSP. When that happens, the EPSPs add together, an effect called **temporal summation (Figure 48.17b)**. Moreover, EPSPs produced nearly simultaneously by *different* synapses on the same postsynaptic neuron can also add together, an effect called **spatial summation (Figure 48.17c)**. Through spatial and temporal summation, several EPSPs can combine to depolarize the membrane at the axon hillock to the threshold, causing the postsynaptic neuron to produce an action potential. Summation applies as well to IPSPs: Two or more IPSPs occurring nearly simultaneously at synapses in the same region or in rapid succession at the same synapse have a larger hyperpolarizing effect than a single IPSP. Through summation, an IPSP can also counter the effect of an EPSP **(Figure 48.17d)**.

The interplay between multiple excitatory and inhibitory inputs is the essence of integration in the nervous system. The axon hillock is the neuron's integrating center, the region where the membrane potential at any instant represents the summed effect of all EPSPs and IPSPs. Whenever the membrane potential at the axon hillock reaches the threshold, an action potential is generated and travels along the axon to its synaptic terminals. After the refractory period, the neuron may produce another action potential, provided the membrane potential at the axon hillock once again reaches the threshold.



▲ Figure 48.17 Summation of postsynaptic potentials. These graphs trace changes in the membrane potential at a postsynaptic neuron's axon hillock. The arrows indicate times when postsynaptic potentials occur at two excitatory synapses (E_1 and E_2, green in the diagrams above the graphs) and at one inhibitory synapse (I, red). Like most EPSPs, those produced at E_1 or E_2 do not reach the threshold at the axon hillock without summation.

Modulated Signaling at Synapses

So far, we have focused on synapses where a neurotransmitter binds directly to an ion channel, causing the channel to open. However, there are also synapses in which the receptor for the neurotransmitter is *not* part of an ion channel. At these synapses, the neurotransmitter binds to a *metabotropic receptor*, so called because the resulting opening or closing of ion channels depends on one or more metabolic steps. Binding of a neurotransmitter to a metabotropic receptor activates a signal transduction pathway in the postsynaptic cell involving a second messenger (see Chapter 11). Compared with the postsynaptic potentials produced by ligand-gated channels, the effects of these second-messenger systems have a slower onset but last longer (minutes or even hours). Second messengers modulate the responsiveness of postsynaptic neurons to inputs in diverse ways, such as by altering the number of open potassium channels.

A variety of signal transduction pathways play a role in modulating synaptic transmission. One of the best-studied pathways involves cyclic AMP (cAMP) as a second messenger. For example, when the neurotransmitter norepinephrine binds to its metabotropic receptor, the neurotransmitter-receptor complex activates a G protein, which in turn activates adenylyl cyclase, the enzyme that converts ATP to cAMP (see Figure 11.11). Cyclic AMP activates protein kinase A, which phosphorylates specific ion channel proteins in the postsynaptic membrane, causing them to open or close. Because of the amplifying effect of the signal transduction pathway, the binding of a neurotransmitter molecule to a metabotropic receptor can open or close many channels.

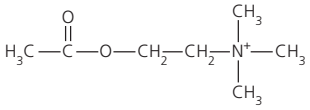
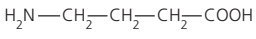
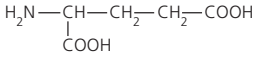
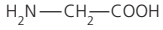
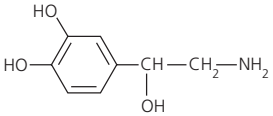
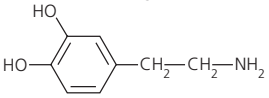
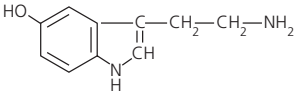
Neurotransmitters

Researchers have identified more than 100 neurotransmitters belonging to five groups: acetylcholine, amino acids, biogenic amines, neuropeptides, and gases (**Table 48.2**, on the next page). The response triggered depends on the particular kind of receptor expressed by the postsynaptic cell. A single neurotransmitter may bind specifically to more than a dozen different receptors, including ionotropic and metabotropic types. Indeed, a particular neurotransmitter can excite postsynaptic cells expressing one receptor and inhibit postsynaptic cells expressing a different receptor. As an example, let's examine **acetylcholine**, a common neurotransmitter in both invertebrates and vertebrates.

Acetylcholine

Acetylcholine is vital for nervous system functions that include muscle stimulation, memory formation, and learning. In vertebrates, there are two major classes of acetylcholine receptor. One type is a ligand-gated ion channel. We know the most about its function at the *neuromuscular junction*, the site where motor neurons synapse with skeletal muscle cells. When acetylcholine released by motor neurons binds this receptor,

Table 48.2 Major Neurotransmitters

Neurotransmitter	Structure
Acetylcholine	
Amino Acids	
GABA (gamma-aminobutyric acid)	
Glutamate	
Glycine	
Biogenic Amines	
Norepinephrine	
Dopamine	
Serotonin	
Neuropeptides (a very diverse group, only two of which are shown)	
Substance P	Arg—Pro—Lys—Pro—Gln—Gln—Phe—Phe—Gly—Leu—Met
Met-enkephalin (an endorphin)	Tyr—Gly—Gly—Phe—Met
Gases	
Nitric oxide	

the ion channel opens, producing an EPSP. This excitatory activity is soon terminated by acetylcholinesterase, an enzyme in the synaptic cleft that hydrolyzes the neurotransmitter.

The acetylcholine receptor active at the neuromuscular junction is also found elsewhere in the PNS, as well as in the CNS. There this ionotropic receptor can bind nicotine, a chemical found in tobacco and tobacco smoke. Nicotine's effects as a physiological and psychological stimulant result from its binding to this receptor.

A metabotropic acetylcholine receptor is found at locations that include the vertebrate CNS and heart. In heart muscle, acetylcholine released by neurons activates a signal transduction pathway. The G proteins in the pathway inhibit adenylyl cyclase and open potassium channels in the muscle cell membrane. Both effects reduce the rate at which the heart pumps. Thus, the effect of acetylcholine in heart muscle is inhibitory rather than excitatory.

A number of natural and synthetic toxins disrupt neurotransmission by acetylcholine. For example, the nerve gas sarin inhibits acetylcholinesterase, causing a buildup of acetylcholine to levels that trigger paralysis and typically death. In contrast, certain bacteria produce a toxin that inhibits presynaptic release of acetylcholine. This toxin causes a rare but severe form of food poisoning called botulism. Untreated botulism is typically fatal because muscles required for breathing fail to contract when acetylcholine release is blocked. Today, the same botulinum toxin is commonly used in cosmetic procedures. Injections of the toxin, known by the trade name Botox, minimize wrinkles around the eyes or mouth by blocking transmission at synapses that control particular facial muscles.

Amino Acids

Amino acid neurotransmitters are active in the vertebrate CNS and PNS. In the CNS, the amino acid **glutamate** is the most common neurotransmitter. When glutamate binds to any of several types of ligand-gated ion channels, it has an excitatory effect on postsynaptic cells. Synapses at which glutamate is the neurotransmitter have a key role in the formation of long-term memory, as we will discuss in Chapter 49.

The amino acid **gamma-aminobutyric acid (GABA)** is the neurotransmitter at most inhibitory synapses in the brain. Binding of GABA to receptors in postsynaptic cells increases membrane permeability to Cl^-, resulting in an IPSP. The widely prescribed drug diazepam (Valium) reduces anxiety through binding to a site on a GABA receptor.

A third amino acid, glycine, acts at inhibitory synapses in parts of the CNS that lie outside of the brain. There, glycine binds to an ionotropic receptor that is inhibited by strychnine, a chemical often used as a rat poison.

Biogenic Amines

The neurotransmitters grouped as **biogenic amines** are synthesized from amino acids and include **norepinephrine**, which is made from tyrosine. Norepinephrine is an excitatory neurotransmitter in the autonomic nervous system, a branch of the PNS discussed in Chapter 49. Outside the nervous system, norepinephrine has distinct but related functions as a hormone, as does the related biogenic amine *epinephrine* (see Chapter 45).

The biogenic amines **dopamine**, made from tyrosine, and **serotonin**, made from tryptophan, are released at many sites in the brain and affect sleep, mood, attention, and learning. Some psychoactive drugs, including LSD and mescaline, apparently produce their hallucinatory effects by binding to brain receptors for these neurotransmitters.

Biogenic amines have a central role in a number of nervous system disorders and treatments (see Chapter 49). The

degenerative illness Parkinson's disease is associated with a lack of dopamine in the brain. In addition, depression is often treated with drugs that increase the brain concentrations of biogenic amines. Prozac, for instance, enhances the effect of serotonin by inhibiting its reuptake after release.

Neuropeptides

Several **neuropeptides**, relatively short chains of amino acids, serve as neurotransmitters that operate via metabotropic receptors. Such peptides are typically produced by cleavage of much larger protein precursors. The neuropeptide *substance P* is a key excitatory neurotransmitter that mediates our perception of pain, while other neuropeptides, called **endorphins**, function as natural analgesics, decreasing pain perception.

In the 1970s, Candace Pert, then a graduate student at Johns Hopkins University, and her research supervisor, Solomon Snyder, discovered endorphins as an outcome of their research on the biochemistry of behavior. Previous studies had suggested that the brain contains receptors for opiates, painkilling drugs such as morphine and heroin. To find these receptors, Pert and Snyder had the insight to apply existing knowledge about the activity of different drugs in the brain **(Figure 48.18)**. In a single, straightforward experiment, they provided the first demonstration that specific opiate receptors exist. Setting out to identify molecules normally present in the brain that could also activate these receptors, they discovered endorphins.

Endorphins are produced in the brain during times of physical or emotional stress, such as childbirth. In addition to relieving pain, they decrease urine output, depress respiration, and produce euphoria, as well as other emotional effects. Because opiates bind to the same receptor proteins as endorphins, opiates mimic endorphins and produce many of the same physiological effects (see Figure 2.18).

Gases

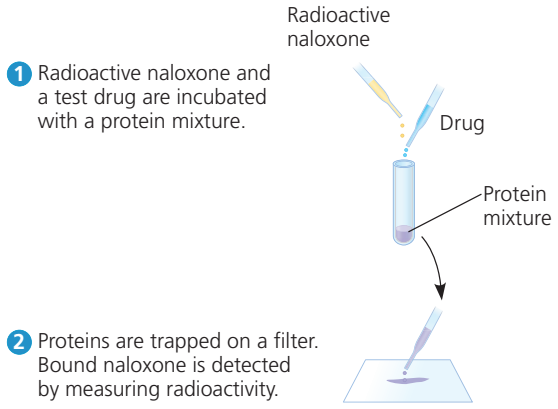
In common with many other types of cells, some neurons in vertebrates release dissolved gases, notably nitric oxide (NO), that act as local regulators. For example, during sexual arousal, certain neurons in human males release NO into the erectile tissue of the penis. In response, smooth muscle cells in the blood vessel walls of the erectile tissue relax, which causes the blood vessels to dilate and fill the spongy erectile tissue with blood, producing an erection. As you read in Chapter 45, the erectile dysfunction drug Viagra increases the ability to achieve and maintain an erection by inhibiting an enzyme that terminates the action of NO.

Unlike most neurotransmitters, NO is not stored in cytoplasmic vesicles but is instead synthesized on demand. NO

▼ Figure 48.18 **INQUIRY**

Does the brain have a specific protein receptor for opiates?

EXPERIMENT In 1973, Candace Pert and Solomon Snyder, of Johns Hopkins University, were searching for an opiate receptor in the mammalian brain. It was known that the drug naloxone antagonizes (opposes) the narcotic effect of opiates. Pert and Snyder reasoned that naloxone acts as an opiate antagonist by binding tightly to the opiate receptor without activating the receptor. They prepared radioactive naloxone and then incubated it with a protein mixture prepared from rodent brains. If proteins that could bind naloxone were present, the radioactivity would become stably associated with the protein mixture. Furthermore, the researchers could determine whether a specific receptor was present by comparing the ability of opiates and non-opiates to interfere with the binding activity.



RESULTS

Drug	Opiate	Concentration That Blocked Naloxone Binding
Morphine	Yes	6×10^{-9} *M*
Methadone	Yes	2×10^{-8} *M*
Levorphanol	Yes	2×10^{-9} *M*
Phenobarbital	No	No effect at 10^{-4} *M*
Atropine	No	No effect at 10^{-4} *M*
Serotonin	No	No effect at 10^{-4} *M*

CONCLUSION Because opiates interfered with naloxone binding, but unrelated drugs did not, Pert and Snyder concluded that the binding activity had the specificity expected of the opiate receptor. They also found that the binding activity was present in tissue from regions of the brain involved in the sensation of pain, but not in tissue from the cerebellum, a brain region that coordinates motor activity.

SOURCE C. B. Pert and S. H. Snyder, Opiate receptor: demonstration in nervous tissue, *Science* 179:1011–1014 (1973).

WHAT IF? Suppose you found a drug that blocks naloxone binding at a concentration of 10^{-8} *M* but has no narcotic effect on animals. What are some possible explanations for this finding?

diffuses into neighboring target cells, produces a change, and is broken down—all within a few seconds. In many of its targets, including smooth muscle cells, NO works like many hormones, stimulating an enzyme to synthesize a second messenger that directly affects cellular metabolism.

Although inhaling air containing the gas carbon monoxide (CO) can be deadly, the vertebrate body produces small amounts of CO, some of which acts as a neurotransmitter. Carbon monoxide is generated by the enzyme heme oxygenase, one form of which is found in certain populations of neurons in the brain and PNS. In the brain, CO regulates the release of hypothalamic hormones. In the PNS, it acts as an inhibitory neurotransmitter that hyperpolarizes the plasma membrane of intestinal smooth muscle cells.

In the next chapter, we will consider how the cellular and biochemical mechanisms we have discussed contribute to nervous system function on the system level.

CONCEPT CHECK 48.4

1. How is it possible for a particular neurotransmitter to produce opposite effects in different tissues?
2. Organophosphate pesticides work by inhibiting acetylcholinesterase, the enzyme that breaks down the neurotransmitter acetylcholine. Explain how these toxins would affect EPSPs produced by acetylcholine.
3. **WHAT IF?** If a drug mimicked the activity of GABA in the CNS, what general effect on behavior might you expect? Explain.
4. **MAKE CONNECTIONS** A change in the concentration of calcium ions is important for fertilization in sea urchins and other animals (see Figure 47.3, on p. 1023). What membrane activity is common to fertilization and neurotransmitter release?

For suggested answers, see Appendix A.

48 CHAPTER REVIEW

SUMMARY OF KEY CONCEPTS

CONCEPT 48.1

Neuron organization and structure reflect function in information transfer (pp. 1045–1047)

- A **central nervous system (CNS)** and a **peripheral nervous system (PNS)** process information in three stages: sensory input, integration, and motor output to effector cells.
- Most neurons have branched **dendrites** that receive signals from other neurons and an **axon** that transmits signals to other cells at **synapses**. Neurons rely on **glia** for functions that include nourishment, insulation, and regulation.

? *How would severing an axon affect the flow of information in a neuron?*

CONCEPT 48.2

Ion pumps and ion channels establish the resting potential of a neuron (pp. 1048–1050)

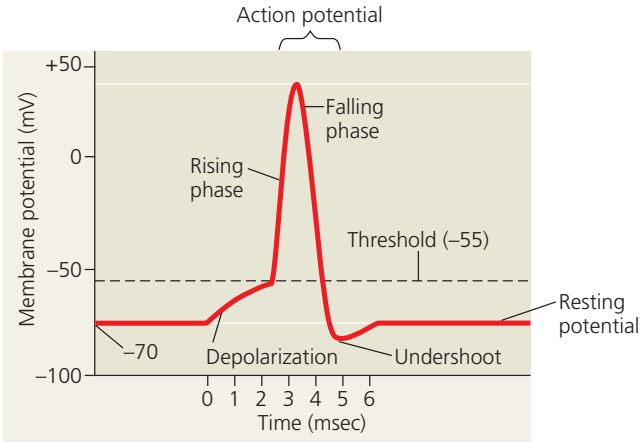
- Ionic gradients generate a voltage difference, or **membrane potential**, across the plasma membrane of cells. The concentration of Na^+ is higher outside than inside; the reverse is true for K^+. In resting neurons, the plasma membrane has many open potassium channels but few open sodium channels. Diffusion of ions, principally K^+, through channels generates a **resting potential**, with the inside more negative than the outside.

? *Suppose you placed an isolated neuron in a solution similar to extracellular fluid and later transferred the neuron to a solution lacking any sodium ions. What change would you expect in the resting potential?*

CONCEPT 48.3

Action potentials are the signals conducted by axons (pp. 1050–1055)

- Neurons have gated ion channels that open or close in response to stimuli, leading to changes in the membrane potential. An increase in the magnitude of the membrane potential is a **hyperpolarization**; a decrease is a **depolarization**. Changes in membrane potential that vary continuously with the strength of a stimulus are known as **graded potentials**.
- An **action potential** is a brief, all-or-none depolarization of a neuron's plasma membrane. When a graded depolarization brings the membrane potential to the threshold, many **voltage-gated ion channels** open, triggering an inflow of Na^+ that rapidly brings the membrane potential to a positive value. A negative membrane potential is restored by the inactivation of sodium channels and by the opening of many voltage-gated potassium channels, which increases K^+ outflow. A **refractory period** follows, corresponding to the interval when the sodium channels are inactivated.



- A nerve impulse travels from the axon hillock to the synaptic terminals by propagation of a series of action potentials along the axon. The speed of conduction increases with the diameter of the axon and, in many vertebrate axons, with **myelination**. Action potentials in myelinated axons jump between the **nodes of Ranvier**, a process called **saltatory conduction**.

? *In what ways do both positive and negative feedback contribute to the shape of an action potential?*

CONCEPT 48.4

Neurons communicate with other cells at synapses (pp. 1055–1060)

- In an electrical **synapse**, electrical current flows directly from one cell to another. In a chemical synapse, depolarization causes synaptic vesicles to fuse with the terminal membrane and release **neurotransmitter** into the synaptic cleft.
- At many synapses, the neurotransmitter binds to **ligand-gated ion channels** in the postsynaptic membrane, producing an **excitatory** or **inhibitory postsynaptic potential** (**EPSP** or **IPSP**). The neurotransmitter then diffuses out of the cleft, is taken up by surrounding cells, or is degraded by enzymes. **Temporal** and **spatial summation** at the axon hillock determines whether a neuron generates an action potential.
- Different receptors for the same neurotransmitter produce different effects. Some neurotransmitter receptors activate signal transduction pathways, which can produce long-lasting changes in postsynaptic cells. Major neurotransmitters include acetylcholine; the amino acids GABA, glutamate, and glycine; biogenic amines; neuropeptides; and gases such as NO.

? *Why are many drugs used to treat nervous system diseases or affect brain function targeted to specific receptors rather than particular neurotransmitters?*

TEST YOUR UNDERSTANDING

LEVEL 1: KNOWLEDGE/COMPREHENSION

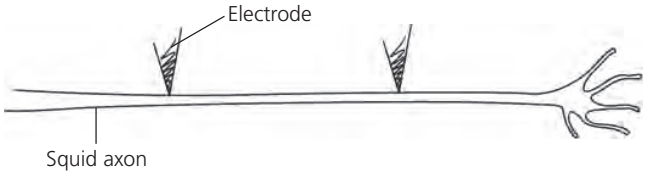
1. What happens when a resting neuron's membrane depolarizes?
   a. There is a net diffusion of Na^+ out of the cell.
   b. The equilibrium potential for K^+ (E_K) becomes more positive.
   c. The neuron's membrane voltage becomes more positive.
   d. The neuron is less likely to generate an action potential.
   e. The cell's inside is more negative than the outside.
2. A common feature of action potentials is that they
   a. cause the membrane to hyperpolarize and then depolarize.
   b. can undergo temporal and spatial summation.
   c. are triggered by a depolarization that reaches the threshold.
   d. move at the same speed along all axons.
   e. require the diffusion of Na^+ and K^+ through ligand-gated channels to propagate.
3. Where are neurotransmitter receptors located?
   a. the nuclear membrane
   b. the nodes of Ranvier
   c. the postsynaptic membrane
   d. synaptic vesicle membranes
   e. the myelin sheath
4. Temporal summation always involves
   a. both inhibitory and excitatory inputs.
   b. synapses at more than one site.
   c. inputs that are not simultaneous.
   d. electrical synapses.
   e. multiple inputs at a single synapse.

LEVEL 2: APPLICATION/ANALYSIS

5. Why are action potentials usually conducted in one direction?
   a. The nodes of Ranvier conduct potentials in one direction.
   b. The brief refractory period prevents reopening of voltage-gated Na^+ channels.
   c. The axon hillock has a higher membrane potential than the terminals of the axon.
   d. Ions can flow along the axon in only one direction.
   e. Voltage-gated channels for both Na^+ and K^+ open in only one direction.
6. Which of the following is a *direct* result of depolarizing the presynaptic membrane of an axon terminal?
   a. Voltage-gated calcium channels in the membrane open.
   b. Synaptic vesicles fuse with the membrane.
   c. The postsynaptic cell produces an action potential.
   d. Ligand-gated channels open, allowing neurotransmitters to enter the synaptic cleft.
   e. An EPSP or IPSP is generated in the postsynaptic cell.

LEVEL 3: SYNTHESIS/EVALUATION

7. **DRAW IT** Suppose a researcher inserts a pair of electrodes at two different positions along the middle of an axon dissected out of a squid. By applying a depolarizing stimulus, the researcher brings the plasma membrane at both positions to threshold. Using the drawing below as a model, create one or more drawings that illustrate where each action potential would terminate.



8. **EVOLUTION CONNECTION** An action potential is an all-or-none event. This on/off signaling is an evolutionary adaptation of animals that must sense and act in a complex environment. It is possible to imagine a nervous system in which the action potentials are graded, with the amplitude depending on the size of the stimulus. What evolutionary advantage might on/off signaling have over a graded (continuously variable) kind of signaling?
9. **SCIENTIFIC INQUIRY** From what you know about action potentials and synapses, propose two or three hypotheses for how various anesthetics might block pain.
10. **WRITE ABOUT A THEME**
    The Cellular Basis of Life In a short essay (100–150 words), describe how the structure and electrical properties of vertebrate neurons reflect similarities and differences with other animal cells.

For selected answers, see Appendix A.

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