

the resting potential for potassium is about -75 mV, high permeability to potassium will tend to return a cell to a polarized state. Neurons use precisely this strategy to transiently depolarize and then repolarize their plasma membranes, as you will see in the next section.

CONCEPT CHECK 22-1

Ouabain is an African plant derivative that has been used historically to make poison-tipped hunting arrows. It disables the main Na^+/K^+ ATPase in neurons. How would the resting potential of neurons in an organism exposed to ouabain change relative to the normal situation? Explain your answer.

22.2 Electrical Excitability and the Action Potential

The establishment of a resting membrane potential and its dependence on ion gradients and ion permeability are properties of almost all cells. The unique feature of electrically excitable cells is their response to membrane depolarization. Whereas a nonexcitable cell that has been temporarily and slightly depolarized will simply return to its original resting membrane potential, an electrically excitable cell that is depolarized to the same degree will respond with an *action potential*.

Electrically excitable cells produce an action potential because, in addition to the leak channels and Na^+/K^+ pumps we have discussed thus far, they contain *voltage-gated channels* in their plasma membranes. To see how nerve cells communicate signals electrically, we need to understand the characteristics of the ion channels in the nerve cell membrane, which can be studied using several important techniques.

Patch Clamping and Molecular Biological Techniques Allow Study of Single Ion Channels

Several modern techniques are used to examine ion channels in neuronal cells. Used together, these techniques provide a powerful set of tools for studying ion channels in unprecedented detail.

Patch Clamping. The clearest picture of how channels operate comes from using a technique that permits the recording of ion currents passing through individual channels. This technique, known as *single-channel recording*, or more commonly as **patch clamping**, was developed by Erwin Neher and Bert Sackmann, who earned a Nobel Prize in 1991 for their discovery. Patch clamping is an extremely important tool in modern neurobiology (see **Key Technique, page 690**).

Frog Oocytes. Much of the present research on ion channels combines patch clamping with molecular biology. It is now possible to synthesize large amounts of channel proteins in the laboratory and to study their functions in lipid bilayers or in frog eggs. Specific molecular modifications or mutations of the channel can be used to determine how various regions of the channel protein are involved in channel function. This approach has been used to study the domains of the sodium and potassium channels responsible for voltage gating.

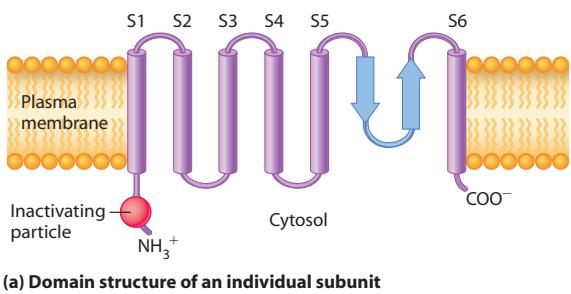
Optogenetics. The ability to measure the electrical properties of single ion channels is powerful, but it would be even more powerful to be able to locally manipulate ion channels in specific regions of single cells. This is now becoming possible using genetically engineered channel proteins that are sensitive to light. This approach, known as *optogenetics*, uses molecular biology techniques to introduce light-sensitive ion channels into neurons. One such protein is bacteriorhodopsin (see Chapter 8), which is used to inhibit some neurons. Another family of bacterial light-sensitive channels known as *channelrhodopsins* is used to activate some neurons. By expressing one of these light-sensitive channels in a neuronal cell in culture or in a transgenic animal (see Chapter 21) and then shining light in a defined region of the cell, the ion concentration can be changed locally and the effects assessed under the microscope. Other light-sensitive molecules are now being engineered to study many events in neurons. Optogenetics clearly has a bright future.

Specific Domains of Voltage-Gated Channels Act as Sensors and Inactivators

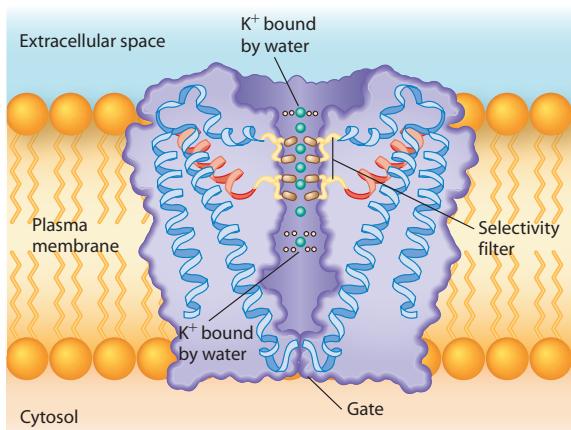
Recall that *leak channels* contribute to the steady-state ionic permeabilities of membranes, allowing resting cells to be somewhat permeable to cations, especially potassium ions. In contrast, **voltage-gated ion channels**, as the name suggests, respond to changes in the voltage across a membrane. Voltage-gated sodium and potassium channels are responsible for the action potential. **Ligand-gated ion channels**, by contrast, open when a particular molecule binds to the channel. (*Ligand* comes from the Latin root *ligare*, meaning “to bind.”) Detailed knowledge of the structure and function of voltage-gated sodium and potassium channels is fundamental to understanding the events of the action potential.

Voltage-gated ion channels fall into two different structural categories. *Voltage-gated potassium channels* are *multimeric* proteins—that is, they consist of four separate protein subunits that come together in the membrane, forming a central pore that ions can pass through. *Voltage-gated sodium channels*, by contrast, are large, *monomeric* proteins (in other words, they consist of a single polypeptide) with four separate domains. Each domain is similar to one of the subunits of the voltage-gated potassium channel. In both kinds of channels, each subunit or domain contains six transmembrane α helices (called subunits S1–S6; **Figure 22-5a**).

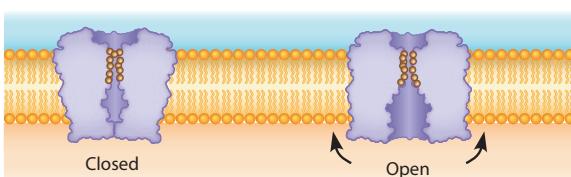
The size of the central pore and, more importantly, the way it interacts with an ion, give a channel its ion selectivity. Figure 22-5b shows why this is so for the bacterial potassium channel KcsA. Vertebrate voltage-gated potassium channels have a similar structure. Oxygen atoms in amino acids lining the center of the channel are precisely positioned to interact with ions as they move through the *selectivity filter*, allowing them to give up their waters of hydration. The fit between potassium ions and oxygens lining the channel is remarkably precise. Na^+ , which is smaller than K^+ , can only interact with oxygen atoms on one side of the channel. This makes it energetically unfavorable for Na^+ to give up its waters of hydration and enter the channel. Roderick MacKinnon received a Nobel Prize in 2003 in part for his work on the pore structure of potassium channels.



(a) Domain structure of an individual subunit



(b) Pore structure



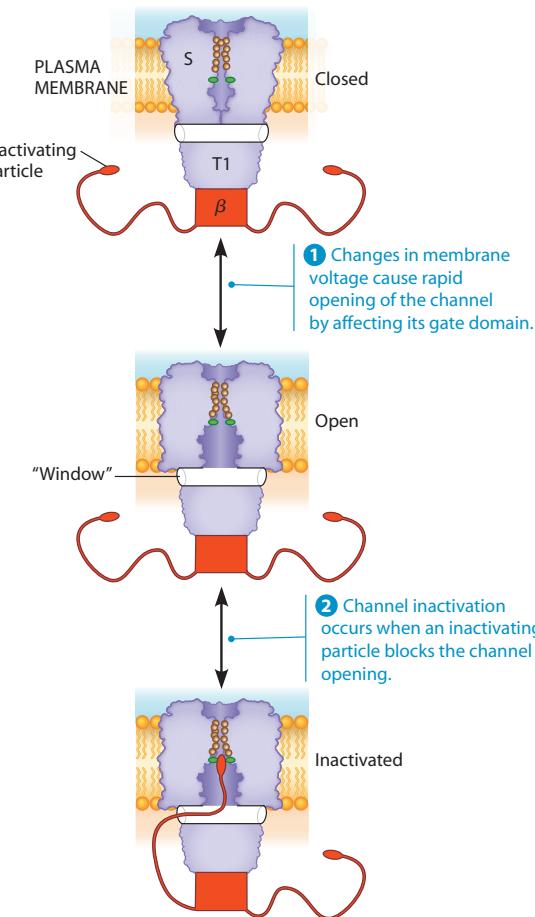
(c) Channel gating



Figure 22-5 The General Structure of Voltage-Gated Ion Channels. (a) Domain structure. Voltage-gated channels for sodium, potassium, and calcium ions all share the same basic structural themes. The channel is essentially a rectangular tube whose four walls are formed from either four subunits (for example, potassium channels) or four domains of a single polypeptide (for example, sodium channels). Each subunit or domain contains six transmembrane helices, labeled S1–S6. The fourth transmembrane helix, S4, is a voltage sensor and part of the gating mechanism. For voltage-gated sodium channels and some types of potassium channels, a region near the N-terminus protrudes into the cytosol and forms an inactivating particle. (b) Ion selectivity of channels. The transmembrane region of a potassium channel in the closed position. This diagram is based on the bacterial KcsA channel, but vertebrate potassium channels are similar. Two of the four subunits of a voltage-gated potassium channel are shown here. Only the transmembrane part of the channel is shown. Hydrated potassium ions (teal) enter the channel, where they give up their water and bind oxygen atoms, precisely positioned in the amino acids lining the selectivity filter (brown). (c) Channel gating. The channel is regulated by a gate, which can open or close, depending on the state of voltage sensor domains in the channel. The channel gate opens and closes depending on the conformational state of channel subunits.

Voltage-gated sodium channels have the ability to open rapidly in response to some stimulus and then to close again, a phenomenon known as **channel gating**. This open or closed state is an all-or-none phenomenon—that is, gates do not appear to remain partially open (Figure 22-5c). One of the transmembrane α helices of vertebrate voltage-gated channels, S4, acts as a **voltage sensor** during channel gating. When positively charged amino acids in S4 are replaced with neutral amino acids, the channel does not open. This result suggests that S4 makes these channels responsive to changes in potential.

Most voltage-gated channels can also adopt a second type of closed state, referred to as **channel inactivation**, which is an important feature of voltage-gated sodium and potassium channels (Figure 22-6). When a channel is inactivated, it

**Figure 22-6 The Function of a Voltage-Gated Ion Channel.**

① Mammalian potassium channels have three major domains: the transmembrane (S) and cytosolic (T1) domains of the α subunit and the β subunit. The N-terminal region of the β subunit contains an inactivating particle. Channel gating occurs because a portion of the transmembrane domain changes conformation when the membrane potential changes. ② Channel inactivation. Here, two of the four inactivating particles are shown for a voltage-gated potassium channel. Channels are inactivated when an inactivating particle moves through a "window" region of the channel, blocking the opening of the pore.

KEY TECHNIQUE

Patch Clamping

PROBLEM: Standard electrical measurement of neurons measures changes in overall cellular voltage, which reflects the opening and closing of many channels at any given time. How can the electrical properties of a single channel be studied?

SOLUTION: Patch clamping allows a tiny patch of membrane to be isolated and its electrical properties studied at the level of the opening and closing of a single channel protein.

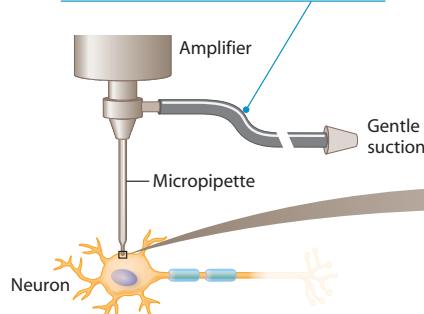
Key Tools: A polished glass microelectrode (micropipette); sensitive voltage recording equipment; access to the neuronal membrane being studied.

Details: To record single-channel currents, a glass micropipette with a tip diameter of approximately $1\text{ }\mu\text{m}$ is carefully pressed against the surface of a cell such as a neuron. Gentle suction is then applied so that a tight seal forms between the pipette and the plasma membrane (**Figure 22A-1, 1**). There is now a patch of membrane under the mouth of the micropipette that is sealed off from the surrounding medium (**2**). This patch is small enough that it usually contains only one or perhaps a few ion channels. Current can enter and leave the pipette only through these channels, thereby enabling an experimenter to study various properties of the individual channels.

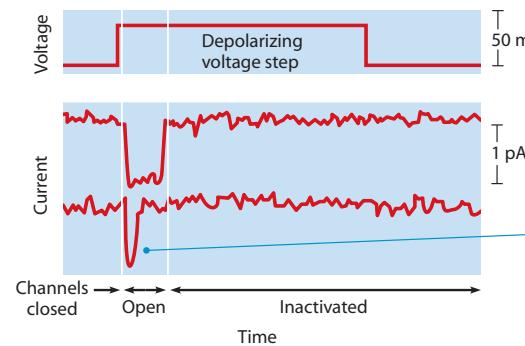
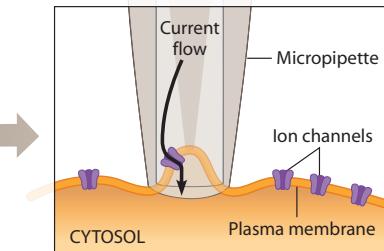
Figure 22A-1 The Basic Patch Clamping Method.

Patch clamping makes it possible to study the behavior of individual ion channels in a small patch of membrane. When each channel opens, the amount of current that flows through it is always the same (1 pA for the sodium channels shown here). Following the burst of channel opening, a quiescent period occurs due to channel inactivation.

1 Patch-clamping setup: A fire-polished micropipette with a diameter of about $1\text{ }\mu\text{m}$ is carefully placed against a cell, such as the neuron shown here.



2 Membrane patch isolation: Gentle suction is applied to form a tight seal between the pipette and the plasma membrane. Typically only one or a few channels will be in the membrane within the pipette.



3 The flow of ions is recorded while the membrane is subjected to a depolarizing step in voltage, yielding traces of individual Na^+ currents during channel opening. Two separate traces are shown.

The channels can be studied in the intact cell, or the patch can be pulled away from the cell so that the researcher has access to the cytosolic side of the membrane (see Figure 22A-3c).

During the experimental process, an amplifier maintains voltage across the membrane with the addition of a sophisticated electronic feedback circuit (a voltage clamp, hence the term *patch clamp*). The voltage clamp keeps the cell at a fixed membrane potential, regardless of changes in the electrical properties of the plasma membrane, by injecting current as needed to hold the voltage constant. The voltage clamp then measures tiny changes in current flow—actual ionic currents through individual channels—from the patch pipette. The patch-clamp method has been used to show that each time a voltage-gated sodium channel opens, it conducts the same amount of *current*—that is, the same number of ions per unit of time. In other words, voltage-gated sodium channels tend to be either open or closed.

Based on these properties of ion channels, a particular channel can be characterized in terms of its conductance. *Conductance* is an indirect measure of the permeability of a channel when a specified voltage is applied across the membrane. In electrical terms, conductance is the inverse of resistance. For voltage-gated sodium channels, when a voltage of 50 mV is applied across the membrane, a current of approximately 1 picoampere (pA) is generated. This current corresponds to about 6 million sodium ions flowing through the channel per second. This can be seen in the traces shown in Figure 22A-1, **3**.

Patch clamping is a very versatile technique. By applying differing amounts of suction to the pipette, patch clamping can be used to isolate and study patches of membrane in various orientations. Starting with a tight membrane seal (Figure 22A-2a), the *whole-cell* mode (Figure 22A-2b), a commonly used patch-clamp mode, involves ripping a patch of membrane away with strong suction so that the inside of the pipette is

A Patch Clamped Neuron.

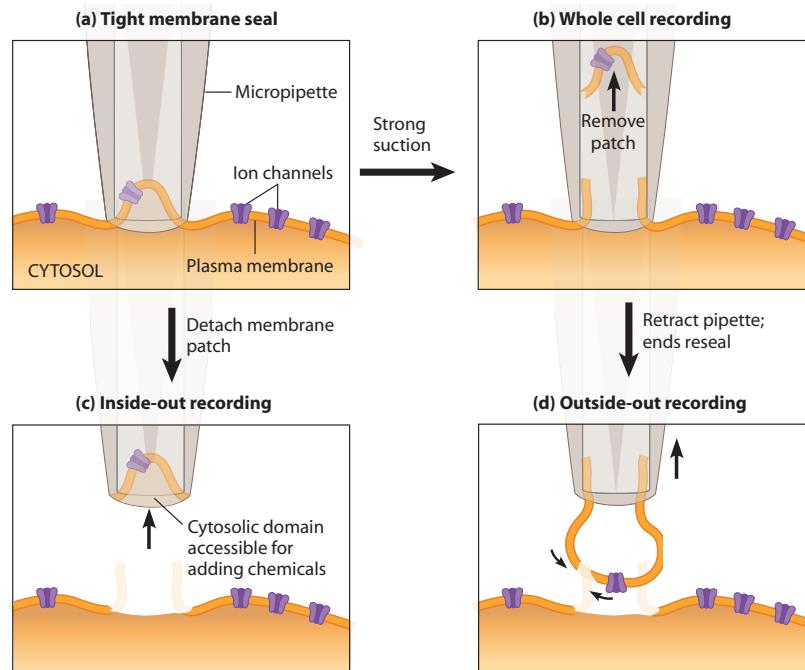
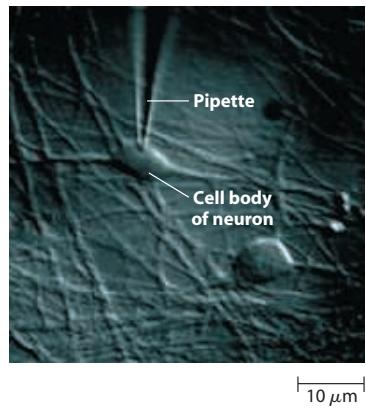


Figure 22A-2 Different Uses of Patch Clamping. Variations on the basic patch clamp method, shown in part (a) include (b) the whole-cell method, which allows measurement of current from an entire cell; (c) the inside-out method, which allows current across a small patch whose cytosolic surface is facing outward, and (d) the outside-out method, which measures current across a patch whose extracellular side is facing outward.

continuous with the cytosol. This allows measurement of current from the entire cell. To record currents from a small patch of membrane, which may include only a single channel, the pipette can be retracted to break loose a small patch of membrane. The patch can be orientated in one of two ways inside the patch pipette. In the *inside-out* configuration the pipette is attached to the cell and then retracted to break off a patch of membrane (Figure 22A-2c). In this case the cytosolic side of membrane is exposed, and chemicals that might normally act in the cytosol can be added to test their effects on the channel.

If the goal is to study neurotransmitters or other molecules that bind to the extracellular part of a channel, the *outside-out* configuration (Figure 22A-2d) is used. In this case the pipette is retracted as in the whole-cell mode, but a small patch of membrane is captured, which reseals to produce a patch with an orientation opposite to that of the inside-out mode. The extracellular side of the patch can then be bathed with chemicals.

QUESTION: You have isolated a toxin from a previously undiscovered poisonous snake. You believe that it binds to sodium channels in nerve cell membranes that are normally tightly regulated, keeping them permanently open. Explain how you could use patch clamping to test your idea, using one of the specific variants of the patch-clamp technique in your answer.

cannot reopen immediately, even if stimulated to do so. Channel inactivation is functionally like placing a padlock on a closed gate; only when the padlock is unlocked can the gate be opened again. Inactivation is caused by a portion of the channel called the *inactivating particle*. Common channels have four such particles. During inactivation, a particle inserts into the opening of the channel. For a channel to reactivate and open in response to a stimulus, the inactivating particle must move away from the pore. When the cytosolic side of the channel is treated with a protease or with antibodies prepared against the fragment of the channel thought to be responsible for inactivation, the inactivating particle can no longer function, and channels can no longer be inactivated.

The regulation of ion channels is crucial for the proper functioning of neurons. Defects in several voltage-gated ion channels have been linked to human neurological diseases (such defects have been termed *channelopathies*). For example, humans carrying mutations in certain K⁺ channels suffer from ataxia (a defect in muscle coordination), and one form of epilepsy is caused by a mutation in one type of voltage-gated Na⁺ channel.

Action Potentials Propagate Electrical Signals Along an Axon

Now we are ready to explore how the coordinated opening and closing of ion channels can lead to an action potential. Let's begin by examining how membrane potential changes during an action potential. Because of its historical importance, we will use the squid giant axon as the model for our discussion.

A resting neuron is a system poised for electrical action. As we have seen, the membrane potential of the cell is set by a delicate balance of ion gradients and ion permeability. Depolarization of the membrane upsets this balance. If the level of depolarization is small—less than about +20 mV—the membrane potential will normally drop back to resting levels without further consequences. Further depolarization brings the membrane to the **threshold potential**. Above the threshold potential, the nerve cell membrane undergoes rapid and dramatic alterations in its electrical properties and permeability to ions, and an action potential is initiated.

An **action potential** is a brief but large electrical depolarization and repolarization of the neuronal plasma membrane caused by the inward movement of sodium ions and the subsequent outward movement of potassium ions. These ion movements are controlled by the opening and closing of voltage-gated sodium and potassium channels. In fact, we can explain the development of an action potential solely in terms of the behavior of these channels. Once an action potential is initiated in one region of the membrane, it will travel along the membrane away from the site of origin by a process called **propagation**.

Action Potentials Involve Rapid Changes in the Membrane Potential of the Axon

As we saw in Figure 22-3b, the development and propagation of an action potential can be readily studied in large axons such as those of the squid. The apparatus shown in Figure 22-3b can also be used to measure the ion currents that flow through the membrane at different phases of an

action potential. To do so, an additional electrode known as the *holding electrode* is inserted into the cell and connected to a *voltage clamp*, thereby enabling the investigator to set and hold the membrane at a particular potential. Using the voltage-clamp apparatus, a researcher can measure the current flowing through the membrane at any given membrane potential. Such experiments have contributed fundamentally to our present understanding of the mechanism that causes an action potential.

Figure 22-7 shows the sequence of membrane potential changes associated with an action potential. In less than a millisecond, the membrane potential rises dramatically from the resting membrane potential to about +40 mV—the interior of the membrane actually becomes positive for a brief period. The potential then falls somewhat more slowly, dropping to about -75 mV (called *undershoot* or *hyperpolarization*) before stabilizing again at the resting potential of about -60 mV. As Figure 22-7 indicates, the complete sequence of events during an action potential takes place within a few milliseconds.

Action Potentials Result from the Rapid Movement of Ions Through Axonal Membrane Channels

In a resting neuron, the voltage-dependent sodium and potassium channels are usually closed. Because of leak channels, at steady state the membrane is roughly 100 times more permeable to potassium than to sodium ions. When a region of the nerve cell is slightly depolarized, a fraction of the sodium channels respond and open. As they do, the increased sodium current acts to further depolarize the membrane. Increasing depolarization causes an even larger sodium current to flow, which depolarizes the membrane even more. This relationship between depolarization, the opening of voltage-gated sodium channels, and an increased sodium current constitutes a positive feedback loop known as the *Hodgkin cycle*.

Subthreshold Depolarization. Under resting conditions, the outward movement of potassium ions through leak channels restores the resting membrane potential. When the membrane is depolarized by a small amount, the membrane potential recovers and no action potential is generated. Levels of depolarization that are too small to produce an action potential are referred to as *subthreshold depolarizations*.

The Depolarizing Phase. If all the voltage-dependent sodium channels in the membrane were to open at once, the cell would suddenly become ten times more permeable to sodium than to potassium. As a result, the membrane potential would be largely a function of the sodium ion gradient. This is effectively what happens when the membrane is depolarized past the threshold potential (Figure 22-7, ① and ②). Once the threshold potential is reached, a significant number of gated sodium channels begin activating. At this point, the membrane potential shoots rapidly upward. When the rate of sodium entry slightly exceeds the maximum rate of movement of potassium through leak channels, an action potential is triggered. When the membrane potential peaks, at approximately +40 mV, the action potential approaches—although it does not actually reach—the equilibrium potential for sodium ions (about +55 mV). (It never

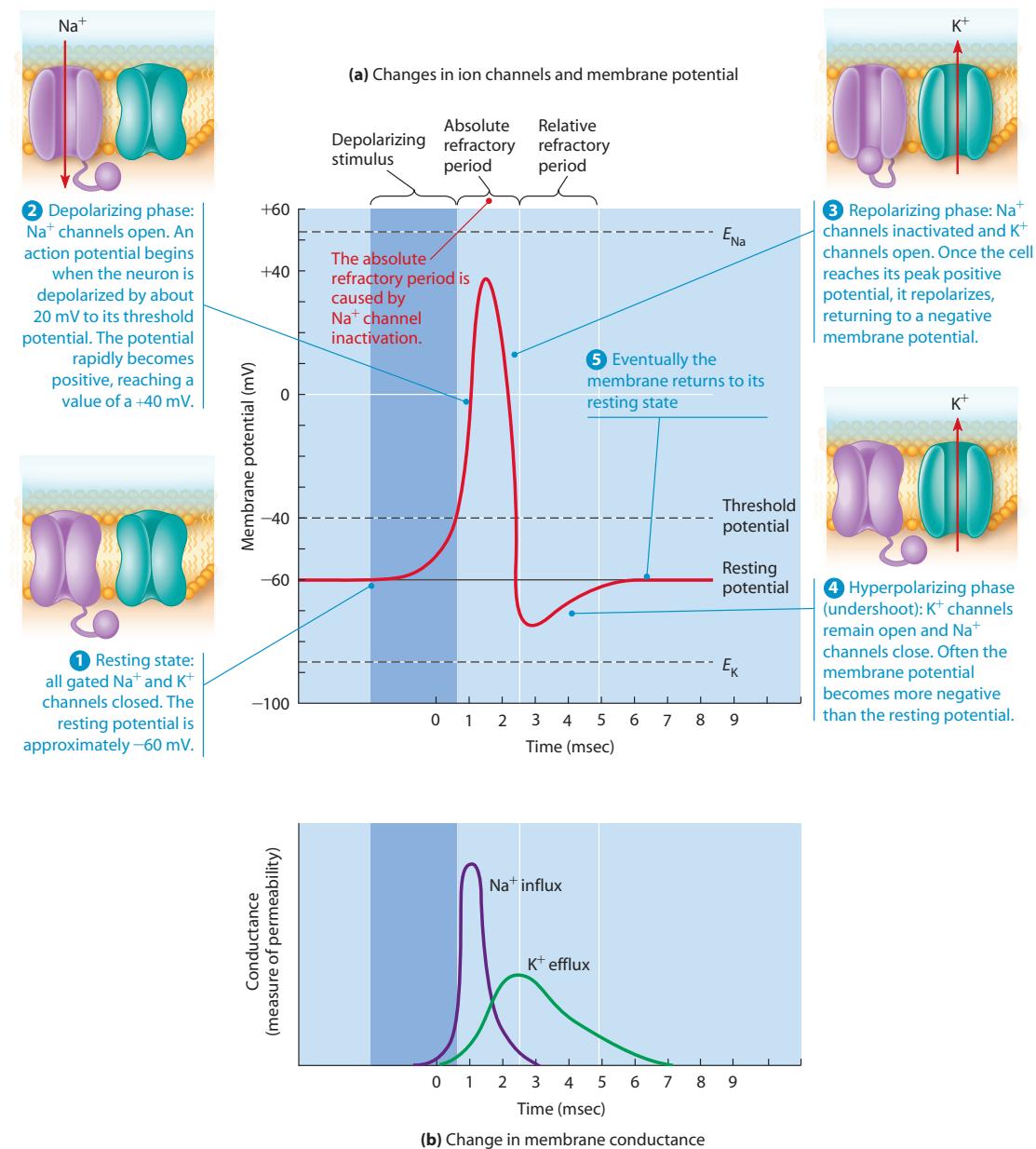


Figure 22-7 Changes in Ion Channels and Currents in the Membrane of a Squid Axon During an Action Potential.

(a) The change in membrane potential caused by movement of Na^+ and K^+ through their voltage-gated channels, which are shown at each step of the action potential. The absolute refractory period is caused by sodium channel inactivation. Notice that at the peak of the action potential, the membrane potential approaches the E_{Na} (sodium equilibrium potential) value of about +55 mV; similarly, the potential undershoots nearly to the E_{K} (potassium equilibrium potential) value of about -75 mV. **(b)** The change in membrane conductance (permeability of the membrane to specific ions). The depolarized membrane initially becomes very permeable to sodium ions, facilitating inward movement of sodium. Thereafter, as permeability to sodium declines, the permeability of the membrane to potassium increases transiently, causing the membrane to hyperpolarize.

actually reaches this value because the membrane remains permeable to other ions during this time.)

The Repolarizing Phase. Once the membrane potential has risen to its peak, the membrane quickly repolarizes (Figure 22-7, **③**). This is due to a combination of the

inactivation of sodium channels and the opening of voltage-gated potassium channels. When sodium channels are inactivated, they close and remain closed until the membrane potential becomes negative again. Channel inactivation thus stops the inward flow of sodium ions. The cell will now automatically repolarize as potassium ions leave the cell.

The difference in response speed between voltage-gated potassium channels and voltage-gated sodium channels plays an important role in generating the action potential. An action potential begins with an increase in the membrane's permeability to sodium, which depolarizes the membrane, followed by an increased permeability to potassium, which repolarizes the membrane.

The Hyperpolarizing Phase (Undershoot). At the end of an action potential, most neurons show a transient **hyperpolarization**, or **undershoot**, in which the membrane potential briefly becomes even more negative than it normally is at rest (Figure 22-7, ④). The undershoot occurs because of the increased potassium permeability that exists while voltage-gated potassium channels remain open. Note that the potential of the undershoot closely approximates the equilibrium potential for potassium ions (about -75 mV for the squid axon). As the voltage-gated potassium channels close, the membrane potential returns to its original resting state (Figure 22-7, ⑤). Notice that the rapid restoration of the resting potential following an action potential does not use the Na^+/K^+ pump but instead involves the passive movements of ions. In cells that have been treated with a metabolic inhibitor so that they cannot produce ATP (and hence their Na^+/K^+ pumps cannot use it), action potentials can still be generated. The pump helps maintain a negative potential once an action potential has passed and the membrane has returned to its resting state.

The Refractory Periods. For a few milliseconds after an action potential, it is impossible to trigger a new action potential. During this interval, known as the **absolute refractory period** (see Figure 22-7, ⑥), sodium channels are inactivated and cannot be opened by depolarization. During the period of undershoot, when the sodium channels have reactivated and are capable of opening again, it is possible but difficult to trigger an action potential. This is because both potassium leak channels and voltage-gated potassium channels are open during this time. This tends to drive the membrane potential to a very negative value, far from the threshold for triggering another round of sodium channel opening. This interval is known as the **relative refractory period** (see Figure 22-7, ⑦).

Changes in Ion Concentrations Due to an Action Potential. Our discussion of ion movements might give the impression that an action potential involves large changes in the cytosolic concentrations of sodium and potassium ions, but this is not the case. In fact, *during a single action potential, the cellular concentrations of sodium and potassium ions hardly change at all*. Remember that the membrane potential is due to a slight excess of negative charge on one side and a slight excess of positive charge on the other side of the membrane. The number of excess charges is a tiny fraction of the total ions in the cell, and the number of ions that must cross the membrane to neutralize or alter the balance of charge is likewise small.

Nevertheless, intense neuronal activity can lead to significant changes in overall ion concentrations. For example, as a neuron continues to generate large numbers of action potentials, the concentration of potassium outside the cell will begin to rise perceptibly. This can affect the membrane potential

of both the neuron itself and surrounding cells. Astrocytes, the glial cells that form the blood-brain barrier, are thought to control this problem by taking up excess potassium ions.

Action Potentials Are Propagated Along the Axon Without Losing Strength

For neurons to transmit signals to one another, the transient depolarization and repolarization that occur during an action potential must travel along the neuronal membrane. The depolarization at one point on the membrane spreads to adjacent regions through a process called the **passive spread of depolarization**. As a wave of depolarization spreads passively away from the site of origin, it also decreases in magnitude. This fading of the depolarization with distance from the source makes it difficult for signals to travel very far by passive means only. For signals to travel longer distances, an action potential must be *propagated*, or actively generated, from point to point along the membrane.

To understand the difference between the passive spread of depolarization and the propagation of an action potential, consider how a signal travels along the neuron from the site of origin at the dendrites to the end of the axon (Figure 22-8). Incoming signals are transmitted to a neuron at synapses that form points of contact between the synaptic boutons of the transmitting neuron and the dendrites of the receiving

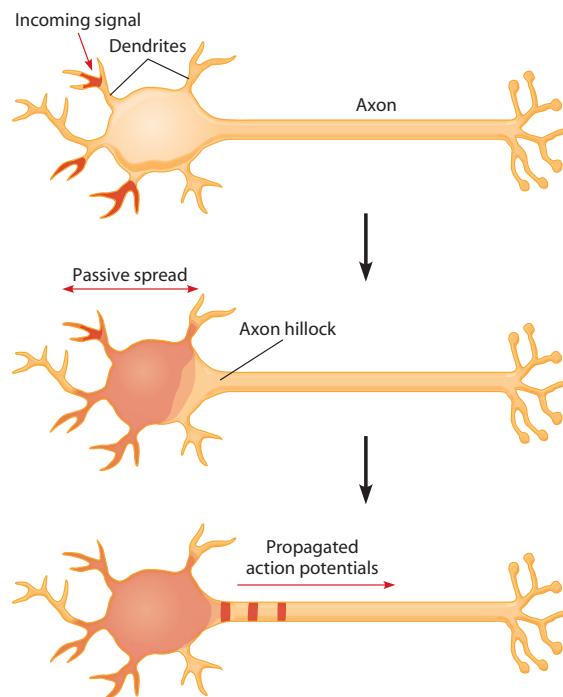


Figure 22-8 The Passive Spread of Depolarization and Propagated Action Potentials in a Neuron. The transmission of a nerve impulse along a neuron depends on both the passive spread of depolarization and the propagation of action potentials. A neuron is stimulated when its dendrites receive a depolarizing stimulus from other neurons. A depolarization starting at a dendrite spreads passively over the cell body to the axon hillock, where an action potential forms. The action potential is then propagated down the axon.

neuron. When these incoming signals depolarize the dendrites of the receiving neuron, the depolarization spreads passively over the membrane from the dendrites to the base of the axon—the **axon hillock**. The axon hillock is the region where action potentials are initiated most easily. This is because sodium channels are distributed sparsely over the dendrites and cell body but are concentrated at the axon hillock and nodes of Ranvier; a given amount of depolarization will produce the greatest amount of sodium entry at sites where sodium channels are abundant. The action potentials initiated at the axon hillock are then propagated along the axon.

The mechanism for propagating an action potential in nonmyelinated nerve cells is illustrated in **Figure 22-9**. Stimulation of a resting membrane results in a depolarization of the membrane and movement of sodium ions into the axon at that location (**1**). Membrane polarity is temporarily reversed at that point, and this depolarization then spreads to an adjacent point (**2**). The depolarization at this adjacent point is sufficient to bring it above the threshold potential, triggering the inward movement of sodium ions (**3**). By this time, the

original region of membrane has become highly permeable to potassium ions. As potassium ions move out of the cell, negative polarity is restored and that portion of the membrane returns to its resting state (**4**).

Meanwhile, the depolarization has spread to a new region, initiating the same sequence of events there (**5**). In this way, the signal moves along the membrane as a ripple of depolarization-repolarization events; the membrane polarity is reversed in the immediate vicinity of the signal but returned to normal again as the signal travels down the axon. The propagation of this cycle of events along the nerve fiber is called a *propagated action potential*, or **nerve impulse**. The nerve impulse can move only away from the initial site of depolarization because the sodium channels that have just been depolarized are in the inactivated state and cannot respond immediately to further stimulation.

Because an action potential is actively propagated, it does not fade as it travels; it is generated anew, as an all-or-none event, at each successive point along the membrane. Thus, a nerve impulse can be transmitted over essentially any distance with no decrease in strength.

The Myelin Sheath Acts Like an Electrical Insulator Surrounding the Axon

Most axons in vertebrates have an additional specialization: they are surrounded by a discontinuous **myelin sheath** consisting of many concentric layers of membrane. The myelin sheath acts as electrical insulation for the segments of the axon that it envelops. The myelin sheath of neurons in the CNS is formed by **oligodendrocytes**; in the peripheral nervous system (PNS), the myelin sheath is formed by **Schwann cells** (see Figure 22-1). Members of both classes of glial cells wrap layer after layer of their own plasma membrane around the axon in a tight spiral (**Figure 22-10**). Because each Schwann cell surrounds a short segment (about 1 mm) of a single axon, many Schwann cells are required to encase a PNS axon with a discontinuous sheath of myelin. Myelination decreases the ability of the neuronal membrane to retain electric charge (that is, myelination decreases its *capacitance*), permitting a depolarization event to spread farther and faster than it would along a nonmyelinated axon.

Myelination does not eliminate the need for propagation, however. For depolarization to spread from one site to the rest of the neuron, the action potential must still be renewed periodically down the axon. This happens at the *nodes of Ranvier*, interruptions in the myelin layer that are spaced just close enough together (1–2 mm) to ensure that the depolarization spreading out from an action potential at one node is still strong enough to bring an adjacent node above its threshold potential (**Figure 22-11**). The nodes of Ranvier are the only places on a myelinated axon where an action potential can be generated because current flow through the membrane is restricted elsewhere and because voltage-gated sodium channels are concentrated there. Thus, action potentials jump from node to node along myelinated axons rather than moving as a steady ripple along the membrane. This so-called *saltatory propagation* is much more rapid than the continuous propagation that occurs in nonmyelinated axons (*saltatory* is derived from the Latin word for “dancing”; see Figure 22-11). Myelination is a crucial

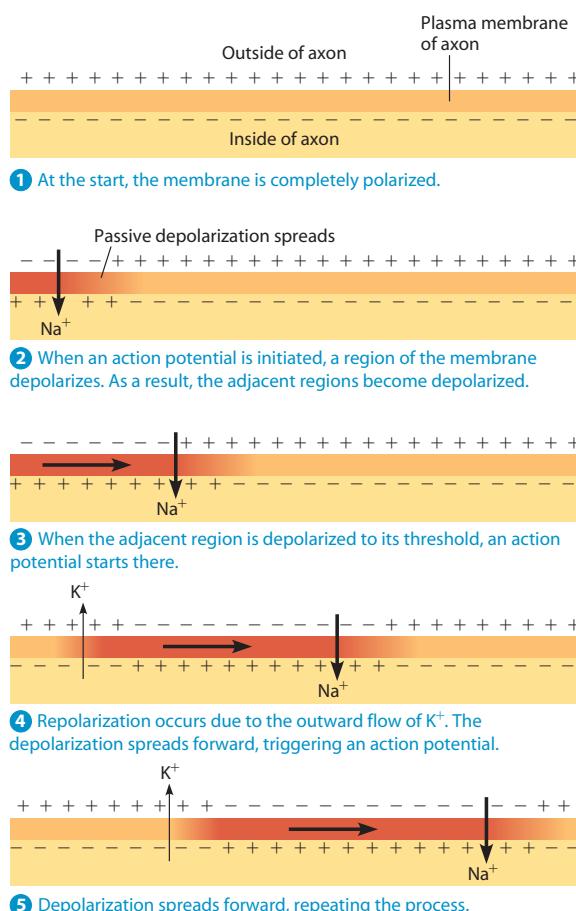
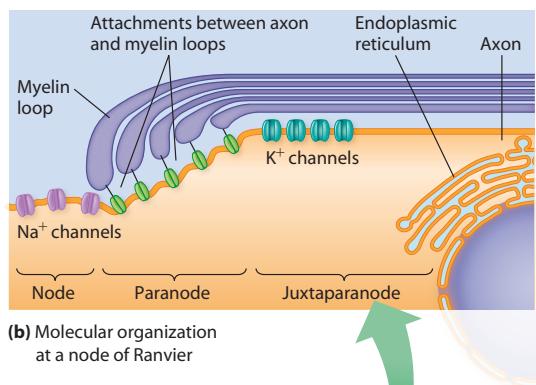
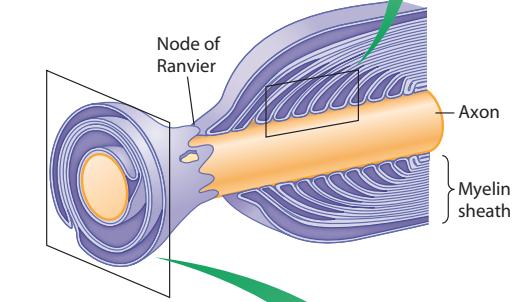


Figure 22-9 The Transmission of an Action Potential Along a Nonmyelinated Axon. A nonmyelinated axon can be viewed as a string of points, each capable of undergoing an action potential. Notice that no backward propagation occurs near sites where action potentials form because sodium channels are in an inactivated state and the membrane is hyperpolarized.



(b) Molecular organization at a node of Ranvier



(a) A myelinated axon in longitudinal section

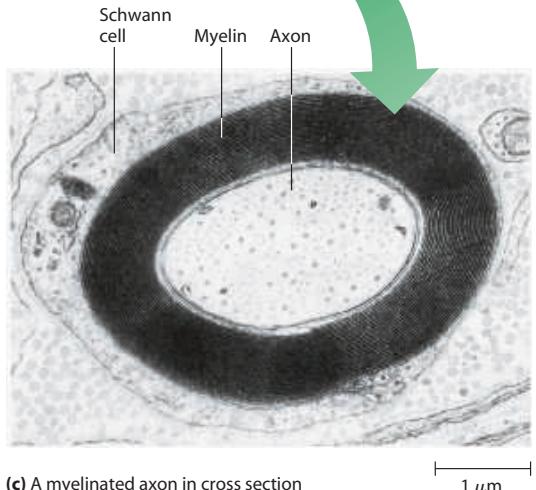
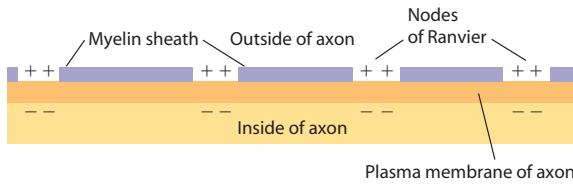
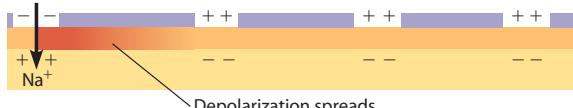


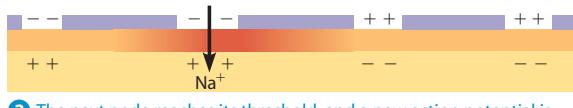
Figure 22-10 Myelination of Axons. (a) An axon of the peripheral nervous system that has been myelinated by a Schwann cell. Each Schwann cell gives rise to one segment of myelin sheath by wrapping its own plasma membrane concentrically around the axon. (b) Organization of a typical node of Ranvier in the peripheral nervous system. Sodium channels (purple) are concentrated in the node. Myelin loops attach to the regions next to the node ("paranodal" regions) via proteins on the axonal membrane and on the myelin loops (green). Potassium channels (teal) cluster next to the paranodal regions. (c) This cross-sectional view of a myelinated axon from the nervous system of a cat shows the concentric layers of membrane that have been wrapped around the axon by the Schwann cell that envelops it (TEM).



1 In myelinated neurons, an action potential is usually triggered at the axon hillock, just before the start of the myelin sheath. The depolarization then spreads along the axon.



2 Because of myelination, the depolarization spreads passively to the next node.



3 The next node reaches its threshold, and a new action potential is generated.



4 This cycle is repeated, triggering an action potential at the next node.



5 The process continues.

Figure 22-11 The Transmission of an Action Potential Along a Myelinated Axon.

a In a myelinated axon, action potentials can be generated only at nodes of Ranvier. Myelination reduces membrane capacitance, thereby allowing a given amount of sodium current, entering at one point of the membrane, to spread much farther along the membrane than it would in the absence of myelin. The result is a wave of depolarization-repolarization events that are propagated along the axon from node to node.

feature of mammalian axons. Loss of myelination results in a dramatic decrease in the electrical resistance of the axonal membrane. Much like the flow of water through a leaky garden hose, this loss of resistance drastically reduces conduction velocity along an axon. The debilitating human disease *multiple sclerosis* results when a patient's immune system attacks his or her own myelinated nerve fibers, causing demyelination. If the affected nerves innervate muscles, the patient's capacity for movement can be severely compromised.

Nodes of Ranvier are highly organized structures that involve close contact between the loops of glial or Schwann cell membrane and the plasma membrane of the axon(s) they myelinate. Three distinct regions are associated with these specialized sites of contact. In the node of Ranvier itself, voltage-sensitive sodium channels are highly concentrated. In the adjacent regions, called *paranodal regions* (*para-* means "alongside"), the axonal and glial cell membranes contain specialized adhesive proteins. Finally, in the region next to the paranodal areas,

called *juxtaparanodal regions* (*juxta-* means “next to”), potassium channels are highly concentrated (see Figure 22-10b). The organization of nodes of Ranvier prevents free movement of the sodium and potassium channels within the axon’s plasma membrane in regions around the nodes.

CONCEPT CHECK 22-2

The poison produced by some species of Central and South American poison dart frogs, called batrachotoxin, binds to voltage-gated sodium channels and maintains them in an open state. Predict what would happen if a neuron were exposed to batrachotoxin. Explain your answer.

22.3 Synaptic Transmission and Signal Integration

How do nerve cells communicate with one another and with glands and muscles at synapses? They do so at structurally distinct close contacts known as *synapses*. In an **electrical synapse**, one neuron, called the **presynaptic neuron**, is connected to a second neuron, the **postsynaptic neuron**, by gap junctions (Figure 22-12; see Chapter 15 for more on gap junctions). As ions move back and forth between the two cells, the depolarization in one cell spreads passively to the connected cell. Electrical synapses provide for transmission with virtually no delay and occur in places in the nervous system where speed of transmission is critical. Similar electrical connections can be found between nonneuronal cells, such as the cardiac muscle cells in the heart (see Chapter 14).

In a **chemical synapse** (Figure 22-13), the presynaptic and postsynaptic neurons are not connected by gap junctions, although they are connected by cell adhesion proteins.

Instead, the presynaptic plasma membrane is separated from the postsynaptic membrane by a small space of about 20–50 nm, known as the **synaptic cleft**. A nerve signal arriving at the terminals of the presynaptic neuron cannot bridge the synaptic cleft as an electrical impulse. For synaptic transmission to take place, the electrical signal must be converted at the presynaptic neuron to a chemical signal carried by a *neurotransmitter*. Neurotransmitter molecules are stored in the synaptic boutons of the presynaptic neuron. An action potential arriving at the terminal causes the neurotransmitter to be secreted into and diffuse across the synaptic cleft. The neurotransmitter molecules then bind to specific proteins embedded within the plasma membrane of the postsynaptic neuron (*receptors*) and are converted back into electrical signals, setting in motion a sequence of events that either stimulates or inhibits the production of an action potential in the postsynaptic neuron, depending on the kind of synapse.

Neurotransmitter receptors fall into two broad groups: *ligand-gated ion channels* (sometimes called *ionotropic* receptors), in which activation directly affects the cell, and receptors that exert their effects indirectly through a system of intracellular messengers (sometimes called *metabotropic* receptors; see Chapter 23; Figure 22-14). Here, we focus on *ligand-gated channels*. These membrane ion channels open in response to the binding of a neurotransmitter, and they can mediate either excitatory or inhibitory responses in the postsynaptic cell.

Neurotransmitters Relay Signals Across Nerve Synapses

A **neurotransmitter** is essentially any signaling molecule released by a neuron. Many kinds of molecules act as neurotransmitters. Most are detected by the postsynaptic cell via

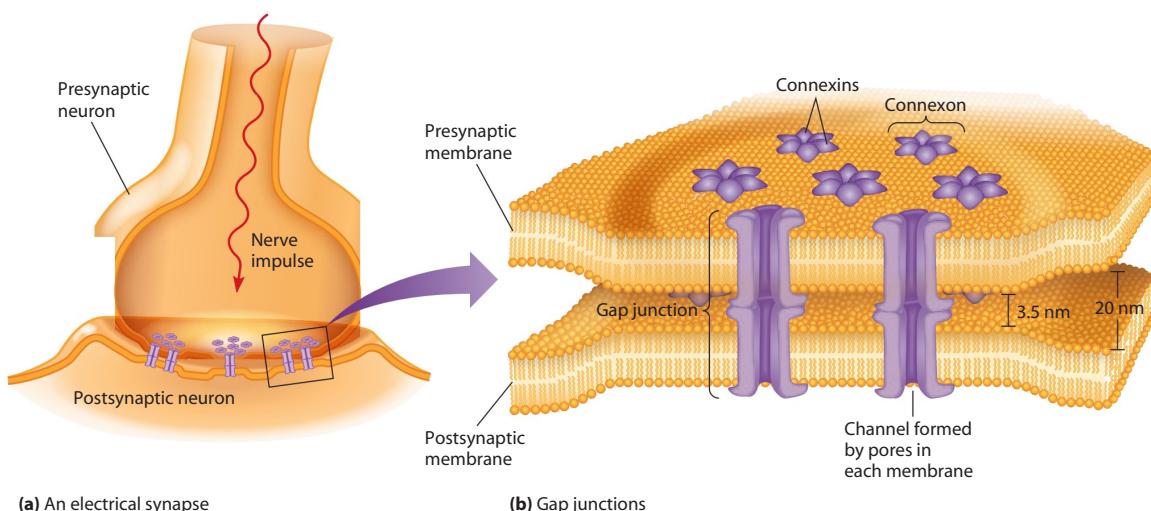


Figure 22-12 An Electrical Synapse. (a) In electrical synapses, the presynaptic and postsynaptic neurons are coupled by gap junctions, which allow small molecules and ions to pass freely from the cytosol of one cell to the next. When an action potential arrives at the presynaptic side of an electrical synapse, the depolarization spreads passively due to the flow of positively charged ions across the gap junction. (b) The gap junction is composed of sets of channels. A channel is made up of six protein subunits, each called a connixin. The entire set of six subunits together is called a connexon. Two connexons, one in the presynaptic membrane and one in the postsynaptic membrane, make up a gap junction.