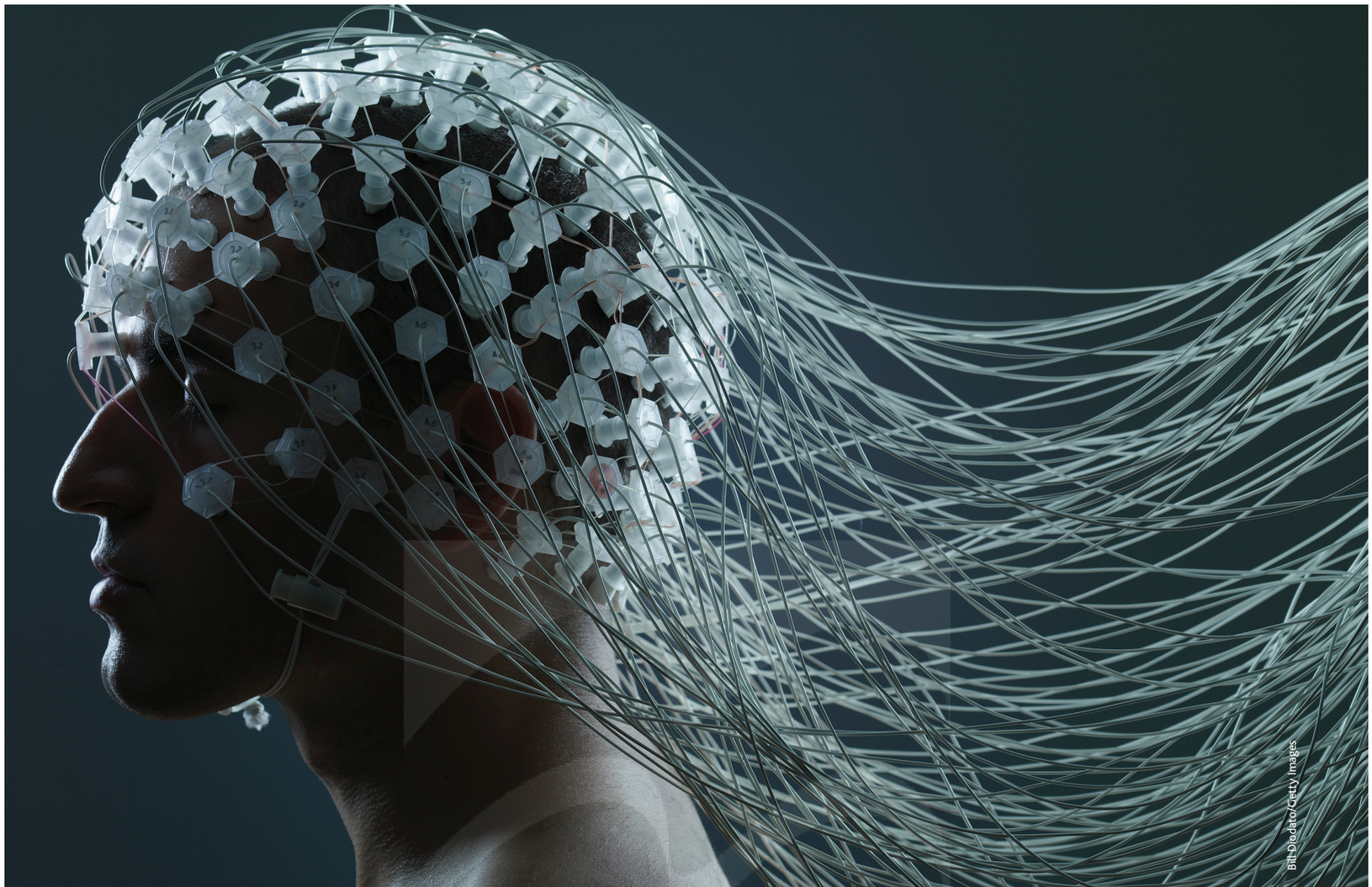

Bill Diodato/Getty Images

How Do Neurons Use Electrical Signals to Transmit Information?

CHAPTER 4

CLINICAL FOCUS 4-1

Epilepsy

J. D. worked as a disc jockey for a radio station and at parties in his off-hours. One evening, he set up on the back of a truck at a rugby field to emcee a jovial and raucous rugby party. Between musical sets, he made introductions, told jokes, and exchanged toasts.

At about 1 A.M., J. D. suddenly collapsed, making unusual jerky motions, then passed out. He was rushed to a hospital emergency room, where he gradually recovered. The attending physician noted that he was not intoxicated, released him to his friends, and recommended that a series of neurological tests be run the next day. Neuroimaging with state-of-the-art brain scans can usually reveal brain abnormalities (Cendes et al., 2016), but it did not do so in J. D.'s case.

AJPhoto/Science Source

The EEG detects electrical signals given off by the brain in various states of consciousness, as explained in Sections 7-2 and 13-3, Section 16-3 details the diagnosis and treatment of epilepsy.

When the electrical activity in J. D.'s brain was recorded while a strobe light was flashed before his eyes, an *electroencephalogram*, or EEG, displayed a series of abnormal electrical patterns characteristic of epilepsy. The doctor prescribed Dilantin (diphenylhydantoin), an antiseizure drug, and advised J. D. to refrain from drinking alcohol. He was required to give up his driver's license to prevent the possibility of an attack while driving. And he lost his job at the radio station.

After 3 uneventful months, medication was stopped, and J. D.'s driver's license was restored. J. D. convinced the radio station that he could resume work, and subsequently he has remained seizure free.

Epilepsy is a common neurological disease marked by periods of excessive neural synchrony called **electrographic seizures.** The disease is electrical in nature. The brain is normally electrically active; if this activity becomes abnormal, even infrequently, the consequences, including loss of conscious awareness, can be severe.

Electrographic seizures often follow innocuous stimuli—events that would not typically cause seizures in people who do not have epilepsy. The core concept is that the brain of a person with epilepsy has a chronically low seizure threshold and so is subject to recurrent seizures. About 4 in 10 cases of epilepsy have been linked to specific neural causes, among them infections, trauma, tumors, structural abnormalities, or genetic mutations in the proteins that make up ion channels (Bhalla et al., 2011). But that leaves the remaining 60 percent without a clear cause.

If seizures occur repeatedly and cannot be controlled by drug treatment, as occurs in about 30 percent of people with epilepsy, other options may include the high-fat/low-carbohydrate ketogenic diet, deep brain stimulation, and surgical resection of the seizure focus (Rho et al., 2010). Removing this small area of brain tissue may prevent seizures and keep them from spreading to other brain regions.

electrographic seizures Abnormal rhythmic neuronal discharges; may be recorded by an electroencephalogram.

The most reproduced drawing in behavioral neuroscience is nearly 350 years old, predating our understanding of the electrical basis of epilepsy by centuries. Taken from René Descartes's book *Treatise on Man* (1664) and reproduced in **Figure 4-1**, it illustrates the first serious attempt to explain how information travels through the nervous system. Descartes proposed that the carrier of information is cerebrospinal fluid flowing through nerve tubes.

Descartes proposed the idea behind dualism—that the nonmaterial mind controls body mechanics; see Section 1-2.

Descartes reasoned that when the fire burns the man's toe, it stretches the skin, which tugs on a nerve tube leading to the brain. In response to the tug, a valve in a brain ventricle opens, and cerebral spinal fluid (CSF) flows down the tube, filling the leg muscles and causing them to contract and pull the toe back from the fire. The flow of fluid through other tubes to other muscles of the body (not shown in Figure 4-1) causes the head to turn toward the painful stimulus and the hand to rub the injured toe.

Descartes's theory was incorrect, yet it is remarkable because he isolated the three basic questions that underlie a behavioral response to stimulation:

1. How do our nerves detect a sensory stimulus and inform the brain about it?
2. How does the brain decide what response to make?
3. How does the brain command muscles to move?

Descartes was trying to explain the very same things that scientists have sought to explain in the intervening centuries. If not by stretched skin tugging on a nerve tube

initiating the message, the message must still be initiated somehow. If not by opening valves to initiate the flow of CSF to convey information, the information must still be sent. If not by filling the muscles with fluid that produces movements, the muscles must contract by some other mechanism.

These mechanisms are the subject of this chapter. We examine how neurons convey information from the environment throughout the nervous system and ultimately activate muscles to produce movement. We begin by describing the clues and tools that were first used to explain the nervous system's electrical activity.

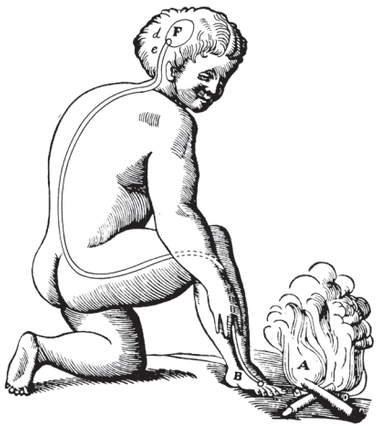

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FIGURE 4-1 Descartes's Theory of Information Flow

4-1

Searching for Electrical Activity in the Nervous System

The first hints about how the nervous system conveys its messages came in the eighteenth century, following the discovery of electricity. Early discoveries about the nature of electricity quickly led to proposals that it plays a role in conducting information in the nervous system. We describe a few milestones that led from this idea to an understanding of how the nervous system really conveys information. If you have a basic understanding of how electricity works and how it is used to stimulate neural tissue, read on. If you prefer to brush up on electricity and electrical stimulation first, turn to The Basics: Electricity and Electrical Stimulation on page 110.

Early Clues That Linked Electricity and Neuronal Activity

In a dramatic demonstration in 1731, Stephen Gray, an amateur scientist, rubbed a rod with a piece of cloth to accumulate electrons on the rod. Then he touched the charged rod to the feet of a boy suspended on a rope and raised a piece of metal foil to the boy's nose. The foil was attracted to the boy's nose, causing it to bend on its approach; as foil and nose touched, electricity passed from the rod through the boy to the foil.

Gray's experiment resembles accumulating electrons by combing your hair. Hold a piece of paper near the comb, and the paper bends toward it. Negative charges on the comb push negative charges on the paper to its backside, leaving the front side positively charged. Because opposite charges attract, the paper bends toward the comb.

Gray speculated that electricity might be the messenger that spreads information through the nervous system. Two other lines of evidence, drawn from electrical stimulation and electrical recording studies, implicated electrical activity in the nervous system's flow of information.

Electrical Stimulation Studies

When the Italian scientist Luigi Galvani, a contemporary of Gray, observed that frogs' legs hanging on a wire in a market twitched during a lightning storm, he surmised that sparks of electricity from the storm were activating the leg muscles. Investigating this possibility, he found that if an electrical current is applied to an exposed nerve, the muscle connected to that nerve contracts. While it was unclear how the process worked, Galvani had discovered **electrical stimulation:** passing an electrical current from the uninsulated tip of an electrode onto a nerve to produce behavior—a muscular contraction.

Among the many researchers who used Galvani's technique to produce muscle contraction, two mid-nineteenth-century scientists, Gustav Theodor Fritsch and Eduard Hitzig, demonstrated that electrical stimulation of the neocortex causes movement. They studied several animal species, including rabbits and dogs, and may even have stimulated the neocortex of a person whom they were treating for head injuries sustained on a Prussian battlefield. They observed their subjects' arm and leg movements in response to the stimulation of specific parts of the neocortex.

In 1874, Roberts Bartholow, a Cincinnati physician, first described the effects of human brain stimulation. His patient, Mary Rafferty, had a skull defect that exposed

electrical stimulation Passage of an electrical current from the uninsulated tip of an electrode through tissue, resulting in changes in the electrical activity of the tissue.

THE BASICS

Electricity and Electrical Stimulation

Electricity powers the lights in your home and the batteries that run so many electronic gadgets, from smartphones to electric cars. *Electricity* is the flow of electrons from a body that contains a higher charge (more electrons) to a body that contains a lower charge (fewer electrons). This electron flow can perform work—lighting an unlit bulb, for instance. When biological tissue contains an electrical charge, the charge can be recorded; if living tissue is sensitive to an electrical charge, the tissue can be stimulated.

How Electricity Works

In the Power Source diagram to the right, negatively charged electrons are attracted to the positive pole because opposite charges attract. The electrons on the negative pole have the potential to flow to the positive pole. This *electrical potential*, or electrical charge, is the ability to do work using stored electrical energy.

Electrical potential is measured in *volts*, the difference in charge between the positive and negative poles. These poles are separated by an insulator. Thus, when not connected, the positive and negative poles in a battery, like the poles in each wall socket in your home, hold voltage between the poles.

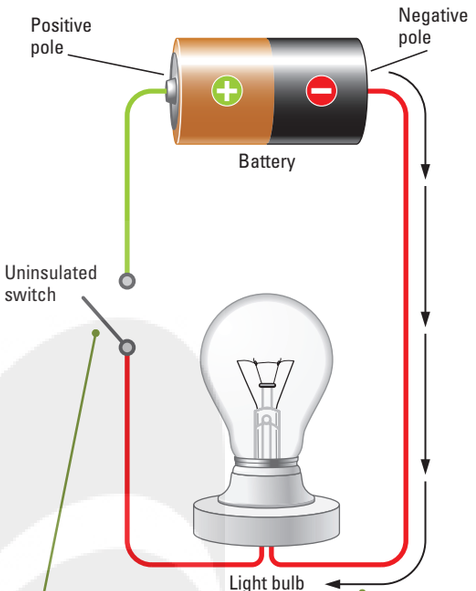
Electrical Activity in Cells

If the bare tip of an insulated wire, or *electrode*, from each pole of a battery comes into contact with biological tissue, current will flow from the electrode connected to the negative pole into the tissue and from the tissue into the electrode connected to the positive pole. The stimulation comes from the electrode's uninsulated tip. Microelectrodes can record from or stimulate tissue as small as parts of a single living cell.

Electrical stimulation, illustrated in part A of the Studying Electrical Activity in Animal Tissue diagram below, is most effective when administered in brief pulses. A timer in the stimulator turns the current on and off to produce the pulses. In electrical recording, voltage can be displayed by the dial on a voltmeter, a recording device that measures the voltage of a battery or of biological tissue (part B).

Power Source

Because electrons carry a negative charge, the negative pole has a higher electrical charge (more electrons) than the positive pole.



1 The battery will light the bulb only when the switch is closed. A conducting medium, such as an uninsulated wire, connects the two poles…

2 …and a flow, or current, of electrons streams through the bulb from the negative (–) to the positive (+) pole, lighting up the bulb.

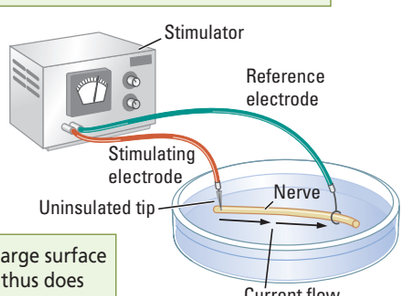
Studying Electrical Activity in Animal Tissue

(A) Electrical stimulation

Current leaves the stimulator through a wire lead (red) that attaches to an electrode. From the uninsulated tip of the electrode, the current enters the tissue and stimulates it. The current flows back to the stimulator through a second lead (green) connected to a reference electrode.

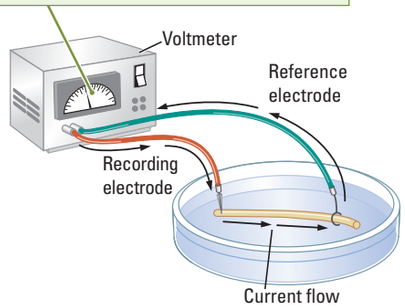
1 A stimulating electrode delivers current (electrons) ranging from 2 to 10 millivolts, intensities sufficient to produce a response without damaging cells.

2 The reference electrode contacts a large surface area that spreads out the current and thus does not excite the tissue here.



(B) Electrical recording

The difference in voltage between the tip of a recording electrode and a reference electrode deflects a needle that indicates the current's voltage.



part of her neocortex. Bartholow stimulated her exposed brain tissue to examine the effects. In one of his observations, he wrote:

> Passed an insulated needle into the left posterior lobe so that the non-insulated portion rested entirely in the substance of the brain. The reference was placed in contact with the dura mater. When the circuit was closed, muscular contraction in the right upper and lower extremities ensued. Faint but visible contraction of the left eyelid, and dilation of the pupils, also ensued. Mary complained of a very strong and unpleasant feeling of tingling in both right extremities, especially in the right arm, which she seized with the opposite hand and rubbed vigorously. Notwithstanding the very evident pain from which she suffered, she smiled as if much amused. (Bartholow, 1874)

As you might imagine, Bartholow's report was not well received! The uproar after its publication forced him to leave Cincinnati. Despite his unethical experiment, Bartholow had demonstrated that the brain of a conscious person could be stimulated electrically to produce movement of the body.

By the 1960s, the scientific community had established ethical standards for research on human and nonhuman subjects (see Section 7-7). Today, low-intensity and non-damaging brain stimulation is standard in many neurosurgical procedures (see Section 16-3).

Electrical Recording Studies

A less invasive line of evidence that information flow in the brain is partly electrical came from the results of electrical recording experiments. Richard Caton, a physician who lived a century ago, was the first to measure the brain's electrical currents with a sensitive **voltmeter**, a device that measures the flow and the strength of electrical voltage by recording the difference in electrical potential between two bodies. When he placed electrodes on a human subject's skull, Caton reported fluctuations in his voltmeter recordings. Today, this type of brain recording, the **electroencephalogram (EEG),** is a standard tool used for, among other things, monitoring sleep stages and detecting the excessive neural synchrony that characterizes electrographic seizures, as described in Clinical Focus 4-1, Epilepsy.

voltmeter Device that measures the strength of electrical voltage by recording the difference in electrical potential between two points.

electroencephalogram (EEG) Graph of electrical activity from the brain, which is mainly composed of graded potentials from many neurons.

Details on these EEG applications appear in Sections 7-2, 13-3, and 16-3.

These pioneering studies provided evidence that neurons send electrical messages, but it would be incorrect to conclude that nerves and tracts carry the kind of electrical current that powers your phone. Hermann von Helmholtz, a nineteenth-century scientist, stimulated a nerve leading to a muscle and measured the time the muscle took to contract. The nerve conducted information at only 30 to 40 meters per second, whereas electricity flows along a wire about a million times faster.

Information flow in the nervous system, then, is much too slow to be a flow of electricity (based on electrons). To explain the electrical signals of a neuron, Julius Bernstein suggested in 1886 that neuronal chemistry (based on ions) produces an electrical charge. He also proposed that the charge could change and thus could act as a signal. Bernstein's idea was that successive waves of electrical change constitute the message conveyed by the neuron.

Moreover, it is not the ions themselves that travel along the axon but rather a *wave* of charge. To understand the difference, consider other kinds of waves. If you drop a stone into a pool of still water, the contact produces a wave that travels away from the site of impact, as shown in **Figure 4-2**. The water itself moves up and down and does not travel away from the impact site. Only the *change in pressure* moves, shifting the height of the water surface and producing the wave effect.

FIGURE 4-2 **Wave Effect** Waves formed by dropping stones into still water do not entail the water's forward movement but rather pressure differences that change the height of the water surface.

Franklin Kappa/Getty Images

Similarly, when you speak, you induce pressure waves in air, and these waves carry your voice to a listener. If you flick a towel, a wave travels to the other end of the towel. Just as waves through the air send a spoken message, Bernstein's idea was that waves of chemical change travel along an axon to deliver a neuron's message.

Tools for Measuring a Neuron's Electrical Activity

Waves that carry messages in the nervous system are minute and are restricted to the surfaces of neurons. Still, we can produce these waves

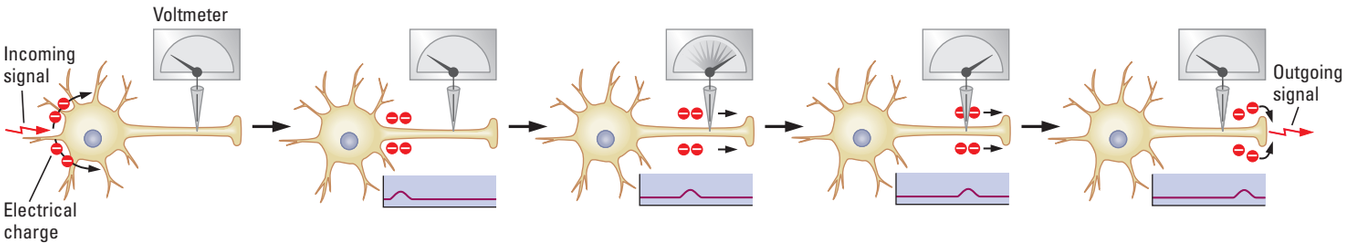


FIGURE 4-3 **Wave of Information** Neurons can convey information as a wave, induced by stimulation on the cell body, traveling down the axon to its terminal. A voltmeter detects the wave's passage

using conventional electrical stimulation and measure them using electrical recording techniques to determine how they are produced. When a single axon is stimulated, it produces a wave of excitation. If an electrode connected to a voltmeter is placed on a single axon, as illustrated in **Figure 4-3**, the electrode can detect a change in electrical charge on that axon's membrane as the wave passes.

As simple as this process may seem, recording a wave and determining how it is produced requires a neuron large enough to record, a recording device sensitive enough to detect a tiny electrical impulse, and an electrode small enough to be placed on the surface of a single neuron. The fortuitous discovery of the giant axon of the squid, the invention of the oscilloscope, and the development of microelectrodes met all these requirements.

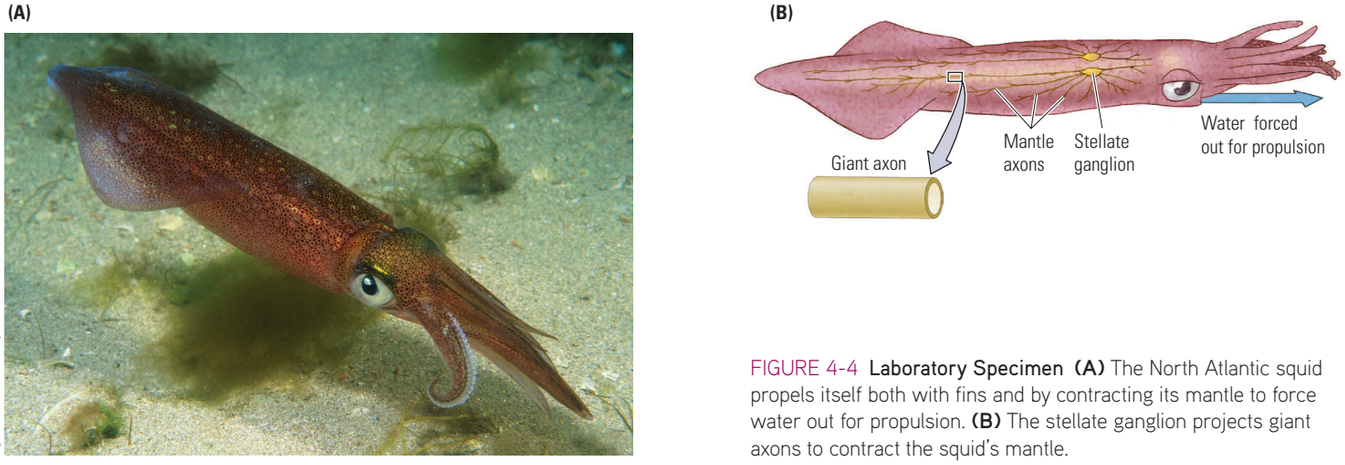
Giant Axon of the Squid

The neurons of most animals, including humans, are tiny, on the order of 1 to 20 micrometers (μm) in diameter—too small to be seen by the naked eye. The zoologist J. Z. Young, when dissecting the North Atlantic squid *Loligo vulgaris*, noticed that it has giant axons, as large as a millimeter (1000 μm, or about 1/25 inch) in diameter. **Figure 4-4** illustrates *Loligo* and the giant axons leading to its body wall, or mantle, which contracts to propel the squid through the water.

1 micrometer (also called a micron) (μm) = one-millionth of a meter, or one-thousandth of a millimeter (mm).

Measuring only about 1 foot long, *Loligo* is not a giant squid. But its axons are giant, as axons go. Each is formed by the fusion of many smaller axons. Because larger axons send messages faster than smaller axons do, these giant axons allow the squid to jet-propel away from predators.

In 1936, Young suggested to Alan Hodgkin and Andrew Huxley, neuroscientists at Cambridge University in England, that *Loligo*'s axons were large enough to be used for electrical recording studies. They dissected a giant axon out of the squid and kept it



age fotostock/Alamy Stock Photo

FIGURE 4-4 **Laboratory Specimen** **(A)** The North Atlantic squid propels itself both with fins and by contracting its mantle to force water out for propulsion. **(B)** The stellate ganglion projects giant axons to contract the squid's mantle.

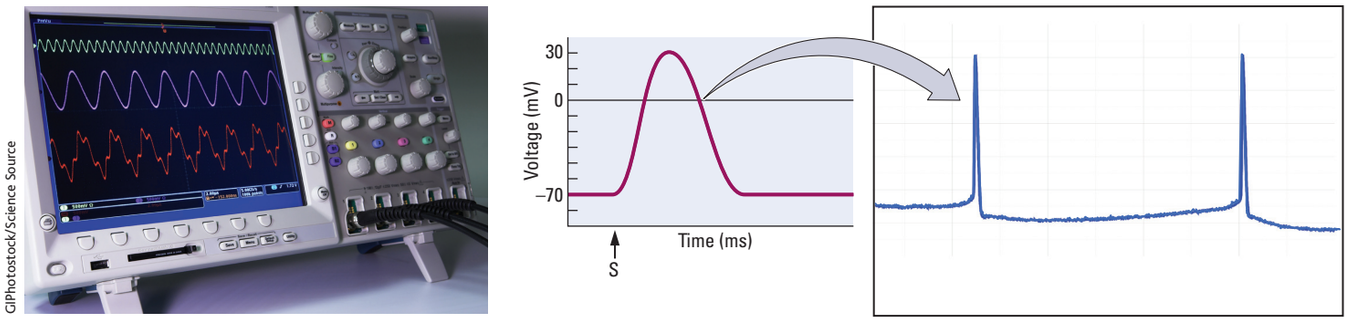


FIGURE 4-5 Oscilloscope Recording
(A) Basic wave shapes are displayed on a digital oscilloscope, a versatile electronic instrument used to visualize and measure electrical signals as they change. **(B)** On the graph of a trace produced by an oscilloscope, S stands for stimulation. The horizontal axis measures time, and the vertical axis measures voltage. By convention, the axon voltage is represented as negative, in millivolts (mV). On the right, one trace of two action potentials from an individual neuron as displayed on a digital oscilloscope screen.

alive and functioning in a bath of salty liquid that approximated the squid's body fluids. In this way, Hodgkin and Huxley (1939) determined the neuron's ionically based electrical activity. In 1963, they received the Nobel Prize for their accomplishment.

Oscilloscope

Hodgkin and Huxley's experiments were made possible by the invention of the **oscilloscope**, a voltmeter with a screen sensitive enough to display the minuscule electrical signals emanating from a nerve or neuron over time (**Figure 4-5A**). As graphed in Figure 4-5B, the units used when recording the electrical charge from a nerve or neuron are millivolts (mV; 1 mV is one-thousandth of a volt) and milliseconds (ms; 1 ms is one-thousandth of a second). Computers interfaced with recording equipment have largely replaced oscilloscopes.

Microelectrodes

The final device needed to measure a neuron's electrical activity is an electrode small enough to place on or in an axon—a **microelectrode**. A microelectrode can deliver electrical current to a single neuron as well as record from it. One way to create a microelectrode is to etch the tip of a piece of thin wire to a fine point about 1 mm in size and insulate the rest of the wire with a synthetic polymer, like plastic. The tip is placed on or in the neuron, as shown in the left-hand image in **Figure 4-6A**.

A microelectrode can also be made from a thin glass tube tapered to a very fine tip (Figure 4-6A, right image). The tip of a hollow glass microelectrode can be as small as 1 mm. When the glass tube is filled with salty water, a conducting medium through which electrical current can travel, it acts as an electrode. A wire in the salt solution connects the electrode to either a stimulating device or a recording device.

Microelectrodes can record from axons in many ways. The tip of a microelectrode placed on an axon provides an extracellular measure of the electrical current from a tiny part of the axon. The tip of one electrode can be placed on the surface of the axon, and the tip of a second electrode can be inserted into the axon. This technique can be used to measure voltage across the cell membrane.

A still more refined use of a glass microelectrode is to place its tip on the neuron's membrane and apply a little suction until the tip is sealed to a patch of the membrane, as shown in Figure 4-6B. This technique, analogous to placing the end of a soda straw against a piece of plastic wrap and

oscilloscope Specialized device that serves as a sensitive voltmeter, registering changes in voltage over time.

microelectrode A microscopic insulated wire or a saltwater-filled glass tube whose uninsulated tip is used to stimulate or record from neurons.

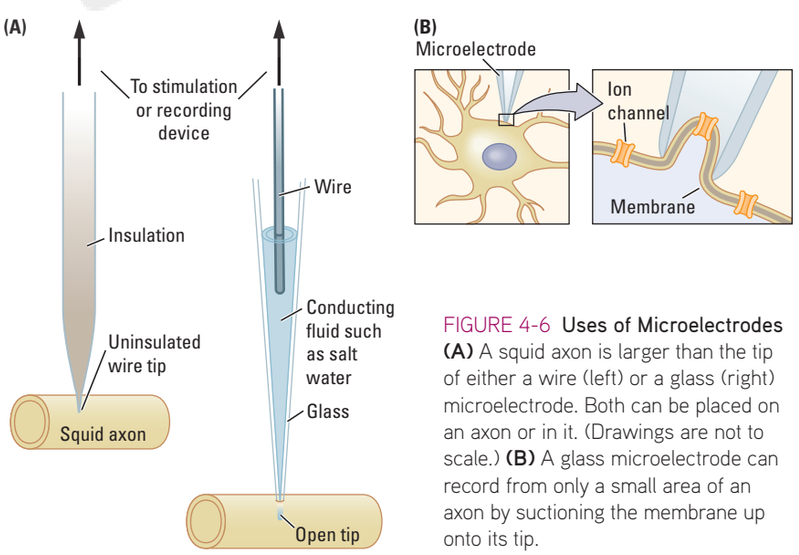


FIGURE 4-6 Uses of Microelectrodes
(A) A squid axon is larger than the tip of either a wire (left) or a glass (right) microelectrode. Both can be placed on an axon or in it. (Drawings are not to scale.) **(B)** A glass microelectrode can record from only a small area of an axon by suctioning the membrane up onto its tip.

diffusion Movement of ions from an area of higher concentration to an area of lower concentration through random motion.

concentration gradient Difference in the relative abundance of a substance among regions of a container; allows the substance to diffuse from an area of higher concentration to an area of lower concentration.

sucking, allows a recording to be made from only the small patch of membrane sealed to the microelectrode tip.

Using the giant axon of the squid, an oscilloscope, and microelectrodes, Hodgkin and Huxley recorded the electrical voltage on an axon's membrane and learned that the *nerve impulse* is a change in the concentration of specific ions across the cell membrane. The basis of electrical activity in nerves is the movement of intracellular and extracellular ions, which carry positive and negative charges across the cell membrane. We discuss the role of electrical activity in cell functioning in the next section, but first, to understand Hodgkin and Huxley's results, you first need to understand the principles underlying the movement of ions.

How Ion Movement Produces Electrical Charges

The intracellular fluid within a neuron and the extracellular fluid surrounding it contain various ions, including Na^+ (sodium) and K^+ (potassium)—positively charged, as the plus signs indicate—and negatively charged Cl^- (chloride). These fluids also contain numerous protein molecules, most of which hold an overall negative charge (A^-). Positively charged ions are called *cations*, and negatively charged ions, including protein molecules, are called *anions*. Three factors influence the movement of anions and cations into and out of cells: diffusion, concentration gradient, and voltage gradient.

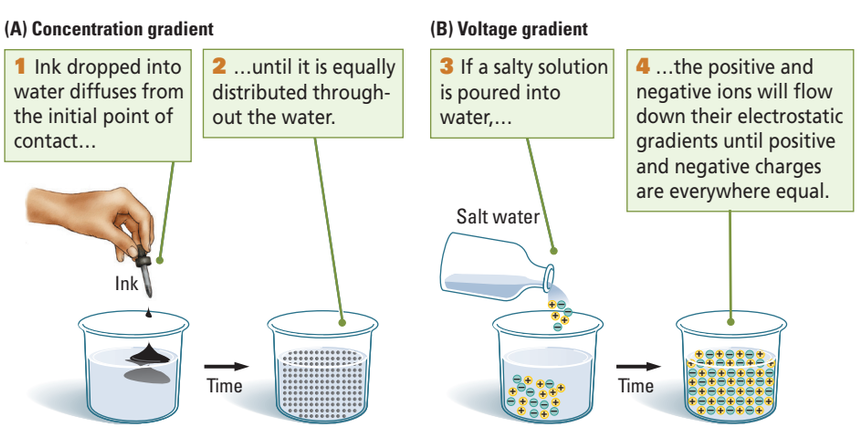
Because molecules move constantly, they tend to spread out from a point of high concentration. This spreading out is **diffusion**. Requiring no additional energy, diffusion results from the random motion of molecules as they move and bounce off one another to gradually disperse in a solution. Diffusion results in a dynamic equilibrium, with a relatively equal number of molecules everywhere in the solution.

Smoke, for example, gradually diffuses through the air in a room until every bit of air contains the same number of smoke molecules. Dye poured into water diffuses in the same way—from its point of contact to every part of the water in the container. Salts placed in water dissolve; their individual ions dissociate and become surrounded by water molecules. The ions and their associated water molecules then diffuse throughout the solution to equilibrium, at which point every part of the container has the same ion concentration.

The Basics, on pages 88-89, covers ions. The Salty Water illustration shows how water molecules dissolve salt crystals.

Concentration gradient describes the relative abundance of a substance in a space. Ions are initially highly concentrated where they enter at the top of a beaker of water, as illustrated in **Figure 4-7**, compared to the bottom of the beaker. As time passes, concentration gradients flow down due to diffusion.

FIGURE 4-7 Moving to Equilibrium



Because ions carry an electrical charge and because like charges repel one another, ion movement can be described by a concentration gradient, the difference in the number of ions between two regions, and a **voltage gradient**, the difference in charge between two regions. Ions move down a voltage gradient from an area of higher charge to an area of lower charge, just as they move down a concentration gradient from an area of higher concentration to an area of lower concentration.

voltage gradient Difference in charge between two regions that allows a flow of current if the two regions are connected.

Figure 4-7B illustrates this process. When salt is dissolved in water, the diffusion of its ions can be described either as movement down a concentration gradient (for sodium and chloride ions) or movement down a voltage gradient (for the positive and negative charges). In a container that allows unimpeded movement of ions, the positive and negative charges eventually balance.

A thought experiment will illustrate how a cell membrane influences ion movement. **Figure 4-8A** shows a container of water divided in half by a solid membrane that is impermeable to water and ions. If we place a few grains of table salt (NaCl) in the left half of the container, the salt dissolves. The ions diffuse down their concentration and voltage gradients until the water in the left compartment is in equilibrium.

The cell membrane is an insulator impermeable to salty solutions: dissolved ions, surrounded by water molecules, do not pass through the membrane's hydrophobic tails (review Figure 3-11).

In the left side of the container, there is no longer a gradient for either sodium or chloride ions because they occur everywhere with the same relative abundance. There are no gradients for these ions on the other side of the container either because the solid membrane prevents the ions from entering that side. But there are concentration and voltage gradients for both sodium and chloride ions *across* the membrane—that is, from the salty side to the freshwater side.

Transmembrane protein molecules embedded in a cell membrane form channels, some with gates, and pumps that allow specific kinds of ions to pass through the membrane. Returning to our thought experiment, we insert a few chloride channels into the membrane that divides the container of water, making the membrane semipermeable—that is, permeable to chloride but not to sodium, as illustrated at the left in Figure 4-8B. Chloride ions will now diffuse through the channels and cross the membrane by moving down their concentration gradient to the side of the container that previously had no chloride ions, shown in the middle of Figure 4-8B. The sodium ions, in contrast, cannot pass through the chloride channels and remain on one side of the cell membrane.

Even though dissolved sodium ions are smaller than chloride ions, they hold water molecules more strongly and thus act like they are bulkier and cannot pass through a narrow chloride channel.

If the only factor affecting the movement of chloride ions were the chloride concentration gradient, the efflux (outflow) of chloride from the salty side to the freshwater side of the container would continue until chloride ions were in equilibrium on both sides. But this is not what happens. Remember that opposite charges attract, so the chloride ions, which carry a negative charge, are attracted to the positively charged sodium ions they left behind. Because they are pulled back toward the sodium ions, the chloride ions cannot diffuse completely. Consequently, the concentration of chloride ions remains somewhat higher in the left side of the container than in the right, as illustrated at the right in Figure 4-8B.

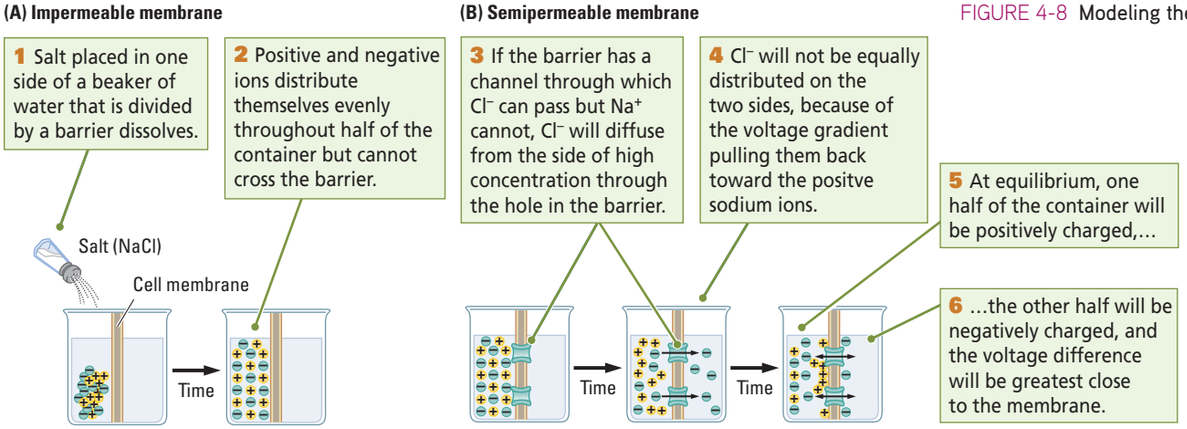


FIGURE 4-8 Modeling the Cell Membrane

In other words, the efflux of chloride ions down the chloride concentration gradient is counteracted by the influx (inflow) of chloride ions down the chloride voltage gradient. At some point, an equilibrium is reached: the chloride concentration gradient on the right side of the beaker is balanced by the chloride voltage gradient on the left. In brief:

concentration gradient = voltage gradient

At this equilibrium, the differential concentration of the chloride ions on the two sides of the membrane produces a difference in charge—voltage. The left side of the container is more positively charged because some chloride ions have migrated, leaving a preponderance of positive (Na^+) charges. The right side of the container is more negatively charged because some chloride ions have entered that chamber, where none were before. The charge is highest on the surface of the semipermeable membrane, the area at which positive and negative ions accumulate. Much the same process happens at the semipermeable membranes of real cells.

4-1 Review

Before you continue, check your understanding. Answers to Self-Test appear at the back of the book.

1. Although he was incorrect, _____ was the first to seriously attempt to explain how information travels through the nervous system.
2. Experimental results obtained over hundreds of years from electrical _____ and more recently from electrical _____ implicated electrical activity in the nervous system's flow of information.
3. By the mid-twentieth century, scientists had solved three technical problems in measuring the changes in electrical charge that travel like a wave along an axon's membrane: _____, _____, and _____.
4. The electrical activity of neuronal axons entails the diffusion of ions. Ions may move down a(n) _____ and down a(n) _____.
5. In what three ways does the semipermeable cell membrane affect the movement of ions in the nervous system?

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4-2

Electrical Activity at a Membrane

Most biological membranes are semipermeable because they have ion channels embedded within them; we will refer to them simply as membranes. Electrical activity in neurons is the movement of specific ions through channels *across* neuronal membranes. It is this process which allows the waves of electrical activity moving *along* membranes to convey information throughout the nervous system. So how are changes in the movement of ions across neuronal membranes achieved?

Resting Potential

Figure 4-9 shows how the voltage difference is recorded when one microelectrode is placed on the outer surface of an axon's membrane and another is placed on its inner surface. In the absence of stimulation, the difference is about 70 mV. Although the charge on the outside of the membrane is actually positive, by convention it is given a charge of zero. Therefore, the inside of the membrane at rest is −70 mV *relative to* the extracellular side.

Why zero? We are interested in the *relative difference*, not the actual charge.

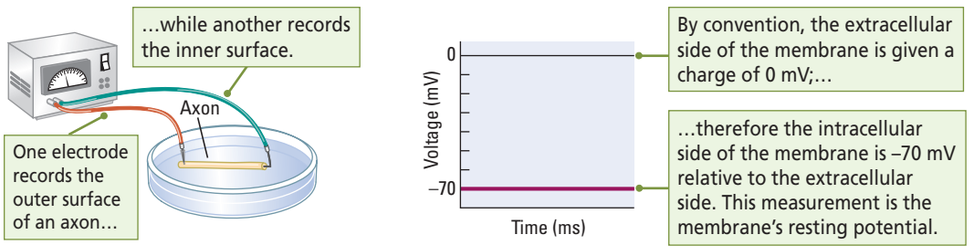


FIGURE 4-9 **Resting Potential** The electrical charge across a resting cell membrane stores potential energy.

If we were to continue to record for a long time, the charge across the unstimulated membrane would remain much the same. The charge can change, given certain changes in the membrane, but at rest the difference in charge on the inside and outside of the membrane produces an electrical *potential*—the ability to use its stored power, analogous to a charged battery. The charge is thus a store of potential energy called the membrane's **resting potential**.

We might use the term *potential* in the same way to talk about the financial potential of someone who has money in the bank; the person can spend the money at some future time. The resting potential, then, is a store of energy that can be used later. Most of your body's cells have a resting potential, but it is not identical on every axon. Resting potentials vary from −40 to −90 mV, depending on neuronal type and animal species.

Four charged particles take part in producing the resting potential: ions of sodium (Na^+), potassium (K^+), chloride (Cl^-), and large negatively charged protein molecules (A^-). These are the cations and anions, respectively, defined in Section 4-1. As **Figure 4-10** shows, these charged particles are distributed unequally across the axon's membrane, with more protein anions and potassium ions in the intracellular fluid and more sodium and chloride ions in the extracellular fluid. How do the unequal concentrations arise, and how does each contribute to the resting potential?

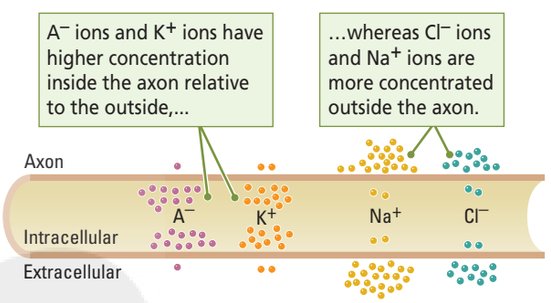


FIGURE 4-10 **Ion Distribution Across the Resting Membrane** The number of ions distributed across the resting cell membrane is unequal. Protein anions are represented by the label A^-.

Use this mnemonic to remember which ions are on which side: we put table salt—sodium chloride—on the outside of our food.

resting potential Electrical charge across the insulating cell membrane in the absence of stimulation; a store of potential energy produced by a greater negative charge on the intracellular side relative to the extracellular side.

Maintaining the Resting Potential

The cell membrane's channels, gates, and pumps maintain the resting potential. **Figure 4-11**, which shows the resting membrane close up, details how these three features contribute to the cell membrane's resting charge:

1. Because the membrane is relatively impermeable to large molecules, the negatively charged proteins (A^-) remain inside the cell.
2. Ungated potassium and chloride channels allow potassium (K^+) and chloride (Cl^-) ions to pass more freely, but gates on sodium channels keep out positively charged sodium ions (Na^+).
3. Na^+–K^+ pumps extrude Na^+ from the intracellular fluid and inject K^+.

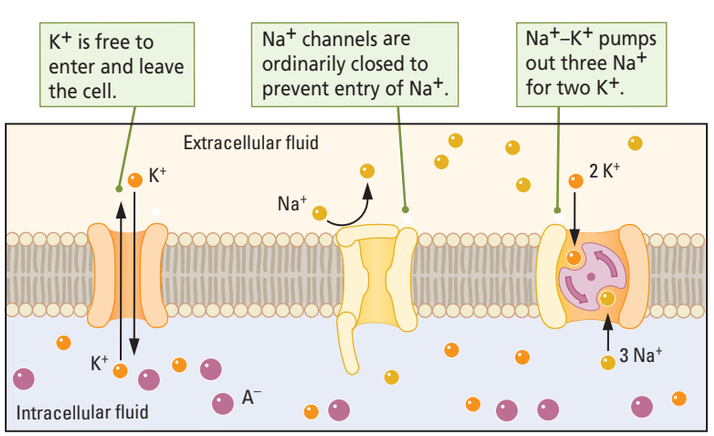


FIGURE 4-11 **Maintaining the Resting Potential** Channels, gates, and pumps in the cell membrane contribute to the transmembrane charge.

Inside the Cell

Large protein anions are manufactured inside cells. No membrane channels are large enough to allow these proteins to leave the cell, and their negative charge alone is sufficient to produce transmembrane voltage, or a resting potential. Because most cells in the body manufacture these large, negatively charged protein molecules, most cells have a charge across the cell membrane.

To balance the negative charge produced by large protein anions in the intracellular fluid, cells accumulate positively charged potassium ions to the extent that about 20 times as many potassium ions cluster inside the cell as outside it. Potassium ions cross the cell membrane through open potassium channels, as shown in Figure 4-11. With this high concentration of potassium ions inside the cell, however, the potassium concentration gradient across the membrane limits the number of potassium ions entering the cell. In other words, not all the potassium ions that could enter do enter. Because the internal concentration of potassium ions is much higher than the external potassium concentration, potassium ions are drawn out of the cell by the potassium concentration gradient.

A few residual potassium ions on the outside of the membrane are enough to contribute to the charge across the membrane. They add to the net negative charge on the intracellular side of the membrane relative to the extracellular side. You may be wondering whether you read the last sentence correctly. If there are 20 times as many potassium ions inside the cell as there are outside, why should the inside of the membrane have a negative charge? Should not all those potassium ions in the intracellular fluid give the inside of the cell a positive charge instead? No, because not quite enough potassium ions are able to enter the cell to balance the negative charge of the protein anions.

Think of it this way: if the number of potassium ions that could accumulate on the intracellular side of the membrane were unrestricted, the positively charged potassium ions inside would exactly match the negative charges on the intracellular protein anions. There would be no charge across the membrane at all. But the number of potassium ions that accumulate inside the cell is limited because when the intracellular K^+ concentration becomes higher than the extracellular concentration, further potassium ion influx is opposed by its concentration gradient.

Outside the Cell

The equilibrium of the potassium voltage and concentration gradients results in some potassium ions remaining outside the cell. It is necessary to have only a few positively charged potassium ions outside the cell to maintain a negative charge inside the cell. As a result, potassium ions contribute to the charge across the membrane.

Sodium (Na^+) and chloride (Cl^-) ions also take part in producing the resting potential. If positively charged sodium ions were free to move across the membrane, they would diffuse into the cell and eliminate the transmembrane charge produced by the unequal distribution of potassium ions inside and outside the cell. This diffusion does not happen because a gate on the sodium ion channels in the cell membrane is ordinarily closed (see Figure 4-11), blocking the entry of most sodium ions. Still, given enough time, sufficient sodium ions could leak into the cell to neutralize its membrane potential. The cell membrane has a different mechanism to prevent this neutralization.

When sodium ions do leak into the neuron, they are immediately escorted out again by the action of a *sodium–potassium pump*, a protein molecule embedded in the cell membrane. A membrane's many thousands of pumps continually exchange three intracellular sodium ions for two potassium ions, as shown in Figure 4-11. The potassium ions are free to leave the cell through open potassium channels, but closed sodium channels slow the reentry of the sodium ions. In this way, sodium ions are kept out to the extent that about 10 times as many sodium ions reside on the outside of the axon membrane as on its inside. The difference in sodium concentrations also contributes to the membrane's resting potential.

Now consider the chloride ions. Unlike sodium ions, chloride ions move in and out of the cell through open channels in the membrane. The equilibrium point, at which the chloride's concentration gradient equals its voltage gradient, is approximately the same as the membrane's resting potential, so chloride ions ordinarily contribute little to the resting potential. At this equilibrium point, there are about 12 times as many chloride ions outside the cell as inside it.

The cell membrane's semipermeability and the actions of its channels, gates, and pumps thus produce voltage across the cell membrane: its resting potential (**Figure 4-12**).

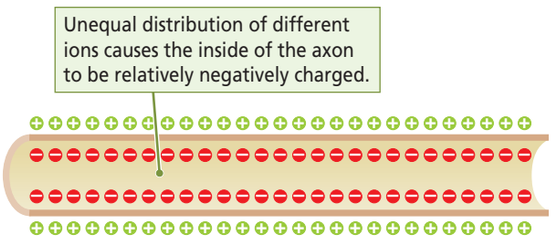


FIGURE 4-12 **Resting Transmembrane Charge**

Graded Potentials

The resting potential provides an energy store that can be used somewhat like the water in a dam: small amounts can be released by opening gates for irrigation or to generate electricity. If the concentration of any of the ions across the unstimulated cell membrane changes, the membrane voltage changes. These **graded potentials** are small voltage fluctuations across the cell membrane.

Stimulating a membrane electrically through a microelectrode mimics the way the membrane's voltage changes to produce a graded potential in the living cell. If the voltage applied to the inside of the membrane is negative, the membrane potential increases in negative charge by a few millivolts. As illustrated in **Figure 4-13A**, it may change from a resting potential of −70 mV to a slightly greater potential of −73 mV.

This change is a **hyperpolarization** because the charge (polarity) of the membrane increases. Conversely, if positive voltage is applied inside the membrane, its potential decreases by a few millivolts. As illustrated in Figure 4-13B, it may change from, say, a resting potential of −70 mV to a slightly lower potential of −65 mV. This change is a **depolarization** because the membrane charge decreases. Graded potentials usually last only a few milliseconds.

graded potential Small voltage fluctuation across the cell membrane.

hyperpolarization Increase in electrical charge across a membrane, usually due to the inward flow of chloride or sodium ions or the outward flow of potassium ions.

depolarization Decrease in electrical charge across a membrane, usually due to the inward flow of sodium ions.

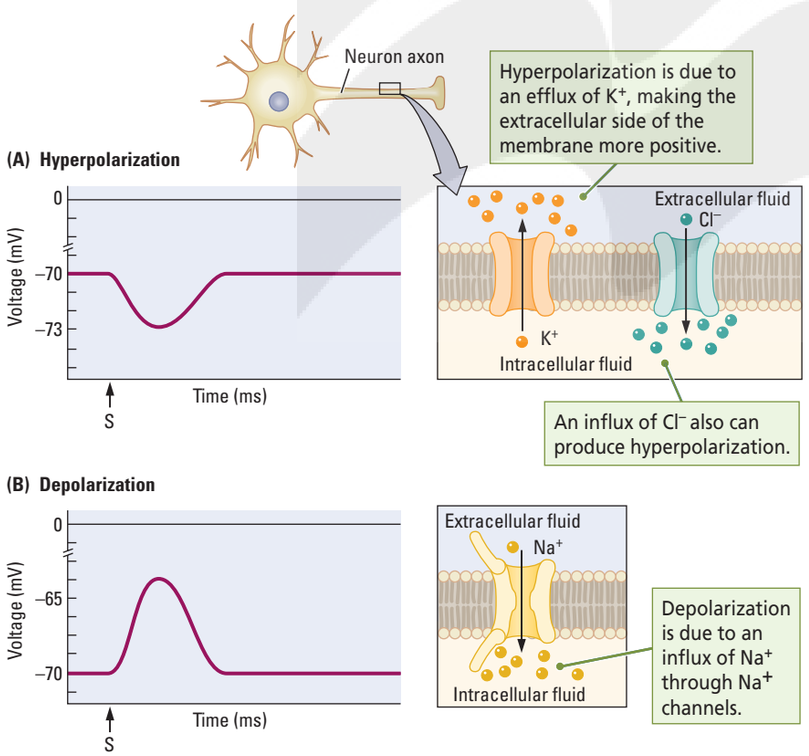
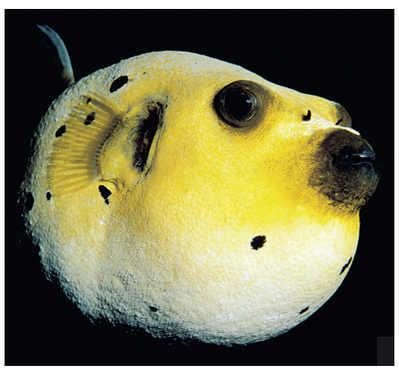


FIGURE 4-13 **Graded Potentials** **(A)** Stimulation (S) that increases relative membrane voltage produces a hyperpolarizing graded potential. **(B)** Stimulation that decreases relative membrane voltage produces a depolarizing graded potential.



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Puffer Fish

Table 6-2 lists a variety of neurotoxins and their sources and summarizes some of their effects.

Hyperpolarization and depolarization typically take place on the soma (cell body) membrane and on neuronal dendrites. These areas contain gated channels that can open and close, thereby changing the membrane potential, as illustrated in Figure 4-13. Three channels—for potassium, chloride, and sodium ions—underlie graded potentials:

1. *Potassium channels.* For the membrane to become hyperpolarized, its extracellular side must become more positive, which can be accomplished with an outward movement, or efflux, of potassium ions. But if potassium channels are ordinarily open, how can the efflux of potassium ions increase? Apparently, even though potassium channels are open, some resistance to the outward flow of potassium ions remains. Reducing this resistance enables hyperpolarization.
2. *Chloride channels.* The membrane can also become hyperpolarized if an influx of chloride ions occurs. Even though chloride ions can pass through the membrane, more ions remain on the outside than on the inside, so a decreased resistance to Cl^- flow can result in brief increases of Cl^- inside the cell.
3. *Sodium channels.* Depolarization can be produced if normally closed sodium channel gates open to allow an influx of sodium ions.

Evidence that potassium channels have a role in hyperpolarization comes from the fact that the chemical tetraethylammonium (TEA), which blocks potassium channels, also blocks hyperpolarization. The involvement of sodium channels in depolarization is indicated by the fact that the chemical tetrodotoxin (TTX), which blocks sodium channels, also blocks depolarization. The puffer fish, considered a delicacy in some countries, especially Japan, secretes TTX—a potentially deadly poison—to fend off would-be predators. Skill is required to prepare this fish for human consumption. It can be lethal to the guests of careless cooks because its toxin impedes the electrical activity of neurons.

Action Potential

Electrical stimulation of the cell membrane at resting potential produces local graded potentials. An **action potential,** on the other hand, is a brief but very large reversal in an axon membrane's polarity (**Figure 4-14A**) that lasts about 1 ms. The voltage across the membrane suddenly reverses, making the intracellular side positive relative to the extracellular side, then abruptly reverses again to restore the resting potential. Because the action potential is brief, many action potentials can occur within a second, as illustrated in Figures 4-14B and C, where the time scales are compressed.

action potential Large, brief reversal in the polarity of an axon membrane

threshold potential Voltage on a neural membrane at which an action potential is triggered by the opening of sodium and potassium voltage-activated channels; about –50 mV relative to extracellular surround. Also called *threshold limit*.

An action potential occurs when a large concentration of first Na^+ and then K^+ crosses the membrane rapidly. The depolarizing phase of the action potential is due to Na^+ influx, and the hyperpolarizing phase is due to K^+ efflux. Sodium rushes in and then potassium rushes out. As shown in **Figure 4-15**, the *combined* flow of sodium and potassium ions underlies the action potential.

An action potential is triggered when the cell membrane is depolarized to about –50 mV. At this **threshold potential**, the membrane charge undergoes a remarkable further change with no additional stimulation. The relative voltage of the membrane

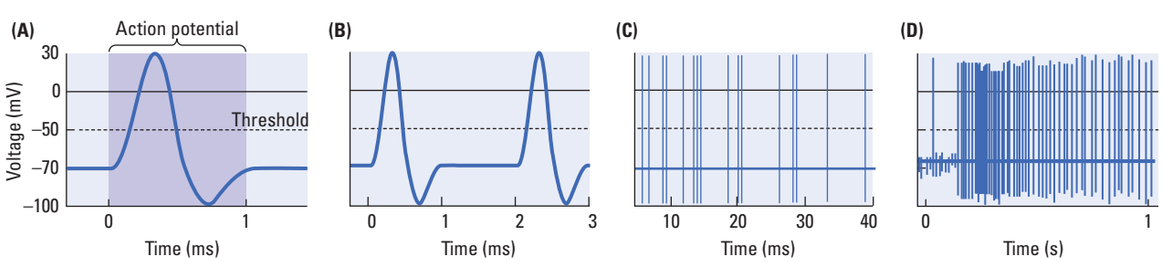


FIGURE 4-14 **Measuring Action Potentials** **(A)** Phases of a single action potential. The time scales on the horizontal axes are compressed to chart **(B)** each action potential as a discrete event, **(C)** the ability of a membrane to produce many action potentials in a short time, (**D**) and the series of action potentials over the course of 1 second (1000 ms).

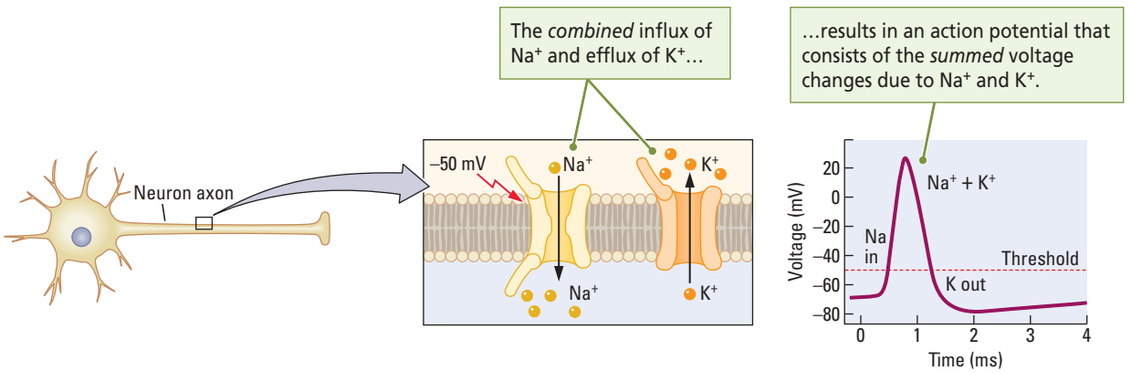


FIGURE 4-15 Triggering an Action Potential

drops to zero and continues to depolarize until the charge on the inside of the membrane is as great as +30 mV—a total voltage change of 100 mV. Then the membrane potential reverses again, becoming slightly hyperpolarized—a reversal of a little more than 100 mV. After this second reversal, the membrane slowly returns to its resting potential at –70 mV.

The action potential normally consists of the summed current changes caused first by the inflow of sodium and then by the outflow of potassium on an axon. Experimental results reveal that if an axon membrane is stimulated electrically while the solution surrounding the axon contains the chemical TEA (to block potassium channels), the result is a smaller-than-normal ion flow due entirely to an Na^+ influx. Similarly, if an axon's membrane is stimulated electrically while the solution surrounding the axon contains TTX (to block sodium channels), a slightly different ion flow due entirely to the efflux of K^+ is recorded. **Figure 4-16** illustrates these experimental results, in which the graphs represent *ion flow* rather than voltage change.

Role of Voltage-Activated Ion Channels

What cellular mechanisms underlie the movement of sodium and potassium ions to produce an action potential? The answer is the behavior of a class of gated sodium

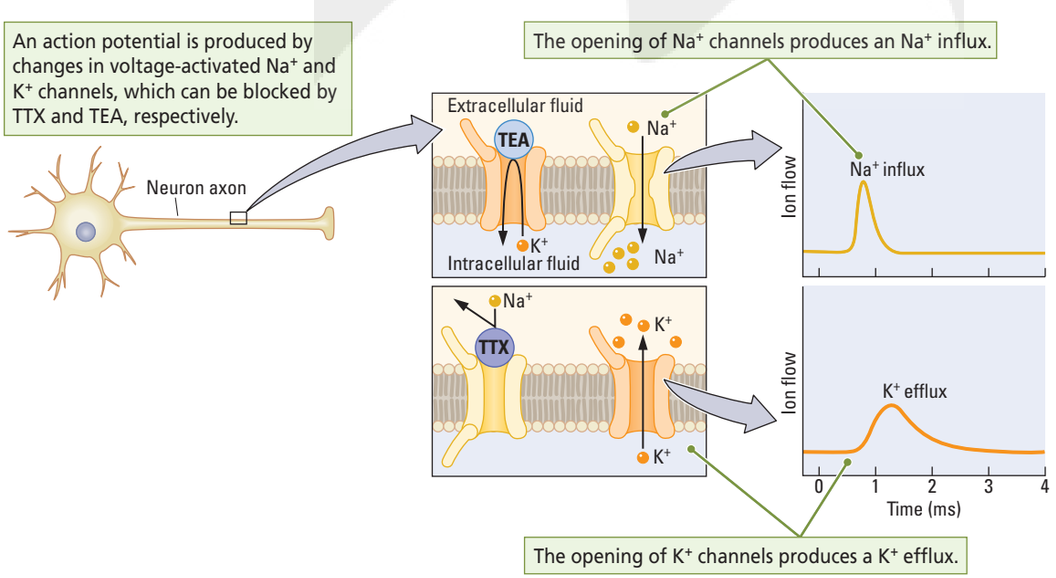


FIGURE 4-16 Blocking an Action Potential

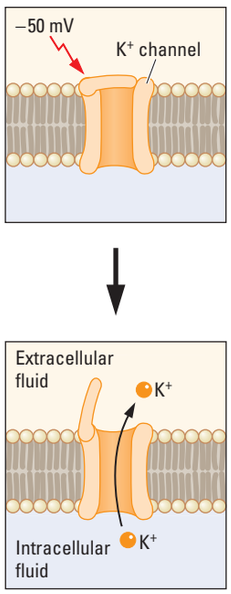


FIGURE 4-17 Voltage-Activated Potassium Channel

and potassium channels sensitive to the membrane's voltage (**Figure 4-17**). These **voltage-activated channels** are closed when an axon's membrane is at its resting potential: ions cannot pass through them. When the membrane reaches threshold voltage, the configuration of the voltage-activated channels alters: they open briefly, enabling ions to pass through, then close again to restrict ion flow. The sequence of actions is as follows:

1. Both sodium and potassium voltage-activated channels are attuned to the threshold voltage of about –50 mV. If the cell membrane changes to reach this voltage, both types of channels open to allow ion flow across the membrane.
2. The voltage-activated sodium channels respond more quickly than the potassium channels. As a result, the voltage change due to Na^+ influx takes place slightly before the voltage change due to K^+ efflux can begin.
3. Sodium channels have two gates. Once the membrane depolarizes to about +30 mV, one of the gates closes. Thus, Na^+ influx begins quickly and ends quickly.
4. The potassium channels open more slowly than the sodium channels, and they remain open longer. Thus, the efflux of K^+ reverses the depolarization produced by Na^+ influx and even hyperpolarizes the membrane.

Action Potentials and Refractory Periods

There is an upper limit to how frequently action potentials occur, and sodium and potassium channels are responsible for it. Stimulation of the axon membrane during the depolarizing phase of the action potential will not produce another action potential. Nor is the axon able to produce another action potential when it is repolarizing. During these times, the membrane is described as being **absolutely refractory**.

If, on the other hand, the axon membrane is stimulated during hyperpolarization, another action potential can be induced, but the second stimulation must be more intense than the first. During this phase, the membrane is **relatively refractory**.

Refractory periods result from the way gates of the voltage-activated sodium and potassium channels open and close. A sodium channel has two gates, and a potassium channel has one gate. **Figure 4-18** illustrates the position of these gates before,

Exceptions do exist: some CNS neurons discharge during the repolarizing phase.

voltage-activated channel Gated protein channel that opens or closes only at specific membrane voltages.

absolutely refractory The state of an axon in the repolarizing period, during which a new action potential cannot be elicited (with some exceptions) because gate 2 of sodium channels, which are not voltage activated, are closed.

relatively refractory The state of an axon in the later phase of an action potential, during which higher-intensity electrical current is required to produce another action potential; a phase during which potassium channels are still open.

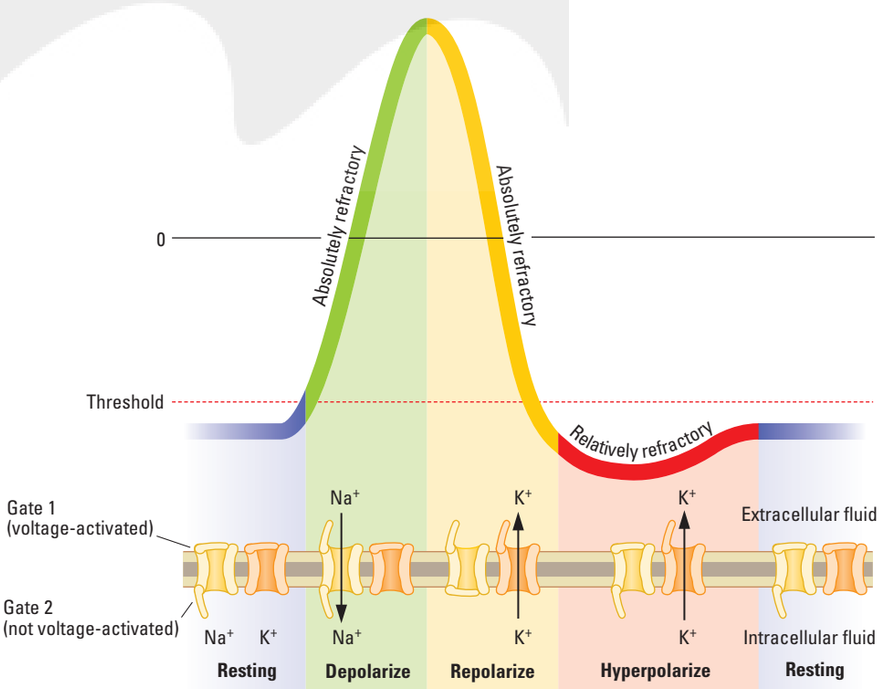


FIGURE 4-18 Phases of an Action Potential Initiated by changes in voltage-activated sodium and potassium channels, an action potential begins with a depolarization: gate 1 of the sodium channel opens, and then gate 2 closes. The slower-opening potassium channel gate contributes to repolarization and hyperpolarization until the resting membrane potential is restored.

during, and after the phases of the action potential. We describe changes first in the sodium channels and then in the potassium channels.

During the resting potential, gate 1 of the sodium channel depicted in Figure 4-18 is closed; only gate 2 is open. At the threshold level of stimulation, gate 1 also opens. Gate 2, however, closes very quickly after gate 1 opens. This sequence produces a brief period during which both sodium gates are open. When both gates are open and when gate 2 is closed, the membrane is absolutely refractory.

The opening of the potassium channels repolarizes and eventually hyperpolarizes the cell membrane. The potassium channels open and close more slowly than the sodium channels do. The hyperpolarization produced by a continuing efflux of potassium ions makes it more difficult to depolarize the membrane to the threshold that reopens the gates underlying an action potential. While the membrane is hyperpolarizing, it is relatively refractory.

The changes in polarity that take place during an action potential are analogous to the action of a lever-activated toilet. Pushing the lever slightly produces a slight water flow that stops when the lever is released. This activity is analogous to a graded potential. A harder lever press brings the toilet to threshold and initiates flushing, a response that is out of all proportion to the lever press. This activity is analogous to the action potential.

During the flush, the toilet is absolutely refractory: another flush cannot be induced at this time. During the refilling of the bowl, in contrast, the toilet is relatively refractory, meaning that flushing again is possible but harder. Only after the cycle is over and the toilet is once again at rest can a full flush be produced again.

nerve impulse Propagation of an action potential on the membrane of an axon.

Nerve Impulse

Suppose you place two recording electrodes at a distance from one another on an axon membrane and then electrically stimulate an area adjacent to one electrode. That electrode would immediately record an action potential. A similar recording would register on the second electrode in a flash. An action potential has arisen near this second electrode also, even though it is some distance from the original point of stimulation.

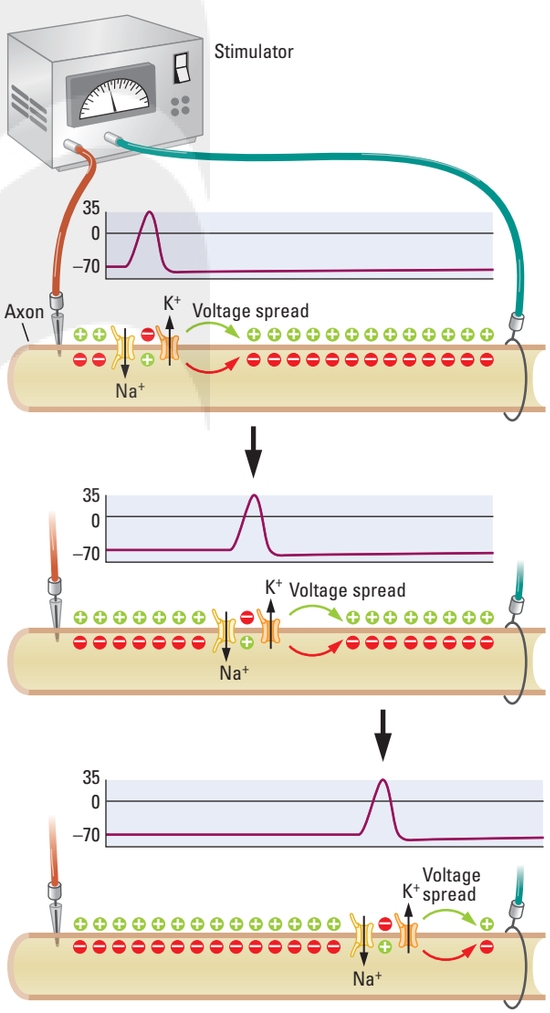
Is this second action potential simply an echo of the first that passes down the axon? No, it cannot be because the action potential's size and shape are exactly the same at the two electrodes. The second is not just a faint, degraded version of the first but is equal in magnitude. Somehow the full action potential has moved along the axon. This propagation of an action potential along an axon is called a **nerve impulse**.

Why does an action potential move? Remember that the total voltage change during an action potential is 100 mV, far beyond the 20-mV change needed to bring the membrane from its resting state of –70 mV to the action potential threshold level of –50 mV. Consequently, the voltage change on the part of the membrane where an action potential first occurs is large enough to bring adjacent parts of the membrane to a threshold of –50 mV.

When the membrane at an adjacent part of the axon reaches –50 mV, the voltage-activated channels at that location pop open to produce an action potential there as well. This second occurrence, in turn, induces a change in the membrane voltage still farther along the axon, and so on and on, down the axon's length. **Figure 4-19** illustrates this process. The nerve impulse occurs because each action potential propagates another action potential on an adjacent part of the axon membrane. The word *propagate* means "to give birth," and that is exactly what happens. Each successive action potential gives birth to another down the length of the axon.

Because they are propagated by gated ion channels acting on the membrane in their own vicinity, action potentials on a nerve or tract are the same magnitude wherever they occur. An action potential depends

FIGURE 4-19 **Propagating an Action Potential** Voltage sufficient to open Na^+ and K^+ channels spreads to adjacent sites of the axon membrane, inducing voltage-activated gates to open. Here, voltage changes are shown on only one side of the membrane.



The Domino Effect

on energy expended where it occurs, and the same amount of energy is typically expended at every site along the membrane as a nerve impulse is propagated.

As a result, action potentials do not dissipate: an action potential is either generated completely or not generated at all. Action potentials are all-or-none events. As the nerve's impulse, or message, the action potential maintains a constant size and arrives unchanged to every terminal on the nerve that receives it.

Think of the voltage-activated channels along the axon as a series of dominoes. When one falls, it knocks over its neighbor, and so on down the line. There is no decrement in the size of the fall. The last domino travels exactly the same distance and falls just as hard as the first one did.

Essentially, the domino effect happens when voltage-activated channels open. The opening of one channel produces a voltage change that triggers its neighbor to open, just as one domino knocks over the next. The channel-opening response does not grow any weaker as it moves along the axon, and the last channel opens exactly like the first, just as the domino action stays constant to the end of the line.

Refractory Periods and Nerve Action

Refractory periods are determined by the position of the gates that mediate ion flow in the voltage-activated channels. This limits the frequency of action potentials to about one every 5 ms. The action potential's refractory phase thus has two practical uses for nerves that are conducting information.

First, the maximum rate at which action potentials can occur is about 200 per second (1 s, or 1000 ms/5 ms limit = 200 action potentials in 1 s). The sensitivity of voltage-activated channels, which varies among kinds of neurons, likewise affects firing frequency.

Second, although an action potential can travel in either direction on an axon, refractory periods prevent it from reversing direction and returning to its point of origin. Refractory periods thus produce a single, discrete impulse that travels away from the initial point of stimulation. When an action potential begins near the cell body, it usually travels down the axon to the terminals.

To return to our domino analogy, once a domino falls, setting it up again takes time. This is its refractory period. Because each domino falls as it knocks down its neighbor, the sequence cannot reverse until the domino is set upright again: the dominos can fall in only one direction. The same principle determines the action potential's direction.

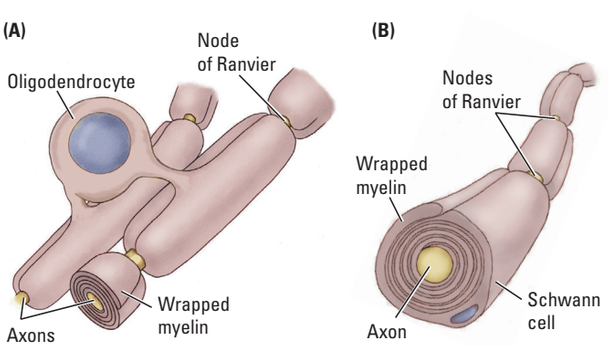
Saltatory Conduction and the Myelin Sheath

Because the giant axons of squid are so large, they can transmit nerve impulses very quickly, much as a large-diameter pipe can rapidly deliver a lot of water. But large axons take up substantial space: a squid cannot accommodate many of them, or its body would be too bulky. For mammals, with our many axons innervating a substantial number of muscles, giant axons are out of the question. Our axons must be extremely slender because our complex movements require a great many of them.

Our largest axons, which run to and from our muscles, are only about 30 μm wide, so the speed with which they convey information should not be especially fast. And yet, like most other vertebrate species, we humans are hardly sluggish creatures. We process information and generate responses with impressive speed. How do we manage to do so if our axons are so thin? The vertebrate nervous system has evolved a solution that has nothing to do with axon size.

Glial cells play a role in speeding nerve impulses in the vertebrate nervous system. Schwann cells in the human peripheral nervous system and oligodendroglia in the central nervous system wrap around some axons, forming the myelin sheath that insulates it (**Figure 4-20**). Action potentials cannot occur where myelin is wrapped around an axon. For one thing, the myelin is an insulating barrier to ionic current

FIGURE 4-20 **Myelination** An axon is insulated by **(A)** oligodendroglia in the CNS and **(B)** Schwann cells in the PNS. Each glial cell is separated by a gap, or node of Ranvier.



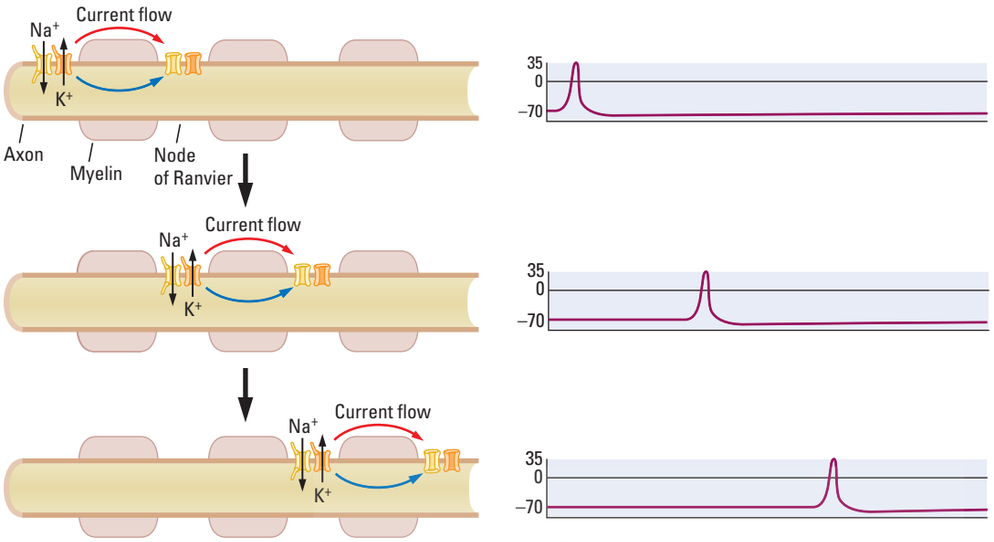


FIGURE 4-21 **Saltatory Conduction** Myelinated stretches of axons are interrupted by nodes of Ranvier, rich in voltage-activated channels. In saltatory conduction, the action potential jumps rapidly from node to node.

flow. For another, axonal regions that lie under myelin have few channels through which ions can flow, and ion channels are essential to generating an action potential.

But axons are not totally encased in myelin. Unmyelinated gaps between successive glial cell wrappings are richly endowed with voltage-activated channels. These tiny gaps in the myelin sheath, the **nodes of Ranvier**, are sufficiently close to one another that an action potential at one node can open voltage-activated gates at an adjacent node. In this way, a relatively slow action potential jumps quickly from node to node, as shown in **Figure 4-21**. This flow of energy is called **saltatory conduction** (from the Latin verb *saltare*, meaning "to leap").

To review glial cell types, appearance, and functions, see Table 3-1.

Myelin has two important consequences for propagating action potentials. First, propagation becomes energetically cheaper, since action potentials regenerate only at the nodes of Ranvier, not along the axon's entire length. Action potential conduction in unmyelinated axons, by contrast, has a significant metabolic energy cost (Crotty et al., 2006). The second consequence is that myelin improves the action potential's conduction speed.

Jumping from node to node speeds the rate at which an action potential can travel along an axon because the current flowing within the axon beneath the myelin sheath travels very fast. While the current moves speedily, the voltage drops quickly over distance. But the nodes of Ranvier are spaced ideally to ensure sufficient voltage at the next node to supersede the threshold potential and thus regenerate the action potential. On larger, myelinated mammalian axons, nerve impulses can travel at a rate as high as 120 meters per second. On smaller, uninsulated axons, they travel only about 30 meters per second.

Spectators at sporting events sometimes initiate a wave that travels around a stadium. Just as one person rises, the next person begins to rise, producing the wave effect. This human wave is like conduction along an unmyelinated axon. Now think of how much faster the wave would complete its circuit around the field if only spectators in the corners rose to produce it. This is analogous to a nerve impulse that travels by jumping from one node of Ranvier to the next. The quick reactions that humans and other mammals are capable of are due in part to this saltatory conduction in their nervous system.

Neurons that send messages over long distances quickly, including sensory and motor neurons, are heavily myelinated. If myelin is damaged, a neuron may be unable to send any messages over its axons. In **multiple sclerosis (MS)**, the myelin formed by oligodendroglia is damaged, which disrupts the functioning of neurons whose axons it encases. Clinical Focus 4-2, Multiple Sclerosis on page 126, describes the course of the disease.

node of Ranvier The part of an axon that is not covered by myelin.

saltatory conduction Fast propagation of an action potential at successive nodes of Ranvier; *saltatory* means "leaping."

multiple sclerosis (MS) Nervous system disorder resulting from the loss of myelin around axons in the CNS.

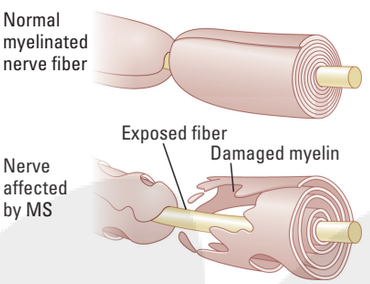
CLINICAL FOCUS 4-2

Multiple Sclerosis

One day, J. O., who had just finished university requirements to begin work as an accountant, noticed a slight cloudiness in her right eye. It did not go away when she wiped her eye. Rather, the area grew over the next few days. Her optometrist suggested that she see a neurologist, who diagnosed optic neuritis, an indication that can be a flag for multiple sclerosis (MS).

MS results from a loss of myelin produced by oligodendroglia cells in the CNS (see illustration). It disrupts the affected neurons' ability to propagate action potentials via saltatory conduction. This loss of myelin occurs in patches, and scarring frequently results in the affected areas.

Eventually, a hard scar, or *plaque*, forms at the site of myelin loss, which can be visualized with magnetic resonance imaging (MRI). (MS is called a *sclerosis* from the Greek word meaning "hardness.") Associated with the loss of myelin is impairment of neuron function, which causes the characteristic MS symptoms sensory loss and difficulty in moving.



Fatigue, pain, and depression are commonly associated with MS. Bladder dysfunction, constipation, and sexual dysfunction all complicate it. MS, about twice as common in women as in men, greatly affects a person's emotional, social, and vocational functioning.

Multiple sclerosis is the most common of nearly 80 **autoimmune diseases,** conditions in which the immune system makes antibodies to a person's own body (Rezania et al., 2012). The FDA has approved 15 medications for modifying the course of multiple sclerosis, but it is doubtful that the disease can be fully arrested with current therapies (Reich et al., 2018).

J. O.'s eye cleared over the next few months, and she had no further symptoms until after the birth of her first child 3 years later, when she felt a tingling in her right hand. The tingling spread up her arm, until gradually she lost movement in the arm for 5 months. Then J. O.'s arm movement returned. But 5 years later, after her second child was born, she felt a tingling in her left big toe that spread along the sole of her foot and then up her leg, eventually leading again to loss of movement. J. O. received corticosteroid treatment, which helped, but the condition rebounded when she stopped treatment. Then it subsided and eventually disappeared.

Since then, J. O. has had no major outbreaks of motor impairment, but she reports enormous fatigue, takes long naps daily, and is ready for bed early in the evening. Her sister and a female cousin have experienced similar symptoms, and recently a third sister began to display similar symptoms in middle age, as has J.O.'s daughter, who is in her mid-20s. Furthermore, one of J. O.'s grandmothers had been confined to a wheelchair, but the source of her problem was never determined.

MS is difficult to diagnose. Symptoms usually appear in adulthood; their onset is quite sudden, and their effects can be swift. Initial symptoms may be loss of sensation in the face, limbs, or body or loss of control over movements or loss of both sensation and control. Motor symptoms usually appear first in the hands or feet.

Early symptoms often go into remission and do not appear again for years. In some forms, however, MS progresses rapidly over just a few years until the person is bedridden.

MS is common in the northern-most and southern-most latitudes, so it may be related to a lack of vitamin D, which is produced by the action of sunlight on the skin. The disease may also be related to genetic susceptibility, as is likely in J. O.'s case. Many MS patients take vitamin D_3 and vitamin B_{12}. While MS is the most prevalent chronic inflammatory disease of the CNS, affecting more than 2 million people worldwide (Reich et al., 2018), the underlying cause for the inflammation and loss of myelin is still unknown. It has been suggested that multiple sclerosis may primarily be a degenerative disease that secondarily elicits an autoimmune response (Stys, 2013). Research aimed at solving this problem is important because the answer would likely influence therapeutic approaches.

4-2 Review

Before you continue, check your understanding. Answers to Self-Test appear at the back of the book.

1. The _____ results from the unequal distribution of _____ inside and outside the cell membrane.
2. Because it is _____ , the cell membrane prevents the efflux of large protein anions and pumps sodium ions out of the cell to maintain a slightly _____ charge in the intracellular fluid relative to the extracellular fluid.
3. For a graded potential to arise, a membrane must be stimulated to the point that the transmembrane charge increases slightly to cause a(n) _____ or decreases slightly to cause a(n) _____.
4. The voltage change associated with a(n) _____ is sufficiently large to stimulate adjacent parts of the axon membrane to the threshold for propagating it along the length of an axon as a(n) _____.
5. Briefly explain why nerve impulses travel faster on myelinated axons than on unmyelinated axons.

autoimmune diseases Illness resulting from an abnormal immune response by the body against substances and tissues normally present in the body.

For additional study tools, visit LaunchPad at launchpadworks.com

4-3

How Neurons Integrate Information

A neuron's extensive dendritic tree is covered with spines, and through them it can establish more than 50,000 connections from other neurons. A neuron's body, which sits between its dendritic tree and axon, can also receive multiple connections. Nerve impulses traveling from other neurons to each of these synaptic locations bombard the receiving neuron with excitatory and inhibitory inputs.

In the 1950s and 1960s, John C. Eccles (1965) and his students performed experiments that helped answer the question of how the neuron integrates such an enormous array of inputs into a nerve impulse. Rather than record from the giant axon of a squid, Eccles recorded from the cell bodies of large motor neurons in the vertebrate spinal cord. In doing so, he refined the electrical stimulating and recording techniques first developed for studying squid axons (see Section 4-1). Eccles received the Nobel Prize in Physiology or Medicine for his work.

Motor neurons, for example, receive input from multiple sources. A spinal cord motor neuron has an extensive dendritic tree with as many as 20 main branches that subdivide numerous times and are covered with dendritic spines. Input from the skin, joints, muscles, spinal cord, and brain make motor cells ideal for studying how a neuron responds to diverse inputs. Each motor neuron sends its axon directly to a muscle. The motor neuron is the final common pathway the nervous system uses to produce behavior.

Excitatory and Inhibitory Postsynaptic Potentials

To study motor neuron activity, Eccles inserted a microelectrode into a vertebrate's spinal cord until the tip was in or right beside a motor neuron's cell body. He then placed stimulating electrodes on sensory nerve fiber axons entering the spinal cord. By teasing apart the many incoming sensory fibers, he was able to stimulate one nerve fiber at a time.

Figure 2-30A diagrams the human spinal cord in cross section.

Experiment 4-1 diagrams the experimental setup Eccles used. As shown at the left in the Procedures section, stimulating some incoming sensory fibers produced a depolarizing graded potential (reduced the charge) on the membrane of the motor neuron to which these fibers were connected. Eccles called these graded potentials **excitatory postsynaptic potentials (EPSPs)**. As graphed on the left side of the Results section, EPSPs reduce (depolarize) the charge on the membrane toward the threshold level and increase the likelihood that an action potential will result.

When Eccles stimulated other incoming sensory fibers, as graphed at the right of the Procedures section, he produced a hyperpolarizing graded potential (increased the charge) on the receiving motor neuron membrane. Eccles called these graded potentials **inhibitory postsynaptic potentials (IPSPs)**. As graphed at the right in the Results section, IPSPs increase the charge on the membrane away from the threshold level and decrease the likelihood that an action potential will result.

You can find several videos online that describe how the initial segment initiates an action potential.

Both EPSPs and IPSPs last only a few milliseconds before they decay and the neuron's resting potential is restored. EPSPs are associated with the opening of sodium channels, which allows an influx of sodium ions. IPSPs are associated with the opening of potassium channels, which allows an efflux of potassium ions (or with the opening of chloride channels, which allows an influx of chloride ions).

Although the size of a graded potential is proportional to the intensity of stimulation, an action potential is not produced on the motor neuron's cell body membrane even when an EPSP is strongly excitatory. The reason is simple: the cell body membrane of most neurons does not contain voltage-activated channels. The stimulation must reach the **initial segment**, an area rich in voltage-gated channels, the area near or overlapping the axon hillock, where the action potential begins (Bender & Trussel, 2012).

excitatory postsynaptic potential (EPSP) Brief depolarization of a neuron membrane in response to stimulation, making the neuron more likely to produce an action potential.

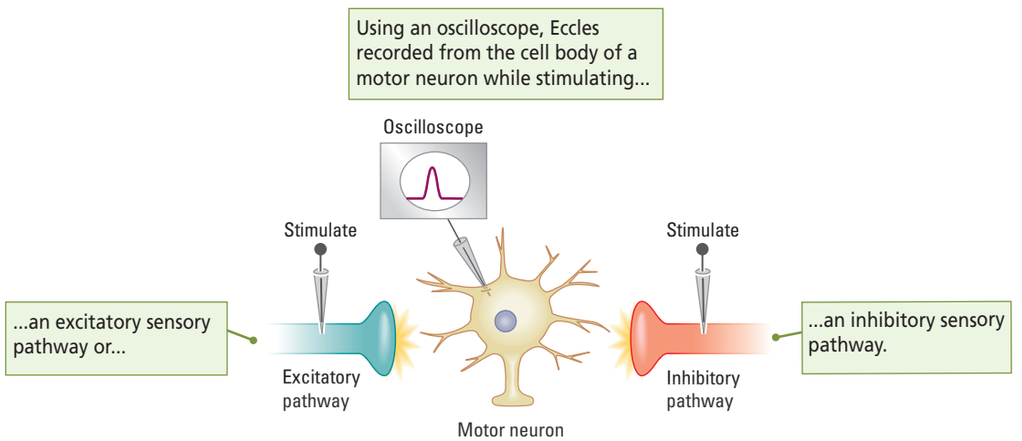
inhibitory postsynaptic potential (IPSP) Brief hyperpolarization of a neuron membrane in response to stimulation, making the neuron less likely to produce an action potential.

initial segment Area near where the axon meets the cell body that is rich in voltage-gated channels, which generate the action potential.

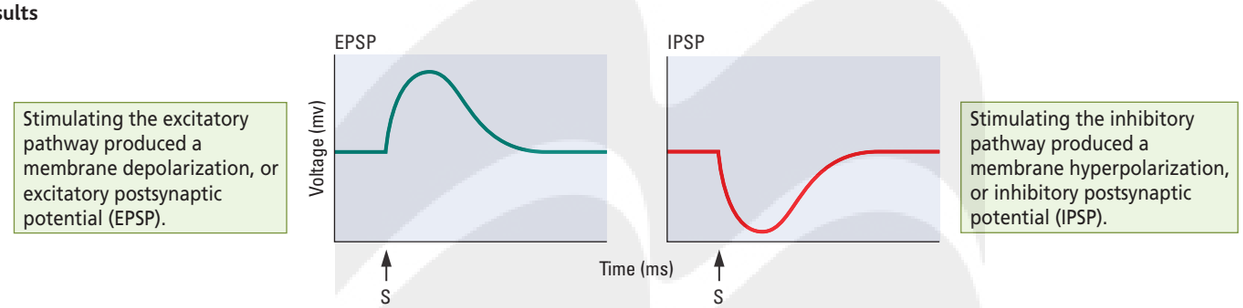
EXPERIMENT 4-1

Question: How does stimulating a neuron influence its excitability?

Procedure



Results



Conclusion: EPSPs increase the likelihood that an action potential will result. IPSPs decrease the likelihood that an action potential will result.

Summation of Inputs

Neurons typically receive both excitatory and inhibitory signals simultaneously and, on a moment-to-moment basis, sum up the information they get.

A motor neuron's myriad dendritic spines can each contribute to membrane voltage, via either an EPSP or an IPSP. How do these incoming graded potentials interact at its membrane? What happens if two EPSPs occur in succession? Does it matter if the time between them increases or decreases? What happens when an EPSP and an IPSP arrive together?

Temporal Summation

If one excitatory pulse is followed some time later by a second excitatory pulse, one EPSP is recorded and then, after a delay, a second identical EPSP is recorded, as shown at the top left in **Figure 4-22**. These two widely spaced EPSPs are independent and do not interact. If the delay between them is shortened so that the two occur in rapid succession, however, a single large EPSP is produced, as shown in the left-center panel of Figure 4-22.

Here, the two excitatory pulses at the same location are summed—added together to produce a larger depolarization of the membrane than either would induce alone. This relationship between two EPSPs occurring close together or even at the same time (bottom-left panel) is called **temporal summation**. The right side of Figure 4-22 illustrates that equivalent results are obtained with IPSPs. Therefore, temporal summation is a property of both EPSPs and IPSPs.

temporal summation Addition of one graded potential to another that occur close in time.

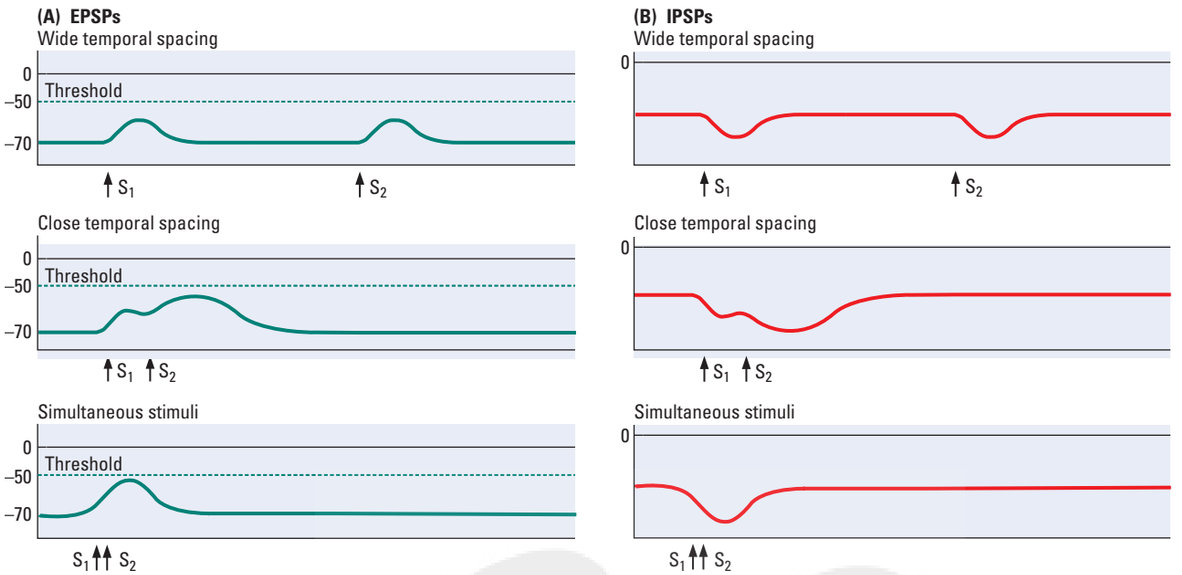


FIGURE 4-22 **Temporal Summation** Stimulation (S_1 and S_2) of two depolarizing pulses separated in time produce two EPSPs similar in size. Pulses close together in time partly sum. Simultaneous EPSPs sum as one large EPSP. Two hyperpolarizing pulses (S_1 and S_2) widely separated in time produce two IPSPs similar in size. Pulses coming fast partly sum. Simultaneous IPSPs sum as one large IPSP.

Spatial Summation

How does physical spacing affect inputs to the cell body membrane? By using two recording electrodes (R_1 and R_2), we can see the effects of spatial relations on the summation of inputs.

If two EPSPs are recorded at the same time but on widely separated parts of the membrane (**Figure 4-23A**), they do not influence one another. If two EPSPs occurring close together in time are also close together on the membrane, however, they sum to form a larger EPSP (Figure 4-23B). This **spatial summation** occurs when two separate inputs are very close to one another both on the cell membrane and in time. Similarly, two IPSPs produced at the same time sum if they occur at approximately the same place and time on the cell body membrane but not if they are widely separated.

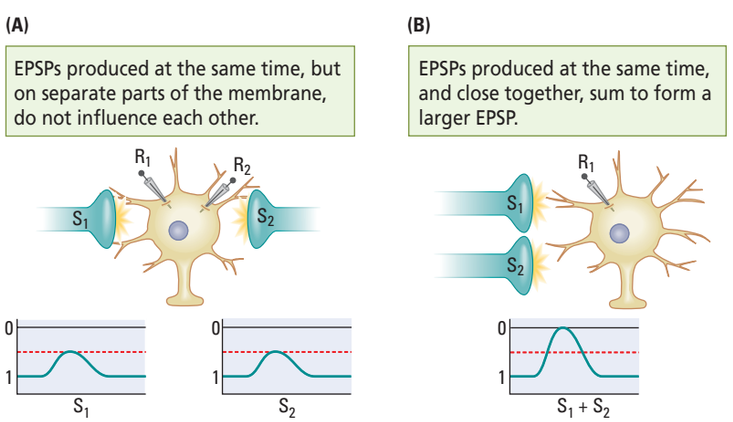
spatial summation Addition of one graded potential to another that occur close in space.

Role of Ions in Summation

Summation is a property of both EPSPs and IPSPs in any combination. These interactions make sense when you consider that ion influx and efflux are being summed. The influx of sodium ions accompanying one EPSP is added to the influx of sodium ions accompanying a second EPSP if the two occur close together in time and space. If the two influxes are remote in time or in space or in both, no summation is possible.

The same is true regarding effluxes of potassium ions. When they occur close together in time and space, they sum; when they are far apart in either or both ways, there is no summation. The patterns are identical for an EPSP and an IPSP. The influx of sodium ions associated with the EPSP is added to the efflux of potassium ions associated with the IPSP, and the difference between them is recorded as long

FIGURE 4-23 **Spatial Summation** The process for IPSPs is equivalent to the process for EPSPs.



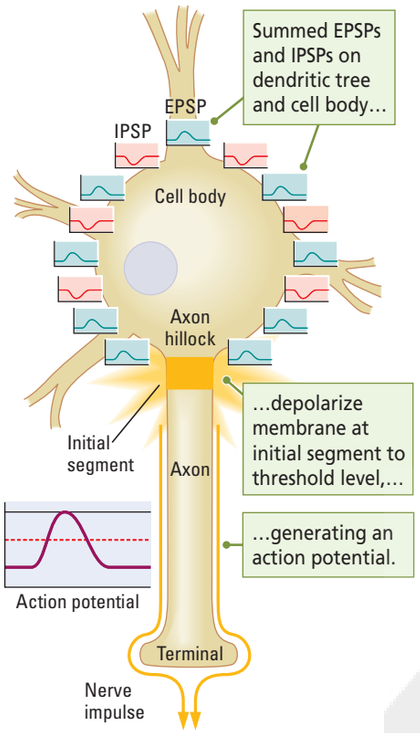


FIGURE 4-24 **Triggering an Action Potential** If the summated graded potentials—the EPSPs and IPSPs—on the dendritic tree and cell body of a neuron charge the membrane to threshold level at the initial segment, an action potential is initiated, and it travels down the axon membrane.

as they are spatially and temporally close together. If, on the other hand, they are widely separated in time or in space or in both, they do not interact, and there is no summation.

A neuron with thousands of inputs responds no differently from one with only a few inputs; it sums all inputs that are close together in time and space. The cell body membrane, therefore, always indicates the summed influences of multiple temporal and spatial inputs. Therefore, a neuron can be said to analyze its inputs before deciding what to do. The ultimate decision is made at the initial segment, the region on the axon that initiates the action potential.

Voltage-Activated Channels and the Action Potential

Unlike the cell body membrane, the axon is rich in voltage-activated channels, beginning at the initial segment (**Figure 4-24**). These channels, like those on the squid axon, open at a particular membrane voltage. The actual threshold voltage varies with the type of neuron, but to keep things simple, we will stay with a threshold level of −50 mV.

To produce an action potential, the summed graded potentials—the IPSPs and EPSPs—on the cell body membrane must depolarize the membrane at the initial segment to −50 mV. If that threshold voltage is obtained only briefly, voltage-activated channels open, and just one or a few action potentials may occur. If the threshold level is maintained for a longer period, however, action potentials will follow one another in rapid succession, just as quickly as the gates on the voltage-activated channels can reset. Each action potential is then repeatedly propagated to produce a nerve impulse that travels from the initial segment down the length of the axon.

Many neurons have extensive dendritic trees, but dendrites and dendritic branches do not have many voltage-activated channels and ordinarily do not produce action potentials. And distant branches of dendrites may have less influence in producing action potentials initiated at the initial segment than do the more proximal branches of the dendrites. Consequently, inputs close to the initial segment are usually much more influential than those occurring some distance away, and those close to the initial segment are usually inhibitory, creating IPSPs. As in all governments, some inputs have more say than others (Höfflin et al., 2017).

The Versatile Neuron

Dendrites collect information as graded potentials (EPSPs and IPSPs), and the initial segment initiates discrete action potentials delivered to other target cells via the axon. Exceptions to this picture of how a neuron works do exist. For example, some cells in the developing hippocampus can produce additional action potentials, called *giant depolarizing potentials*, when the cell would ordinarily be refractory. It is thought that giant depolarizing potentials aid in developing the brain's neural circuitry (Khalilov et al., 2015).

Because the cell body membrane does not contain voltage-activated channels, a typical neuron does not initiate action potentials on its dendrites. In some neurons, however, voltage-activated channels on dendrites do enable action potentials. The reverse movement of an action potential from the initial segment into the dendritic field of a neuron is called **back propagation**. Back propagation, which signals to the dendritic field that the neuron is sending an action potential over its axon, may play a role in plastic changes in the neuron that underlie learning. For example, back propagation may make the dendritic field refractory to incoming inputs, set the dendritic field to an electrically neutral baseline, or reinforce signals coming in to certain dendrites (Schiess et al., 2016).

The neurons of some nonmammalian species have no dendritic branches. And some ion channels, rather than responding to voltage, respond to light by opening and allowing ions to pass. The many differences among neurons suggest that the nervous system capitalizes on structural and functional modifications to produce adaptive behavior in each species. In research to determine the neuron's specific functions, neuroscientists have incorporated into certain types of neurons ion channels that respond to light, as described in Research Focus 4-3, Optogenetics and Light-Sensitive Ion Channels.

back propagation Reverse movement of an action potential into the soma and dendritic field of a neuron; postulated to play a role in plastic changes that underlie learning.

Principle 2: Neuroplasticity is the hallmark of nervous system functioning.

We explore the neuronal basis of learning in Sections 5-4 and 14-4.

Section 7-1 describes the promise of optogenetics for neuroscience research and for clinical applications.

RESEARCH FOCUS 4-3

Optogenetics and Light-Sensitive Ion Channels

Membrane channels that are responsive to light have been discovered in nonmammalian animal species. Using the transgenic technique of **optogenetics,** researchers have successfully introduced light-sensitive channels into a variety of species including worms, fruit flies, and mice.

Optogenetics combines genetics and light to control targeted cells in living tissue. Here, we examine how introducing different light-sensitive channels into a species changes the organism's behavior with one wavelength and reverses them with another wavelength.

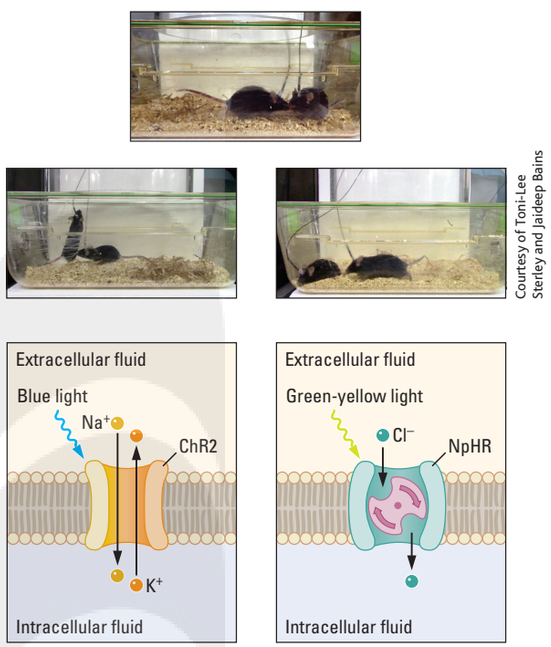
One class of light-activated ion channels in the green alga *Chlamydomonas reinhardtii* is channelrhodopsin-2 (ChR2). The ChR2 light-activated channel absorbs blue light and, in doing so, opens briefly to allow the passage of Na^+ and K^+. The resulting depolarization excites the cell to generate action potentials.

Halorhodopsin (NpHR) is a light-driven ion pump, specific for chloride ions and found in phylogenetically ancient bacteria (archaea) known as halobacteria. When illuminated with green-yellow light, the NpHR pumps chloride anions into the cell, hyperpolarizing it and thereby inhibiting its activity.

The behavior of animals with genetically introduced light-sensitive channels has been controlled when their nervous system cells were illuminated with appropriate wavelengths of light. Using optogenetic techniques, light-sensitive channels can be incorporated into specific neural circuits so that light stimulation controls only a subset of neurons.

Stress has both behavioral and hormonal consequences for individuals, which can be transmitted socially to others. Using optogenetic techniques in mice, Sterley and colleagues (2018) *silenced* a specific collection of neurons in the hypothalamus during stress, thus preventing changes to the brain that would normally occur after stress. They then took it one step further and silenced the neurons in a partner mouse of a stressed individual, and the stress did not transfer to the partner. The group next performed the opposite experiment: in the absence of stress, they optogenetically *activated* the same hypothalamic neurons, causing the same changes in the brain as actual stress. They also observed that the partner mouse interacted with the light-activated-stressed individual in the same fashion as they would approach a naturally stressed mouse (Sterley et al., 2018).

The experimental power of optogenetics is unprecedented because we can learn the contribution of specific neuronal types to a behavior or in a disease state. But can optogenetics become a clinical tool to be used in people suffering from a CNS malady such as depression? One major hurdle is that specific viruses are used to transfer the light-activated channels to neurons in localized brain regions, and the usage of viruses in human populations is still fraught with difficulties. There are studies suggesting that impaired vision due to the loss of the light-sensitive cells of the eye could be restored with light-activated channels in surviving retinal neurons (Pan et al., 2015).



Light-Sensitive Channels

4-3 Review

Before you continue, check your understanding. Answers to Self-Test appear at the back of the book.

1. Graded potentials that decrease the charge on the cell membrane, moving it toward the threshold level, are called _____ because they increase the likelihood that an action potential will occur. Graded potentials that increase the charge on the cell membrane, moving it away from the threshold level, are called _____ because they decrease the likelihood that an action potential will result.
2. EPSPs and IPSPs that occur close together in both _____ and _____ are summed. This is how a neuron _____ the information it receives from other neurons.
3. The membrane of the _____ does not contain voltage-activated ion channels, but if summed inputs excite the _____ to a threshold level, action potentials are triggered and then propagated as they travel along the cell's _____ as a nerve impulse.
4. Explain what happens during back propagation.

For additional study tools, visit LaunchPad at launchpadworks.com

optogenetics Transgenic technique that combines genetics and light to excite or inhibit targeted cells in living tissue.

stretch-activated channel Ion channel on a tactile sensory neuron that activates in response to stretching of the membrane, initiating a nerve impulse.

4-4

Into the Nervous System and Back Out

The nervous system allows us to respond to afferent (incoming) sensory stimuli by detecting them and sending messages about them to the brain. The brain interprets the information, triggering efferent (outgoing) responses that contract muscles and produce behavior. Until now, we have been dealing only with the middle of this process—how neurons convey information to one another, integrate the information, and generate action potentials. Now we explore the beginning and end of the journey.

To fill in the missing pieces, we explain how a sensory stimulus initiates a nerve impulse and how a nerve impulse produces a muscular contraction. Once again, ion channels are vitally important, but, in muscles, the channels are different from those described so far.

How Sensory Stimuli Produce Action Potentials

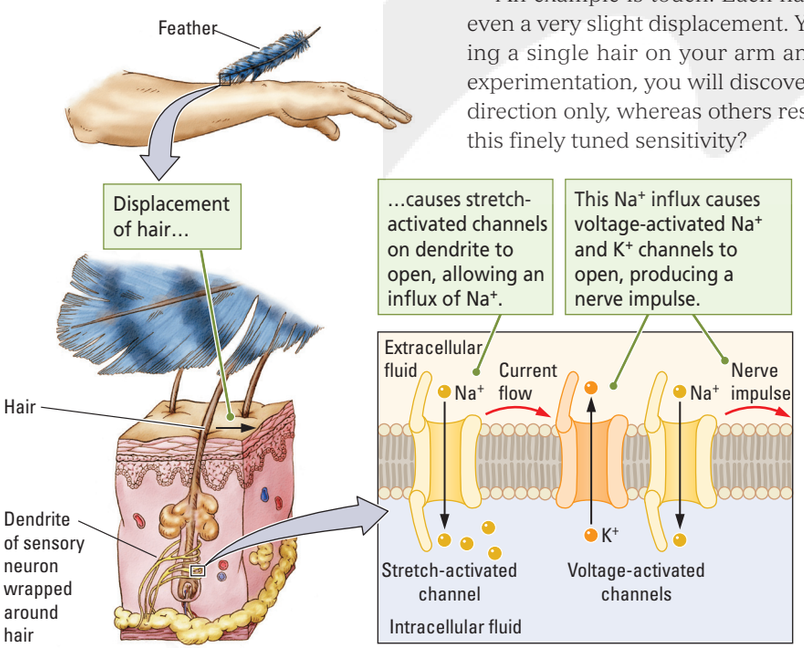
For detail on how sensory receptors transduce external energy into action potentials:
Hearing, Section 10-1
Sensation and perception, Section 9-1
Smell and taste, Section 12-2
Touch, pain, and balance, Section 11-4
Vision, Section 9-2

We receive information about the world through bodily sensations (touch and balance), auditory sensations (hearing), visual sensations (sight), and chemical sensations (taste and olfaction). Each sensory modality has one or more separate functions. In addition to touch, for example, the body senses include pressure, joint sense, pain, temperature, and itch. Receptors for audition and balance are modified touch receptors. The visual system has receptors for light and for colors. And taste and olfactory senses respond to a plethora of chemical compounds.

Processing all these varied sensory inputs requires a remarkable array of sensory receptors. But in all our sensory systems, the neurons related to these diverse receptors have one thing in common: conduction of information begins at ion channels. Ion channels initiate the chain of events that produces a nerve impulse.

An example is touch. Each hair on the human body allows an individual to detect even a very slight displacement. You can demonstrate this sensitivity yourself by selecting a single hair on your arm and bending it. If you are patient and precise in your experimentation, you will discover that some hairs are sensitive to displacement in one direction only, whereas others respond to displacement in any direction. What enables this finely tuned sensitivity?

FIGURE 4-25 **Tactile Stimulation** A hair's touch receptor activated by a feather results in a nerve impulse heading to the brain.



The base of each hair is wrapped in a dendrite of a touch neuron. When you bend a hair or otherwise mechanically displace it, the encircling dendrite is stretched (**Figure 4-25**).

The displacement opens **stretch-activated channels** in the dendrite's membrane. When open, these channels allow an influx of sodium ions sufficient to depolarize the dendrite to threshold. At threshold, the voltage-activated sodium and potassium channels initiate a nerve impulse that conveys touch information to your brain.

Other kinds of sensory receptors have similar mechanisms for *transducing* (transforming) the energy of a sensory stimulus into nervous system activity. When displaced, the *hair receptors* that provide information about hearing and balance likewise open stretch-activated channels. In the

visual system, photons (light particles) strike opsin proteins in receptors within specialized cells in the eye. The resulting chemical change activates ion channels in *relay neuron* membranes. An odorous molecule in the air that lands on an olfactory receptor and fits itself into a specially shaped compartment opens chemical-activated ion channels. When tissue is damaged, injured cells release chemicals that activate channels on a pain nerve. The point here is that ion channels originate conduction of information in all our sensory systems.

How Nerve Impulses Produce Movement

Principle 1: The nervous system produces movement in a perceptual world the brain constructs.

What happens at the end of the neural journey? After sensory information has traveled to the brain and been interpreted, how does the brain generate output—muscular contractions—as a behavioral response? Behavior, after all, is movement, and for movement to take place, muscles must contract. Motor neurons in the spinal cord are responsible for activating muscles. Without them, movement becomes impossible and muscles atrophy, as described in Clinical Focus 4-4, ALS: Amyotrophic Lateral Sclerosis.

Motor neurons send nerve impulses to synapses on muscle cells. These synapses are instrumental in making the muscle contract. Each motor neuron axon contacts one

CLINICAL FOCUS 4-4

ALS: Amyotrophic Lateral Sclerosis

In 1869, French physician Jean-Martin Charcot first described ALS, amyotrophic lateral sclerosis. *Amyotrophic* means "muscle weakness"; *lateral sclerosis* means "hardening of the lateral spinal cord."

In North America, ALS is also known as Lou Gehrig disease. A baseball legend who played for the New York Yankees from 1923 until 1939, Gehrig had set a host of individual records. He was an outstanding hitter, and his incredible durability earned him the nickname The Iron Horse.

Gehrig played on many World Series championship teams, but ALS sapped his strength, forcing him to retire from baseball at age 36. His condition deteriorated rapidly, and he died just 2 years later.

ALS is due primarily to the death of spinal motor neurons, but it can affect brain neurons as well in some instances. It strikes most commonly at age 50 to 75, although its onset can be as early as the teenage years. About 5000 new cases are reported in the United States each year, and roughly 10 percent of people with ALS have a family history of the disorder.

While death often occurs within 5 years of diagnosis, internationally renowned theoretical physicist and cosmologist Stephen Hawking was a notable exception. Diagnosed at age 21, Hawking had a rare early-onset and slowly progressing form of ALS. As a doctoral student at Oxford, he grew increasingly clumsy, and his speech was slightly slurred. In his late twenties, he began to use crutches. In his thirties, his speech deteriorated to the point that only his family and close friends could understand him. In his seventies, and confined to a wheelchair, Hawking, pictured at right, was still able to communicate by using a single cheek muscle attached to a speech-generating device.

ALS typically begins with general weakness, at first in the throat or upper chest and in the arms and legs. Gradually, walking becomes difficult and falling common. ALS does not usually affect any sensory systems, cognitive functions, bowel or bladder control, or even sexual function. Even as his motor neurons continued to die, Stephen Hawking's mind-blowing advancements continued to enrich our understanding of the universe. Sadly, we lost Stephen Hawking in March 2018.

At present, no cure for ALS exists, although some newly developed drugs appear to slow its progression and offer some hope for future treatments. In 2014, the ALS Ice Bucket Challenge first appeared on YouTube to promote awareness of ALS and encourage donations to research. The Challenge went viral and has been revived every summer since.

Tom Dymond/REX/Shutterstock

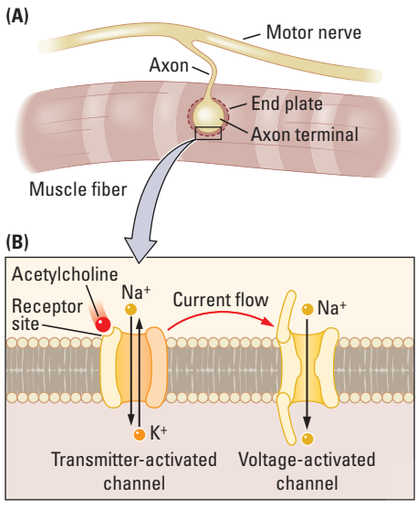
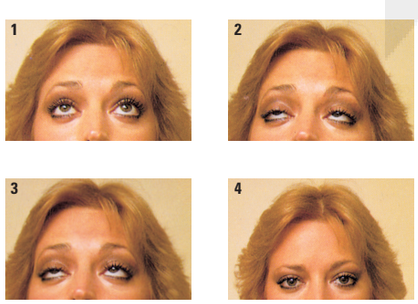


FIGURE 4-26 **Muscle Contraction** **(A)** When a motor neuron's axon collaterals contact a muscle fiber end plate, **(B)** acetylcholine attaches to receptor sites on the end plate's transmitter-activated channels, opening them. These large membrane channels allow simultaneous influx of Na^+ and efflux of K^+, generating current sufficient to activate voltage-activated channels, triggering action potentials, and causing the muscle to contract.

Sections 5-2 and 5-3 describe the varieties of chemical transmitters and how they function.

FIGURE 4-27 **Myasthenia Gravis** When this patient follows the direction to look up **(1)**, her eyelids quickly become fatigued and droop **(2, 3)**. After a few minutes of rest, her eyelids open normally **(4)**.



Courtesy of Y. Harati, M.D./Baylor College of Medicine, Houston, Texas

end plate On a muscle, the receptor–ion complex that is activated by the release of the neurotransmitter acetylcholine from the terminal of a motor neuron.

transmitter-activated channel Receptor complex that has both a receptor site for a chemical and a pore through which ions can flow.

or a few synapses with its target muscle (**Figure 4-26A**). The axon terminal contacts a specialized area of the muscle membrane called an **end plate**, where the axon terminal releases the chemical transmitter *acetylcholine*.

Acetylcholine does not enter the muscle but rather attaches to **transmitter-activated channels** on the end plate (Figure 4-26B). When these channels open in response, they allow a flow of Na^+ and K^+ across the muscle membrane sufficient to depolarize the muscle to the threshold for its action potential. Yes, to contract, muscles generate action potentials. At this threshold, adjacent voltage-activated channels open. They in turn produce an action potential on the muscle fiber, as they do in a neuron.

The transmitter-activated channels on muscle end plates are somewhat different from the channels on axons and dendrites. A single end plate channel is larger than two sodium and two potassium channels on a neuron combined. So when its transmitter-activated channels open, they allow both Na^+ influx and K^+ efflux through the same pore. Generating a sufficient depolarization on the end plate to activate neighboring voltage-activated channels on the muscle membrane requires the release of an appropriate amount of acetylcholine.

If the acetylcholine receptors on muscle end plates are blocked, acetylcholine released from the motor neuron cannot properly exert its depolarizing effect. This prevents muscular contraction in conditions such as the autoimmune disease *myasthenia gravis*. In affected individuals, the thymus, an immune system gland that normally produces antibodies that bind to foreign material like viruses, makes antibodies that bind to the acetylcholine receptors on muscles, causing weakness and fatigue (see **Figure 4-27**).

Unlike MS, another autoimmune disease, myasthenia gravis is usually well controlled with treatment, including drugs that suppress the immune system or inhibit acetylcholine breakdown, extending the time the transmitter can act, or by removal of the thymus gland (thymectomy).

The actions of membrane channels can explain a wide range of neural events. Some channels generate the transmembrane charge. Others mediate graded potentials. Still others trigger the action potential. Sensory stimuli activate channels on neurons to initiate a nerve impulse, and the nerve impulse eventually activates channels on motor neurons to produce muscle contractions.

These various channels and their different functions evolved over a long time as new species of animals and their behaviors evolved. We have not described all the different ion channels that neural membranes possess, but you will learn about some additional ones in subsequent chapters.

4-4 Review

Before you continue, check your understanding. Answers to Self-Test appear at the back of the book.

1. Across all sensory systems, the conduction of sensory information that occurs within the neuron begins at the _____.
2. A(n) _____ membrane contains a mechanism for transducing sensory energy into changes in ion channels. In turn, the channels allow ion flow to alter the membrane voltage to the point that _____channels open, initiating a nerve impulse.
3. Sensory stimuli activate ion channels to initiate a nerve impulse that activates channels on _____ neurons, which in turn contract _____.
4. In myasthenia gravis, a(n) _____ disease, the thymus gland produces antibodies to _____ receptors on muscles, causing weakness and fatigue.
5. Why have so many kinds of ion channels evolved on cell membranes?

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Summary

4-1 Searching for Electrical Activity in the Nervous System

Electrical stimulation studies dating as far back as the eighteenth century show that stimulating a nerve with electrical current induces a muscle contraction. In more recent recording studies, the brain's electrical current, measured using an oscilloscope, shows that electrical activity in the nervous system is continuous.

In the twentieth century, researchers used giant axons of the squid to measure the electrical activity of a single neuron. Using microelectrodes that they could place on or in the cell, they recorded small, rapid electrical changes with an oscilloscope. Today, digital oscilloscopes and computers record these measurements.

A neuron's electrical activity is generated by ions flowing across the cell membrane. Ions flow down a concentration gradient (from an area of relatively high concentration to an area of lower concentration) as well as down a voltage gradient (from an area of relatively high voltage to an area of lower voltage). The opening, closing, and pumping of ion channels in neural cell membranes also affect ion distribution.

4-2 Electrical Activity at a Membrane

Unequal ion distribution on a cell membrane's two sides generates the neuron's resting potential. At rest, the intracellular membrane registers about −70 mV relative to the extracellular side. Negatively charged protein anions are too large to leave the neuron, and the cell membrane actively pumps out positively charged sodium ions. Unequal distributions of potassium cations and chloride anions contribute to the resting potential as well.

Graded potentials, which are short-lived small increases or decreases in transmembrane voltage, result when the neuron is stimulated. Voltage changes affect the membrane's ion channels and in turn change the cross-membrane ion distribution. An increase in transmembrane voltage causes hyperpolarization; a decrease causes depolarization.

An action potential is a brief but large change in axon membrane polarity triggered when the transmembrane voltage drops to a threshold level of about –50 mV. During an action potential, transmembrane voltage suddenly reverses—the intracellular side becomes positive relative to the extracellular side—and abruptly reverses again. Gradually, the resting potential is restored. These membrane changes result from voltage-activated channels—sodium and potassium channels sensitive to the membrane's voltage.

When an action potential is triggered at the initial segment, it can propagate along the axon as a nerve impulse. Nerve impulses travel more rapidly on myelinated axons because of saltatory conduction: the action potentials leap rapidly between the nodes separating the glial cells that form the axon's myelin sheath.

4-3 How Neurons Integrate Information

Inputs to neurons from other cells can produce both excitatory postsynaptic potentials and inhibitory postsynaptic potentials. The membrane sums their voltages both temporally and spatially to integrate the incoming information. If the summed EPSPs and IPSPs move the membrane voltage at the initial segment to threshold, the axon generates an action potential.

The neuron is a versatile kind of cell. Some species' ion channels respond to light rather than to voltage changes, an attribute that genetic engineers are exploiting. Most of our neurons do not initiate action potentials on the cell body because the cell body membrane does not contain voltage-activated channels. But some voltage-activated channels on dendrites do enable action potentials. Back propagation, the reverse movement of an action potential from the initial segment into the dendritic field of a neuron, may play a role in plastic changes that underlie learning.

4-4 Into the Nervous System and Back Out

Sensory receptor cells convert sensory energy to graded potentials. These changes, in turn, alter transmembrane voltage to trigger an action potential and propagate a nerve impulse that transmits sensory information to relevant parts of the nervous system.

Ion channels come into play to activate muscles as well because the chemical transmitter acetylcholine, released at the axon terminal of a motor neuron, activates channels on the end plate of a muscle cell membrane. The subsequent ion flow depolarizes the muscle cell membrane to the threshold for its action potential. In turn, this depolarization opens voltage-activated channels, producing an action potential on the muscle fiber—hence the muscle contractions that enable movement. In myasthenia gravis, antibodies to the acetylcholine receptor prevent muscle depolarization, which is the basis of weakness and fatigue.

Key Terms

absolutely refractory, p. 122
action potential, p. 120
autoimmune disease, p. 126
back propagation, p. 130
concentration gradient, p. 114
depolarization, p. 119
diffusion, p. 114
electrical stimulation, p. 109
electroencephalogram (EEG), p. 111
electrographic seizures, p. 108
end plate, p. 134
excitatory postsynaptic potential (EPSP), p. 127
graded potential, p. 119
hyperpolarization, p. 119
inhibitory postsynaptic potential (IPSP), p. 127
initial segment, p. 127
microelectrode, p. 113
multiple sclerosis (MS), p. 125
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threshold potential, p. 120
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voltage-activated channel, p. 122
voltage gradient, p. 115
voltmeter, p. 111

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