4

Communication: Chemical and Electrical Signaling

Major Themes

- Cell-to-cell communication is critical for homeostasis and life.
- Communication requires a *sender*, a *signal*, a *medium* to carry the signal, and a *receiver* to accept the signal.
- Signals must be "translated" from a code into action.
- The effect of the signal is determined by the receiver, not merely by the signal.
- There are two kinds of physiological signals: chemical and electrical.

Chapter Objectives

The Nature of Communication 112

1. Identify the four components required for communication.

Chemical Signaling 113

2. Explain the difference between paracrine factors, hormones, neurotransmitters, and neurohormones.
3. Name three types of cell membrane receptors, and explain how they enable signaling molecules to affect intracellular events without entering the cell.
4. Explain why every cell may encounter a chemical signal, but not every cell responds to the chemical signal.
5. List the steps involved in signaling by lipophilic signal molecules at intracellular receptors.

Electrical Signaling 120

6. Define membrane potential, and explain the difference between a membrane potential of –100 mV and a membrane potential of +30 mV.
7. Explain why the resting membrane potential is negative.

8. Sketch a neuron, labeling the cell body, dendrites, axon, and myelin.
9. Compare and contrast action potentials and graded potentials.
10. Name the four phases of the action potential, and discuss the involvement of sodium and/or potassium channels in each phase.
11. Compare action potential propagation in myelinated and unmyelinated neurons.
12. Using the example of gamma aminobutyric acid (GABA), list all of the events that occur at a chemical synapse.

Caffeine and Communication: The Case of Andy M. 132

13. Explain why Andy's synaptic activity is reduced when he drinks decaffeinated coffee. In your explanation, use the following terms (not necessarily in order): *caffeine, adenosine, first* and *second messengers, endogenous ligands,* and *receptor antagonists;* also explain the importance of changes in receptor number and action potential thresholds.
14. Using examples from the case study, discuss the roles of senders, signals, mediums, and receivers in person-to-person and cell-to-cell communication.

Case Study: "I must be getting the flu"

As you read through the following case study, assemble a list of the terms and concepts you must learn in order to understand Andy's condition.

During the yearly Christmas visit with his in-laws, Andy M. began to feel bad.

"I must be getting the flu," he said to his wife. He hadn't felt right since the day after they'd arrived earlier in the week. "Max pounded me yesterday," he added, referring to a squash match with his brother-in-law. "I can usually whip him without much trouble, but yesterday I just couldn't get going. I'm tired and cranky, I can't maintain enough focus to read a paragraph, and to top it all, I have this splitting headache. I've been popping aspirin all day, but nothing helps!"

After dinner that night, his mother-in-law offered coffee. "It's decaffeinated," she said, "so it won't disturb your sleep."

Suddenly, Andy's muddled brain began to focus. *Decaffeinated.* "Barbara," he asked, "what kind of coffee have you been serving during the day?"

"Oh, it's decaf!" his mother-in-law answered cheerily. "After all, we're on holiday. Dick and I drink regular coffee during the work week and decaf on weekends. Too much caffeine isn't good for your health."

Eureka! Andy retreated to the kitchen, where he fished out some regular coffee and fired up the coffeemaker. As soon as the brew was ready, he guzzled two cups filled to the brim. Then he returned to the dining room, smiling and relieved. His "flu" had magically disappeared. "Sorry if I've been a bit testy," he said to his mother-in-law. "I feel better already. I confess—I'm a caffeine addict, and believe me, caffeine withdrawal is no picnic."

Andy's story illustrates the adverse effects of chronic overconsumption of caffeine, which is a type of drug called a *stimulant*. It all comes back to communication—drugs often interfere with signals passing from one cell to another. Caffeine, for instance, blocks sleep-inducing signals carried by a molecule called *adenosine*. Used moderately, caffeine enhances performance and improves mood and energy levels. But as with many drugs, a regular high intake can result in *addiction*, and caffeine withdrawal is an unpleasant experience. Read on to discover how caffeine exerts its effects by altering chemical and electrical communication.

Need to Know

It is important to understand the terms and concepts listed below before tackling the new information in this chapter.

- Homeostasis and negative feedback (← Chapter 1)
- Ions, hydrophobic, hydrophilic, proteins, steroids, and enzymes (← Chapter 2)
- Glands, cell membrane, concentration gradients, diffusion, active transport, and exocytosis (← Chapter 3)

Communication is so much a part of our daily life that we forget about it: we live in a hurricane of television images, music, text messages, conversations, phone calls, and e-mails . . . and we scarcely give a thought to anything but the message. We fail to appreciate the marvel of communication itself—its many parts or its varied means. And deep inside our bodies rages an even greater storm of communication: cells exchanging billions of messages every day. All communication is in code. The letters of this sentence, which your brain decodes and assigns a meaning, are really nothing more than curious shapes of ink on paper. And in our case, the spoken word *decaf* is nothing more than a sound that describes a type of coffee, which your brain decodes because you understand the sound codes called English. Your brain assigns meaning—"a drug that makes me alert"—to the sound code *caffeine* according to your stored knowledge of caffeinated beverages.

This chapter examines our internal communications—how signals originate and how they are transmitted, received, and interpreted. From the external environment we receive a variety of signals by means of our senses: eyes, light; ears, sound; nose, odors; tongue, taste; and skin, touch. In our internal environment, however, there are but two ways of signaling—chemical and electrical.

The medium is the message.

Marshall McLuhan (1911–1980), Canadian educator, scholar and philosopher, in his book *Understanding Media* (1964), arguing that the medium itself—television, for example—is an essential part of the message.

The Nature of Communication

Communication is the transmission and reception of information by a signal. It requires a *sender*, a *signal*, a *medium* (through which the signal is transmitted), and a *receiver*. Let's go back to the case, when Barbara tells Andy that his coffee was decaffeinated (Fig. 4.1).

1. Barbara is the *sender*. She wants to send Andy a message that the coffee is decaffeinated.
2. The coordinated contraction of Barbara's muscles expels air from her chest and manipulates the resulting sound into a *signal*—a specific series of sound waves that will be interpreted as "It's decaf."
3. The sound waves (the signal) travel through the *medium* of air to Andy.
4. Andy is the *receiver*. His ears receive the sound waves, and his brain decodes them with the meaning *I have been drinking decaffeinated coffee.*

Bodily Signals Are Chemical or Electrical

In everyday life we send many types of signals, from e-mails to smiles. Cell-to-cell signals take two forms, and these are the topic of the two main divisions of this chapter: *Chemical signals* are proteins, lipids, or even gases secreted by cells that prompt an effect in neighboring or distant cells. *Electrical signals* are changes in the overall balance of negative and positive ions inside

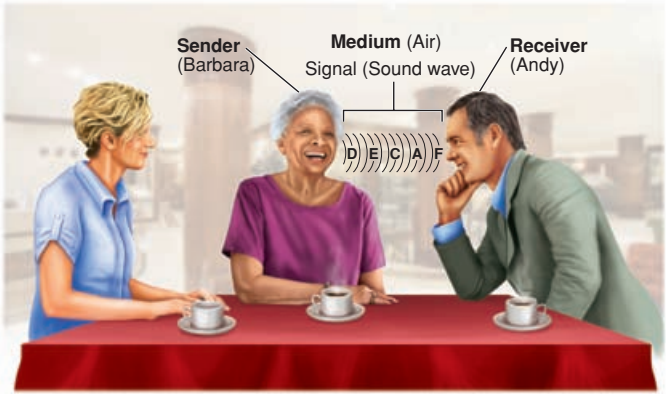


Figure 4.1. Communication. All communication requires a sender, a signal, a medium, and a receiver. *What is the medium in the example?*

and outside a cell that transmit signals along the cell membrane.

Messages can be carried by a series of electrical and chemical signals, much as a note is passed hand to hand across a classroom. For example, Barbara's brief words "It's decaf!" began as an electrical signal traveling from one end to the other of a brain cell (a *neuron*). Next, a chemical signal passed the signal to the next neuron in the series, which used an electrical signal to transmit the signal down its entire length. The signal continued to pass from neuron to neuron in this way until it reached Barbara's speech muscles, causing them to contract and produce and manipulate sound waves.

Communication Is Critical in Homeostasis

Recall that in ← Chapter 1 we introduced the term *homeostasis* and defined it as "The body's collective *communication* and control effort to maintain constant, healthy internal conditions." Homeostasis is the core goal of all physiological activity and depends on the ability of every cell to send and receive communications.

All cells participate in many homeostatic signal loops; that is, they both transmit and receive signals that help maintain the body in good health. Recall that all physiological conditions—blood pressure, for example—have a set point; that is, a value near which the condition must be maintained for optimal health. The cells that regulate each of the body's physiological conditions have sensors (receivers) that detect deviations from the set point. When a cell's sensor detects a deviation, it generates a signal asking for an opposing change. This activity, which you will recognize as negative feedback, requires continual back-and-forth communication.

Problems with communication can cause disease. For instance, caffeine normally blocks the activity of a calming chemical signal called *adenosine*. Without his normal intake of caffeine, Andy was suffering from too many adenosine signals. The first gulp of caffeinated coffee stopped the adenosine signals like the cutting of a telephone line, and Andy suddenly felt much better.

Case Note

4.1. In Andy's case, what disrupted his homeostasis?

4.1 Name the two types of homeostatic signals.

4.2 If a dolphin sends a sound wave signal to another dolphin, what is the medium?

Chemical Signaling

Chemical signals are molecules that serve bodily communication. Some chemical signals are small molecules, such as adenosine. Recall from Chapter 2 that adenosine is a building block of adenosine triphosphate (ATP), deoxyribonucleic acid (DNA), and ribonucleic acid (RNA). It is also a chemical signal that, as we will see throughout this chapter, plays a critical role in our case study. Other chemical signals include *amines,* which are modified amino acids; *steroids,* which are modified cholesterol molecules; and *proteins*. Even gases can act as chemical signals.

Regardless of their structure, all chemical signals share the same travel itinerary—they are released from a *secreting cell,* travel through a fluid to a *target cell,* and affect the activity of the target cell by binding a specific *receptor.* Because they bind to receptors, chemical signals are also referred to as **ligands** (Latin *ligare* = "to bind").

Chemical Signals Require Specific Receptors

Could you read a message in Braille? Probably not. If you're like most sighted people, you lack the "decoder" (information in your brain) necessary to interpret the raised dots of Braille code (you can read more about

Braille in the nearby History of Science box, titled *Braille: A Reading Code for the Blind*). In the same way, chemical signals come into contact with every cell in the body, but only those with the correct decoder can understand the message. Decoders of chemical signals are cell **receptors,** proteins that change the activity of the cell when bound by the chemical signal.

To put it another way, chemical signals exert an effect only on cells that contain the correct receptor; that is, cells to which they can bind. Cells without the correct receptor do not bind the signal molecule and do not respond. This principle is illustrated on the right side of Figure 4.2. One chemical signal (circles) will bind to the receptor on the upper cell, conveying the message that the cell should divide. A different signal (triangles), conversely, will bind to the receptor on the lower cell, conveying the message to undergo apoptosis and die. Neither cell receives the message intended for the other cell, because they do not have the other type of receptor.

Remember This! **Ligands are chemical signals; receptors are receivers that bind the ligand.**

Chemical Signals Affect Neighboring and Distant Cells

Communication between different cells of the body works the same way as communication between people: there is a sender, a signal, a medium, and a receiver. Chemical signals can be classified according to the sender and the medium.

- **Hormones** are released by body cells and travel through the bloodstream (the medium) to act on *distant* cells (Fig. 4.2). They are also described as endocrine secretions (endo = internal), or endocrines for short. Although virtually all cells release hormones, the main purpose of specialized *endocrine glands* is hormone production (see Fig. 1.6). For example, the testes make *testosterone,* which travels through blood to muscle cells, where it binds to receptors and stimulates the growth of muscle cells. Some hormones are released by nerve cells, in which case they are sometimes called *neurohormones.*
- **Paracrine factors** (or paracrines) are chemical signals released by body cells that act on *nearby* cells. Paracrine signals reach their target by diffusion through the extracellular fluid. For example, the

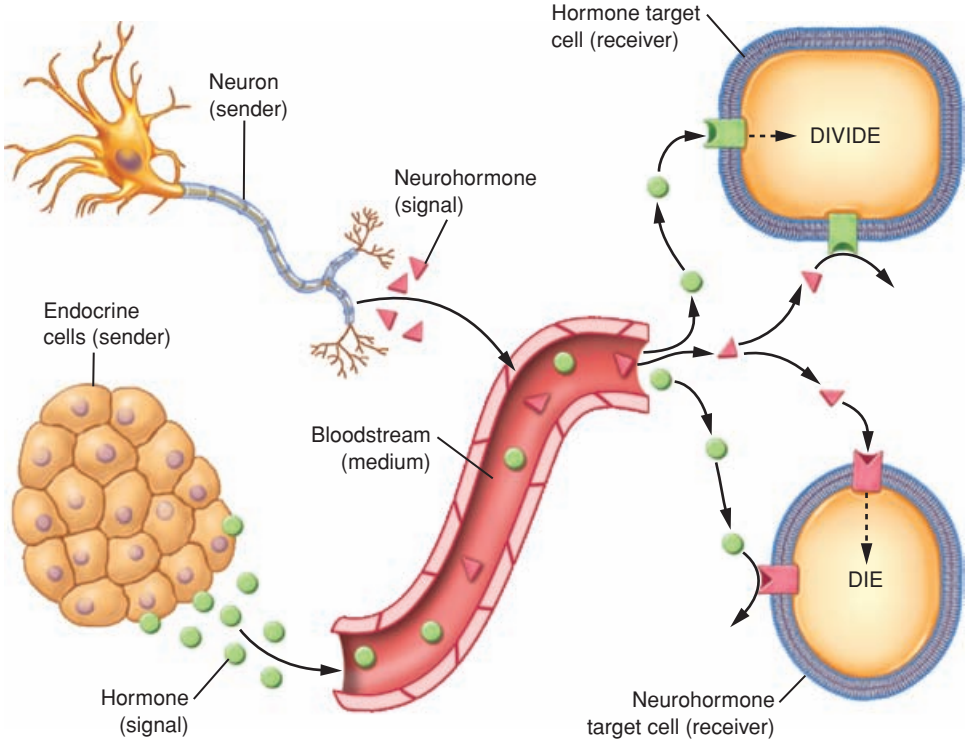


Figure 4.2. Chemical signaling. Endocrine glands or neurons send signals (hormones or neurohormones) through the medium of blood to target cells (receivers). Only cells with the correct receptor will receive the signal and be affected. *Which signal contains the message to divide—the hormone or the neurohormone?*

THE HISTORY OF SCIENCE

Braille: A Reading Code for the Blind

The Braille system, which enables blind people to read by deciphering (decoding) a code with their fingertips, is a product of the genius of Louis Braille (1809–1852), the son of a saddle and harness maker living in the French countryside near Paris. At age 3, while playing in his father's workshop, he accidentally punctured an eye with an awl, a sharp tool for making holes in leather. He quickly lost sight in the injured eye and, by the time he was 4, was completely blind in both eyes presumably because of an immune reaction (Chapter 12) in his other eye.

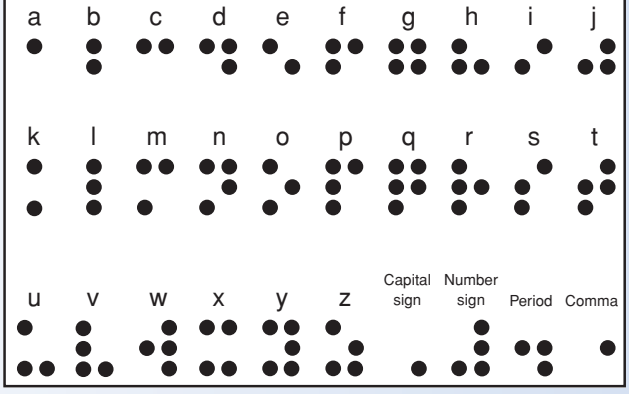
Young Braille was very bright and kept up his studies orally in a standard classroom. At age 10, he was enrolled in the Royal Institution for Blind Youth in Paris, which also taught students orally; however, the library contained a few volumes of bulky books written with very large, raised conventional letters, which Braille used for a while but abandoned as much too slow for practical use. Louis performed well in his regular studies and displayed exceptional musical talent at the piano, which honed his tactile skills.

Then, one day in 1821, when Braille was only 12, in one of those casual moments that change world history, he met Charles Barbier, a former French soldier who was visiting the school. While in the army, Barbier had invented a system of coding military messages in raised dots so that they could be read (decoded) by touch at night, without having to wait for dawn or lighting a flame, which might reveal their position to an enemy. Barbier recognized that his system might help the blind and discussed it with Braille, who quickly realized its potential. However, Barbier's system was crude, cumbersome, and slow. Young Braille simplified and streamlined the code, and the rest is history.

Braille's system, now known simply as Braille, has been adopted worldwide and has evolved to enable the blind to write and read music and mathematical formulas as well as to use computers. A skilled Braille reader can read a Braille version of this sentence almost as fast as you can read it visually.

Braille Alphabet

The six dots of the braille cell are arranged and numbered:	1 4 2 5 3 6
The capital sign, dot 6, placed before a letter makes a capital letter.	6
The number sign, dots 3, 4, 5, 6, placed before the characters a through j, makes the numbers 1 through 0. For example: a preceded by the number sign is 1, b is 2, etc.	3 4 5 6



Decoder for Braille. This decoder enables users to understand the Braille signal, much as receptors enable body cells to decode chemical signals.

uncomfortable effects of hay fever reflect the release of *histamines* from white blood cells in response to pollens. Histamines signal nearby blood vessels to enlarge (red eyes) or nearby epithelial cells to secrete mucus (runny nose).

- **Neurotransmitters** are a special class of paracrine factors. They are released by neurons and travel a very short distance across a narrow intercellular space (a *synapse*, discussed further below) to another neuron or an effector cell to induce an electrical signal. For example, the neurotransmitter *acetylcholine* travels from a nerve to a muscle cell to induce an electrical signal that stimulates contraction.

Case Note

4.2. Recall that caffeine affects brain function by interfering with the action of adenosine. If adenosine is released by a neuron and travels a short distance to change the activity of a neighboring neuron, is it acting as a paracrine factor or a hormone?

Chemical Signals Vary According to Their Lipid Solubility and Binding Site

Recall that all chemical signals must bind to protein receptors in order to alter cell function. Some receptors are hidden deep within the cell, in the cytosol or even within the nucleus. And also recall from ⬅ (Chapter 2) that *hydrophilic* substances are soluble in water and *hydrophobic* substances are soluble in lipid but not in water. Only hydrophobic signals—lipid-soluble molecules that can cross the lipid layer of the cell membrane—can reach these intracellular receptors. Conversely, it is much more difficult for hydrophilic molecules to reach intracellular receptors because they are not lipid-soluble and cannot cross the cell membrane. Instead, hydrophilic signals usually bind membrane receptors—integral membrane proteins oriented to bind chemical signals in the watery extracellular fluid. As discussed below, intracellular and membrane receptors utilize very different strategies to alter target cell activity.

Hydrophobic Chemical Signals Bind to Intracellular Receptors

Hydrophobic signal molecules typically act by binding intracellular receptors and stimulating the synthesis of specific proteins. This is a relatively slow process that may take an hour or more to produce a response. The most common hydrophobic signal molecules are steroid hormones. The steroid hormone testosterone, for instance, stimulates the production of proteins that, in turn, stimulate sperm production and muscle development.

The signal transduction pathway for hydrophobic hormones and other hydrophobic ligands is essentially as follows (Fig. 4.3):

1. The hormone crosses the cell membrane by simple diffusion.
2. The hormone binds to a receptor in the cytosol or nucleus; the receptor changes shape.
3. If the receptor is in the cytoplasm, the hormone–receptor complex enters the nucleus through a nuclear pore.
4. The hormone–receptor complex binds to the regulatory region of a particular gene. Remember that genes are segments of DNA that code for a particular protein.
5. The gene is transcribed into mRNA strands.
6. Ribosomes translate the mRNA into a protein, which exerts its effect within the cell or by traveling to other cells.

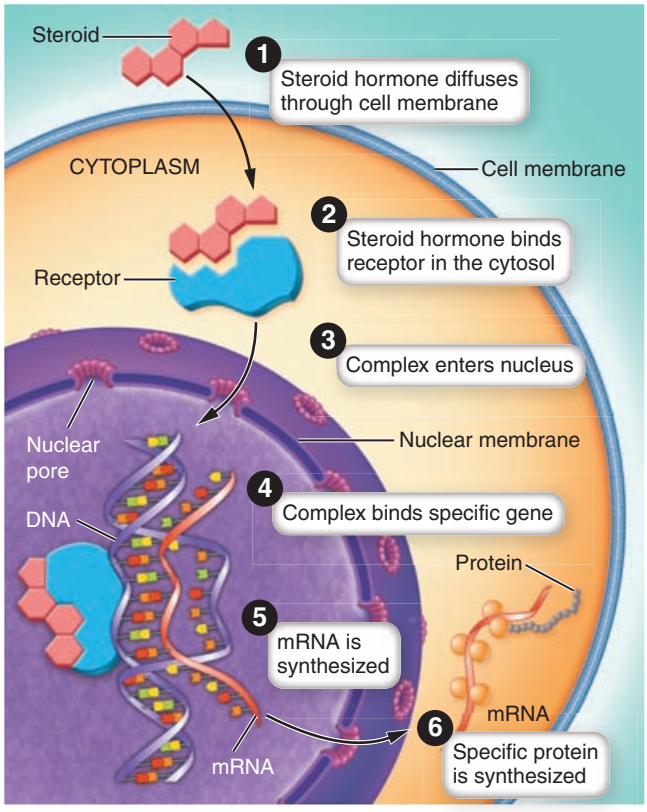


Figure 4.3. Signaling: intracellular receptors. *What binds to DNA—the ligand or the receptor?*

Hydrophilic Signal Molecules Bind to Receptors on the Cell Surface

We've said that hydrophilic signal molecules, which cannot cross the lipid layer of the cell membrane, must bind with protein receptors in the cell membrane. These receptors span the full thickness of the membrane: the ligand binding site is external and exposed to the extracellular fluid; the internal portion is exposed to the cytosol. There are three main categories of cell membrane receptors, each with a unique function (Fig. 4.4):

- Ligand-gated channel receptors
- Enzyme-linked receptors
- G-protein–linked receptors

Recall that hydrophobic signal pathways can require an hour or more to produce an effect. In contrast, the response to hydrophilic signal pathways can be very rapid, often a fraction of a second.

Case Note

4.3. Adenosine is water-soluble. Do you think it acts upon membrane receptors or intracellular receptors?

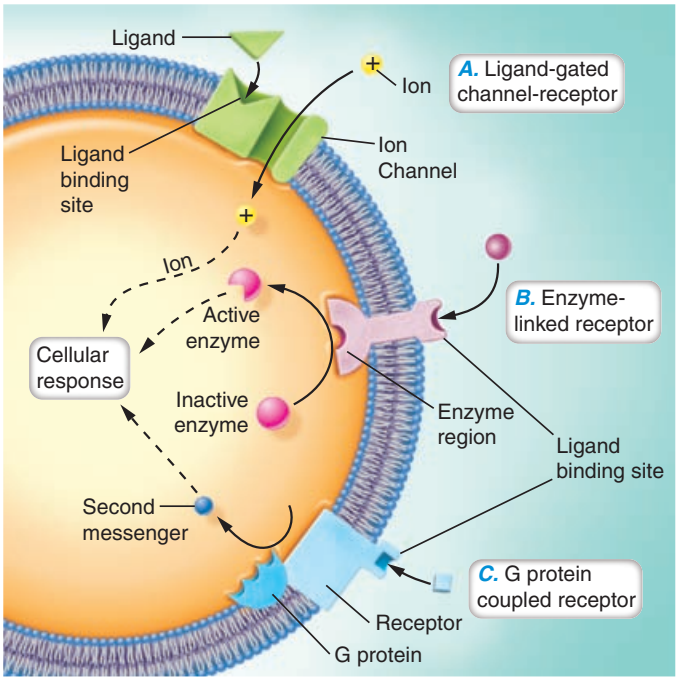


Figure 4.4. Signaling: cell membrane receptors. *Which ligand results in the production of a second messenger—the sphere, the triangle, or the square?*

Ligand-Gated Channel Receptors Modify Ion Flux

Ligand-gated channel receptors act as gates that can open to allow ions to cross the cell membrane (Fig. 4.4A). Binding of the ligand opens or closes the channel. These receptors are large proteins that contain two parts—one part binds the ligand and the other constitutes an ion channel that spans the cell membrane from outside to inside. Binding of the ligand can open or close the channel and modulate the flow (flux) of ions into or out of the cell. The ions subsequently cause a cellular response. As discussed later in the text, ligand-gated channels frequently convert a chemical signal (the ligand) into an electrical signal.

Enzyme-Linked Receptors Generate Active Enzymes

Enzyme-linked receptors also have two functional regions: the binding site is exposed to the extracellular fluid and the enzyme portion is exposed to the cytosol (Fig. 4.4B). Ligand binding to the extracellular side of the receptor activates the intracellular enzyme, which in turn activates another enzyme, which in turn activates a third enzyme, and so on. Eventually, the activated enzyme induces a functional change in the cell, such as the breakdown of glucose for energy.

G Protein Receptors Activate Intracellular Second Messengers

A ligand conveys a message, so it is a messenger. In the case of ligand-gated channels, the ligand acts alone and the information it contains is sufficient to achieve the end result—opening or closing the gate. There are, however, certain reactions in which the ligand is merely a *first messenger,* which activates a **second messenger**—a small molecule that transmits a cell surface signal to sites of action in the cytoplasm or nucleus. You can think of second messengers as secret agents that carry coded messages from outsiders (i.e., hydrophilic ligands) who cannot penetrate the cell's border security.

G protein–coupled receptors (GPCRs) are a class of membrane receptors that utilize second messengers to propagate intracellularly an extracellular signal. GPCRs have two structural components: an extracellular portion that binds to the ligand and an intracellular part that interacts with a protein complex called a **G protein** (Fig. 4.4C). Note that the GPCR and the G protein itself are not the same. The ligand binds with the GPCR, which in turn activates the G protein. The G protein subsequently regulates the production of a specific second messenger.

Many GPCRs use *cAMP* (cyclic AMP, cyclic adenosine monophosphate) as their second messenger. For example, the hormone *glucagon* activates the cAMP pathway when the body needs more glucose to burn for energy. Figure 4.5 illustrates the steps in glucagon action.

1. Glucagon, the first messenger in this system, travels through the bloodstream to liver cells.
2. Glucagon binds to its receptor (a GPCR).
3. The bound GPCR activates a G protein.
4. The G protein, through a sequence of intervening steps, prompts production of the second messenger, cAMP.
5. Through a number of intervening steps, cAMP activates enzymes.
6. The enzymes increase glucose production by the liver.

This example also highlights one of the advantages of second messenger systems—at certain stages, succeeding products in the cascade are produced in greater quantity than the preceding products; that is, the signal is amplified. A single glucagon molecule can prompt the synthesis of many cAMP molecules, each of which stimulates ever-increasing activity from many enzymes. Hormones that act via second messenger systems are very effective in extremely small amounts.

It should be noted that other substances, even ions, can also function as second messengers. Calcium (Ca^{2+}) ions, for instance, that enter the cell through ion channels

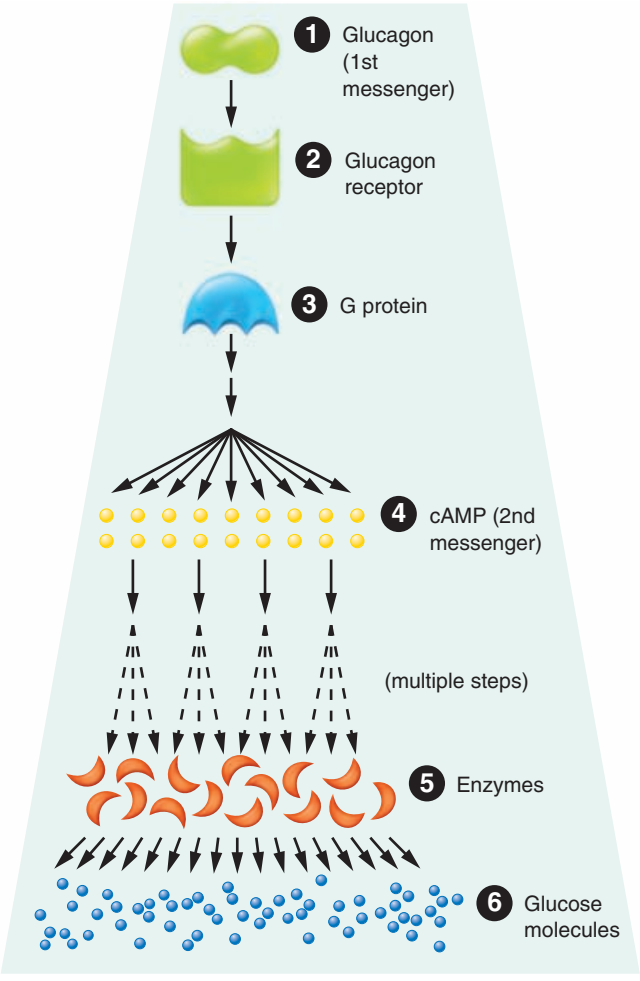


Figure 4.5. Second messengers and amplification. A single glucagon molecule can prompt the production of many glucose molecules. *How many G proteins are activated by one glucagon molecule?*

can tell an intestinal muscle cell to contract or a gland cell to secrete.

Case Note

4.4. The adenosine receptor uses cAMP as a second messenger. Is this receptor a G protein–coupled receptor or an enzyme-linked receptor?

Remember This! **An enzyme is part of the receptor protein in enzyme-linked receptors but not in G protein–linked receptors.**

Target Cell Response Is Determined by the Cell or the Signal

People respond differently to different signals. For example, the statement, "It's decaf!" might prompt relief in a dinner guest who suffers from insomnia but outrage in Andy, our caffeine-addict. Similarly, a particular ligand can induce one response in one cell and a different response in another. The response of a cell to a particular ligand varies according to any of the factors discussed below.

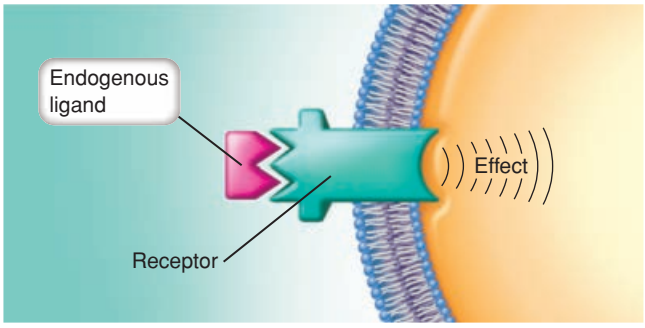
A Particular Ligand Can Bind to More than One Type of Receptor

A particular ligand can incite reaction X by binding to receptor type X in one cell; it can incite reaction Y in another cell by binding to receptor type Y. For example, the adrenal hormone epinephrine (adrenalin) can cause muscle cell contraction in one organ and muscle cell relaxation in another depending on the type of receptor it encounters. (For further information about epinephrine, see *The Many Talents of Epinephrine* on our Web site at **http://thepoint.lww.com/McConnelland Hull.**) For adenosine the principle is the same—one ligand, two effects. Adenosine binds type II receptors on blood vessels but type I receptors on brain cells. The type II receptor (the A2R) in blood vessels increases cAMP production when adenosine binds to it, which widens the vessel, delivering more blood. In contrast, the type I receptor (the A1R) in brain cells decreases cAMP production when adenosine binds it, which reduces the electrical activity of the nerve cell.

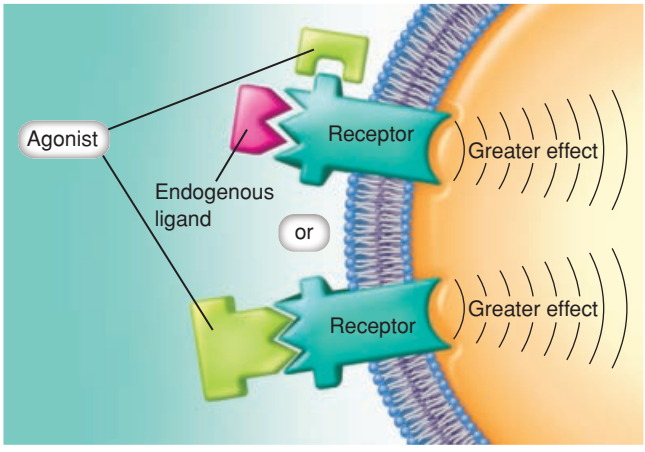
Receptor Activity Can Be Modified by Agonists and Antagonists

The naturally occurring ligand for a particular receptor is called the *endogenous* ligand (Fig. 4.6A); that is, a ligand that originates within the body. By contrast an *exogenous* ligand is one originating outside the body. For example, epinephrine produced by the body is an endogenous ligand, while epinephrine administered as a drug is an exogenous ligand. Both bind to the same receptors (called *adrenergic receptors*), but their origin is not the same.

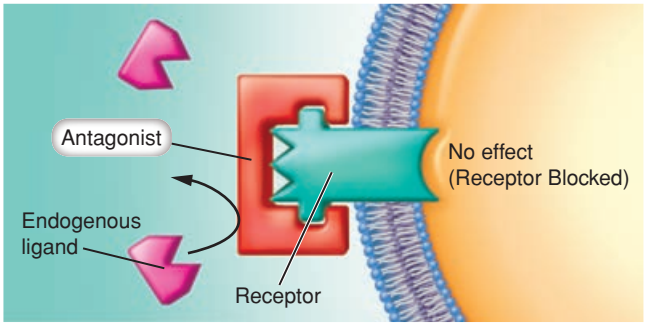
An **agonist** is a ligand that mimics the effect of an endogenous ligand. Some exogenous agonists bind with and activate a receptor in the absence of the endogenous ligand. For example, a common asthma medication (albuterol) is an adrenergic agonist. It binds to the same site on the adrenergic receptor as endogenous epinephrine and, like endogenous epinephrine, causes the airways to widen. Other agonists enhance the response to the endogenous ligand by binding to a different part of the receptor (Fig. 4.6B). The Clinical Snapshot later in this chapter, titled *Relaxing with GABA,* explains how alcohol acts as an agonist in this manner.



(a) The endogenous ligand



(b) Agonists



(c) Antagonists

Figure 4.6. Ligands, agonists, and antagonists. A. The endogenous ligand is produced by the body. It binds and activates the receptor, producing an effect. **B.** Some agonists bind to the receptor when the endogenous ligand is also bound, amplifying its effect. Other agonists bind to and activate the receptor, much like the endogenous ligand. **C.** Antagonists inhibit the ability of the endogenous ligand to activate the receptor, often by blocking the ligand binding site. *True or false: Both antagonists and agonists sometimes bind to the ligand-binding site of the receptor.*

Antagonists have an effect opposite to that of agonists. Some exogenous antagonists bind to a receptor and block the binding site, preventing the endogenous ligand from binding (Fig. 4.6C). Alternatively, antagonists can bind to a related receptor and *decrease* the effect of the endogenous ligand even if the endogenous ligand binds to its receptor. Either way, they don't turn off the receptor; they just prevent it from turning on or limit its effect. For example, certain breast cancer cells need estrogen to survive and have estrogen receptors to bind estrogen. For such breast cancers, the drug tamoxifen is useful treatment because it is an estrogen antagonist: it interferes with cancer cell survival by preventing estrogen action.

Case Note

4.5. Caffeine binds to the adenosine receptor and prevents adenosine from binding. Is caffeine an agonist or an antagonist for the adenosine receptor?

Cells Can Vary the Number and Sensitivity of Their Receptors

Cells can have thousands of receptors for one ligand and can increase or decrease this number in response to changing conditions. Cells with more receptors of a particular type are able to bind more ligand, which produces a more intense reaction to the ligand; the reverse is also true.

Commonly, if a ligand is present in excess for a long time, cells decrease their responsiveness by reducing the number of receptors. Alternatively, the cell may subtly alter the receptor's structure so that it responds less strongly to the ligand, much in the same way that our eyes respond to bright light by becoming less sensitive. The "high" from abused drugs typically lessens with time because cell receptors decrease or become less sensitive to the drug (ligand). People in this condition are said to be drug-tolerant, a condition that can have serious, even fatal consequences.

For example, heroin binds to brain cells and induces a dreamy euphoria, but at the same time it also binds to other cells that suppress breathing. Heroin addicts frequently become so drug-tolerant (partly because of the reduced receptor number) that to achieve the desired mental effect they must take doses that depress breathing. Addicts must walk a fine line between killing themselves and not getting the high they crave—a little too much drug and respirations become incapable of sustaining life. What's more, after withdrawal from heroin, the receptors return to normal (high)

sensitivity. This, too, poses a danger: a recovered addict suffers a relapse and "shoots up" again, thinking that a big dose is needed. But the recovered receptors are numerous and sensitive, including the respiratory ones, and the addict sinks dreamily into respiratory paralysis and death.

Case Note

4.6. Remember that caffeine antagonizes adenosine action. How do you think Andy's body will compensate for the constant caffeine exposure? Will it increase or decrease the number of adenosine receptors? Explain.

4.3 What is the name of a chemical signal released from a gland into blood in order to influence cells in a distant part of the body?

4.4 True or false: If the concentration of a hormone is high enough, every body cell will respond to it.

4.5 Which type of ligand usually binds intracellular receptors—hydrophobic or hydrophilic?

4.6 Does the steroid receptor bind to DNA or mRNA?

4.7 Which portion of the receptor activates the G protein—the extracellular or intracellular portion?

4.8 Imagine that a young student is conducting research that she hopes will enable her to win a scholarship for graduate school. She is assisted in her studies by a professor who believes in her abilities, but she is blocked by an envious fellow student who steals her research data. Identify the agonist and the antagonist in our scenario.

Electrical Signaling

Chemical signals transmit most messages through blood or other fluid, but they are slow—too slow for some purposes, such as sending a message to the legs to run when danger appears. Such fast signals are transmitted electrically—somewhat like a lightning bolt, though not quite as fast. Electrical signals are the "spark of life" in every cell. As shown below, the inside and outside of the cell membrane have differing electrical charges like the positive and negative poles of a battery, a condition that must be maintained for the cell to live and function normally. Keeping this "battery" charged is one of the most basic requirements of life: no cell can survive without it. Electrical signals travel along the cell membrane as disturbances of these charges. As they do, they transmit messages from one part of the cell membrane to another or, less commonly, to an adjacent cell.

Neurons Signal Electrically

Electrical signals occur to one degree or another in all cells but are most important in muscle and nerve cells. So to facilitate our discussion of electrical signaling, let's take a brief look at neuron structure (Fig. 4.7). As discussed in ➡ Chapter 8, there is considerable variation in the appearance of neurons, but all share the same basic components:

- The **cell body** comprises the main mass of the neuron and contains the nucleus and most of the organelles. The cell body integrates signals received by dendrites.
- **Dendrites** are branched, short cytoplasmic extensions of the neuron cell body that convey electrical signals from another cell *toward* the neuron cell body.
- The **axon** is a single, usually quite long, cytoplasmic extension from the neuron cell body, which conveys electrical signals *away* from the cell body and to other cells. Small axon branches, called *collaterals,* may branch off the main axon.
- Sections of most axons are covered with **myelin,** a fatty whitish substance that accelerates the transmission of electrical signals. As you can see in ➡ Figure 8.4, the myelin coating is actually the cytoplasmic extensions of specialized nervous system cells.

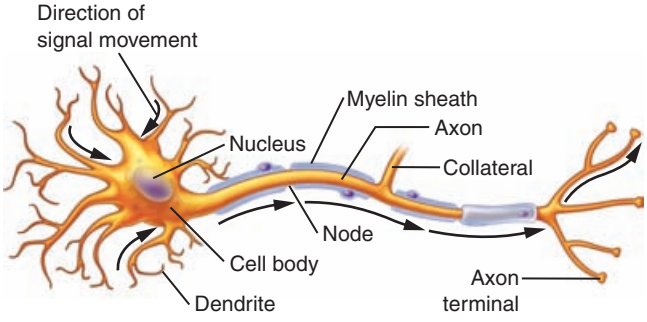


Figure 4.7. Structure of a neuron. This figure shows a myelinated neuron; unmyelinated neurons are similar but do not have a myelin sheath. *Does myelin wrap around the neuron's axon or its dendrites?*

Remember This! **A neuron can have many dendrites but only one axon.**

Case Note

4.7. Adenosine receptors are present in the neuron component that commonly receives signals. Name this component.

Ions Carry Electrical Signals

Before we can understand how neurons and other cells send and receive electrical signals, we must review some electrical basics.

- *An excess of protons (+) or electrons (–) in an atom or molecule creates ions* that are positively or negatively charged. Positively charged ions such as sodium (Na^+) and potassium (K^+) are called **cations;** negatively charged ions such as chloride (Cl^-) or many proteins (abbreviated as Pr-) are called **anions.**
- *Similar charges repel one another*: positive repels positive, and negative repels negative.
- *Opposite charges attract one another*; that is, cations are attracted to anions. If a cation pairs up with an anion, the net charge is zero (0).
- *Energy is required to keep opposite charges apart.* A barrier that keeps positive and negative charges separated is an *insulator*. The cell membrane is an insulator, keeping opposite charges on opposite sides of the cell membrane.

Case Note

4.8. In some cells, adenosine increases the movement of potassium ions across the cell membrane. Is potassium an anion or a cation?

Electrical Signaling Relies on the Electrical Gradient

Recall from ⬅ Chapter 1 that a gradient is a difference in the quantity of something between two areas. For example, a temperature gradient exists across a wall if it is hot on one side of the wall, cold on the other. An **electrical gradient,** reflecting different numbers of anions and cations on either side of the cell membrane, exists in every cell and is the basis of electrical communication. This electrical gradient is also known as the **membrane potential** because (a) it exists at the cell membrane and (b) like a battery, it is a source of *potential energy* (⬅ Chapter 2).

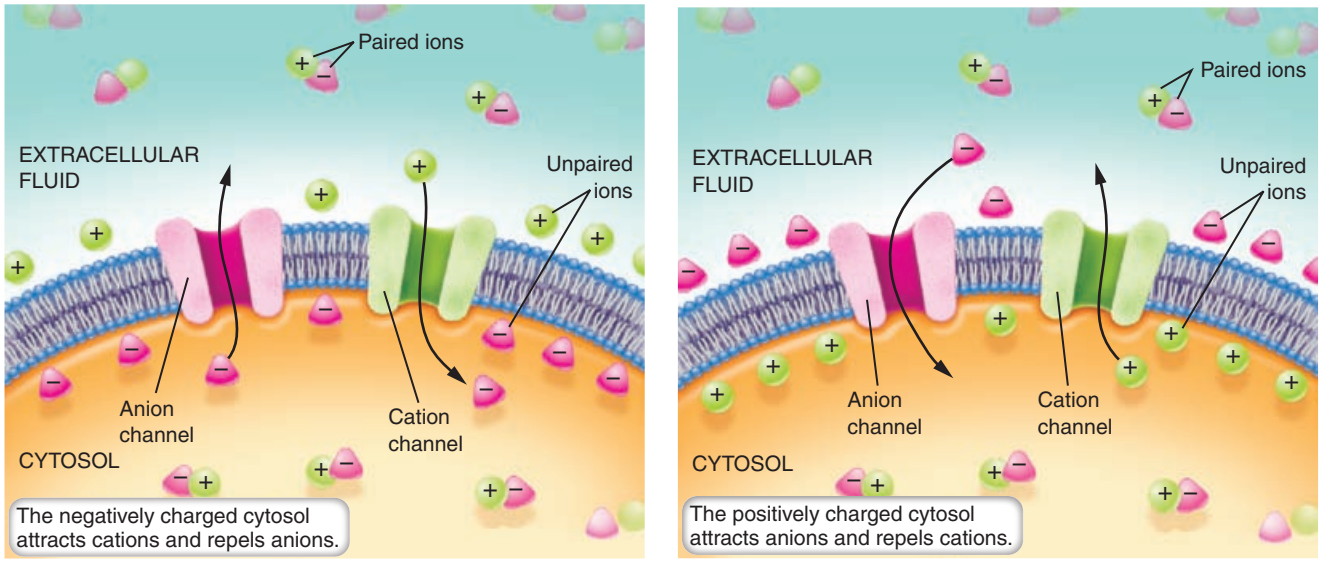
There are millions of positively and negatively charged ions in the cytosol and extracellular fluid. Except under very unusual circumstances, the overall electrical balance of the body is neutral: for every negative charge there must be a positive one. Ions in the same fluid will pair up, each cation pairs with an anion neighbor, so the net charge is zero. However, the cell membrane prevents some ions from pairing up. Thus, if the cytosol accumulates an excess of anions (–), it follows that the extracellular fluid *must* have an excess of cations (+). As a result, the cytosol will be negatively charged (Fig. 4.8A). Conversely, a relative excess of cations in the cytosol (and anions in the extracellular fluid) would result in positively charged cytosol (Fig. 4.8B).

In both cases, an electrical gradient, the membrane potential, is created. This gradient exerts a force on all ions inside and outside the cell. If the cytosol is negatively charged, it will attract cations (+) and repel anions (–). Conversely, a positively charged cell interior will attract anions and repel cations. The insulating lipid of the cell membrane prevents these ions from rushing into or out of the cell to join one another. However, certain types of ion channels exist within the cell membrane to control ion passage into or out of the cell. These ion channels are discussed below.

The strength of the electrical charge, the membrane potential, is measured in millivolts (mV). By convention such measurements quantify the unpaired charges in the cytosol. That is, a negative membrane potential means that the cytosol contains unpaired anions. The value of the membrane potential in nerve or skeletal muscle cells "at rest" (that is, not transmitting electric signals), known as the **resting membrane potential,** is about –70 mV. This value informs us that the strength of the electrical gradient is 70 mV. The minus sign signifies that the cytosol contains excess anions—it is negatively charged. The membrane potential is absolutely necessary for electrical communication and thus for many body functions, from the heartbeat to respiration. Before discussing why this membrane potential exists and how the cell uses it for signaling, it is important to understand two other elements governing electric signaling: *concentration gradients* and *ion channels*.

Case Note

4.9. When Andy was drinking decaf, the resting membrane potential of some of his brain cells changed from –70 mV to –71 mV. Does the cytosol of his cells contain more or fewer anions than usual?



(a) Membrane potential = −70 mV (Resting membrane potential) **(b) Membrane potential = +30 mV**

Figure 4.8. Membrane potential. An electrical gradient, or membrane potential, is created by an electrical imbalance between the extracellular fluid (ECF) and the cytosol. If ion channels are open (in this example, one ion channel for cations and one ion channel for anions), ions will cross the membrane. **A.** A negative membrane potential is created by a relative excess of negative ions in the cytosol. If open ion channels are present, anions will leave the cytosol and positive ions will enter the cytosol. **B.** A positive membrane potential is created by a relative excess of positive ions in the cytosol. If open ion channels are present, cations will leave the cytosol and anion ions will enter the cytosol. *Calcium is a cation. In cell B (assuming open calcium channels), will calcium enter or leave the cell?*

Sodium and Potassium Concentration Gradients Exist in Every Cell

Electrical signaling not only relies on the *electrical* gradient but also requires well-defined *concentration* gradients for numerous ions. The extracellular fluid bathing all cells, for instance, contains a high concentration of sodium (Na^+) and a low concentration of potassium (K^+) (Fig. 4.9). The intracellular fluid also contains sodium and potassium, but the concentrations are reversed: potassium is in high concentration and sodium low. Thus, if ion channels were to permit them to cross the cell membrane:

- Sodium would flow down its concentration gradient *into* the cell.
- Potassium would flow down its concentration gradient *out* of the cell.

The sodium and potassium concentration gradients are created and maintained by active transport (← Chapter 2), specifically the sodium–potassium ATP pump (abbreviated as the Na^+/K^+-ATPase). The Na^+/K^+-ATPase uses energy to force sodium ions out of the cell and potassium ions into the cell, each traveling "uphill" against their respective concentration gradients. Because of constant activity of the Na^+/K^+-ATPase, these concentration gradients are fixed—they do not change in the living body.

Although sodium and potassium are the star players in electrical communication, negative ions play supporting roles. Intracellular protein anions help keep the cytosol negatively charged, and, as discussed further on, chloride anions in the extracellular fluid can participate in electrical signaling.

Remember This! **Sodium is always more concentrated outside the cell. Potassium is always more concentrated inside the cell.**

Ions Move Down Gradients Using Ion Channels

Recall from ← Chapter 3 that ions cannot freely pass across the cell membrane; they require the assistance of membrane proteins such as ion channels. Many types of channels exist for each ion. Of these, three are particularly important in our discussion of electric signaling:

- *Leak channels:* Leak channels are always open, allowing ions to "leak" in or out of the cell down a concentration or electrical gradient. Most cells contain many

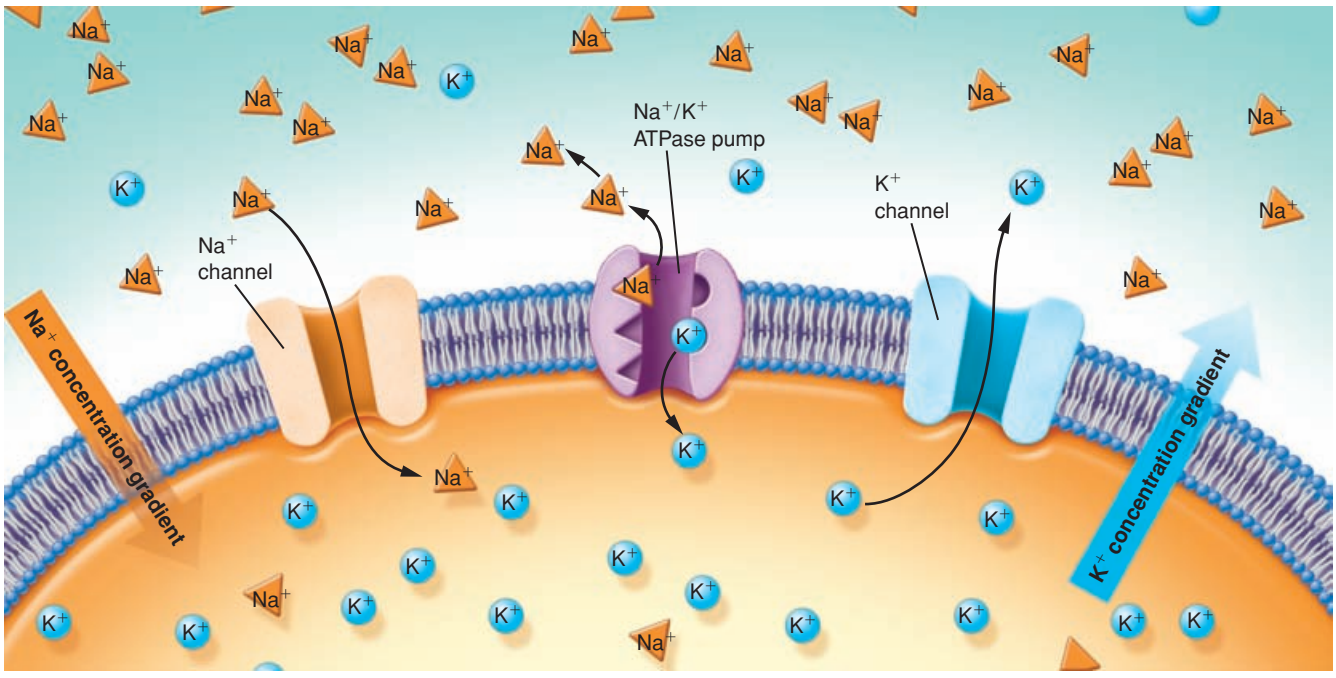


Figure 4.9. Sodium and potassium gradients. A. The sodium concentration gradient attempts to force sodium ions into the cell. **B.** The potassium concentration gradient attempts to force potassium out of the cell. These two gradients are opposed by the sodium–potassium ATPase pump. *True or false: The sodium–potassium ATPase pump actively transports sodium out of the cell.*

potassium leak channels to let K^+ out of the cell but very few sodium leak channels to let Na^+ in.

- *Ligand-gated channels:* These channels open in response to a specific chemical signal—a *ligand*. They play starring roles in converting a chemical signal (the ligand) into an electrical signal (a change in membrane potential).
- *Voltage-gated channels:* These channels open in response to a change in membrane potential and are responsible for long-distance electrical signals, discussed further on.

Because Na^+ and K^+ are ions and differ in their concentration inside and outside the cell, their movement through these channels will be affected by both concentration and electrical gradients. Consider, for instance, a negatively charged cytosol with open Na^+ and K^+ channels. Na^+ would enter the cell down both its concentration and electrical gradients. K^+, conversely, would be tugged in both directions: the negative interior pulling inwardly and the chemical gradient acting in the opposite direction to draw K^+ out of the cell. The net movement of K^+ would depend on whether the electrical or the chemical gradient were the stronger one.

The opposite would apply if the cytosol were positively charged. Assuming that Na^+ and K^+ channels are open, this time potassium would be driven out of the cell by both electrical and concentration gradients. Sodium, on the other hand, would be the one tugged in both directions: the positive cytosol would be acting to force Na^+ outward and the chemical gradient would be acting to keep it inside. The net flow of Na^+ would depend on the balance of these two conflicting forces.

Remember This! **Ion movement by facilitated diffusion requires (a) a gradient and (b) an open ion channel.**

The Resting Membrane Potential Is Determined by Potassium

The resting membrane potential, in which the cytosol is negatively charged in comparison to the extracellular fluid, is based on two simple elements:

- K^+ is more concentrated inside the cell than outside it.
- K^+ leak channels are always open, permitting K^+ to leak out of the cell.

The net result of potassium leakage is that the interior of the cell, the cytosol, becomes electrically negative.

CLINICAL SNAPSHOT

The Resting Membrane Potential and Open Heart Surgery

It's difficult to operate on the beating heart; so for most heart surgery the heartbeat must be stopped. How do surgeons do it, and even more important, how do they get it going again? It's actually quite simple: just infuse some potassium chloride (KCl; that is, K^+ and Cl^- in solution) into the coronary arteries (Chapter 11) and the heart stops; wash it out and the heart begins beating again. To understand why, let's revisit the topic of resting membrane potential.

Recall that the interior of the cell membrane is negatively charged and contains more potassium ions (K^+) than the outside, while the outside is positively charged and contains more sodium ions (Na^+) than the inside. Recall, too, that the resting membrane potential is critical for cell function—in this case, for the contractions of the heart muscle that create the heartbeat.

Now, what happens down at the level of the cell membrane if we drastically increase the *extra*cellular K^+ concentration, as surgeons do to arrest the heartbeat? The injection of KCl into the coronary arteries increases *extra*cellular K^+ to a level equal to *intra*cellular K^+. The net result is that *the chemical concentration gradient that would normally urge the flow of K^+ out of cells is destroyed.* K^+ will not flow out of the cell; therefore a resting membrane potential cannot be maintained. The heart muscle immediately stops contracting and the surgeons go to work.

Once surgery is finished, surgeons wash out the extracellular K^+ by using an artificial fluid that is the rough equivalent of normal extracellular fluid, which is high in sodium, low in potassium. As *extra*cellular potassium falls, the chemical concentration gradient is reestablished, potassium begins to leak out of cells as described in this chapter, and the resting membrane potential is restored.

Without the potassium gradient, the membrane potential does not exist. See the nearby box, The Resting Membrane Potential and Open Heart Surgery, for the clinical implications of this fact. Below we discuss the many and varied changes in the electrical character of the cell membrane as a method of electrical signaling.

For a more detailed discussion of the resting membrane potential, read the text box *The Resting Membrane Potential: It's All About Potassium,* at **http://thepoint.lww.com/McConnellandHull**.

Remember This! **The resting membrane potential is simply an electrical gradient, reflecting an excess of anions inside the cell and a corresponding excess of cations outside the cell.**

A Cell's Electrical Signal Is a Wave of Change in the Membrane Potential

Unlike concentration gradients, electrical gradients are exquisitely sensitive—the movement of just a few ions can change the membrane potential with lightning speed and without appreciably altering the concentration gradient.

What's more, since positive and negative ions are attracted to each other, any change in membrane potential will spread to neighboring regions. As discussed in the next section, electrical signals in cells are transmitted as very short-lived changes in membrane potential, which spread from one region of the cell membrane to another. This wave of temporary change in membrane potential is what we have been referring to as the "electrical signal," and it is the means of electrical communication between cells.

It is important to realize that molecules racing along from one end of the cell to the other is not the way electrical waves travel. Rather, waves reflect temporary local activity—a disturbance—that moves from one place to another. It is similar to fans in a stadium participating in a wave that moves around a stadium: the fans stay in place and stand up briefly to continue the wave. They do not race from one section to the other. So it is with membrane potential: The electrical potential changes briefly, propagating the wave, and then returns to its previous status.

Remember This! **In cell signaling, the sodium and potassium concentration gradients do not change significantly. However, the membrane potential (the electrical gradient) *does* change, and when it does, it travels as an electrical signal.**

Changes in Membrane Potential Are Depolarization, Hyperpolarization, and Repolarization

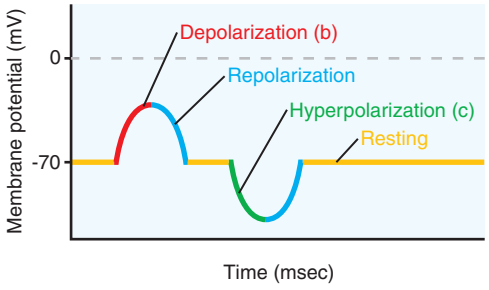
In many cells, the resting membrane potential never changes; the cells are able to do their work in ways that do not disturb their electrical balance. But in other cells, especially (but not exclusively) nerve and muscle cells, electrical activity is ceaseless, as changes in membrane potential convey signals during every millisecond of life.

Understanding the changes in membrane potential requires that you understand the concept of **electrical polarity.** In daily life, we use the adjective *polarized* to describe a situation in which groups, such as political parties, are on opposite sides of an issue. In reference to the cell membrane, a *polarized membrane* is one with an excess of negative charges on one side and an excess of positive charges on the other. The cell membrane of every cell in the body is polarized in this way.

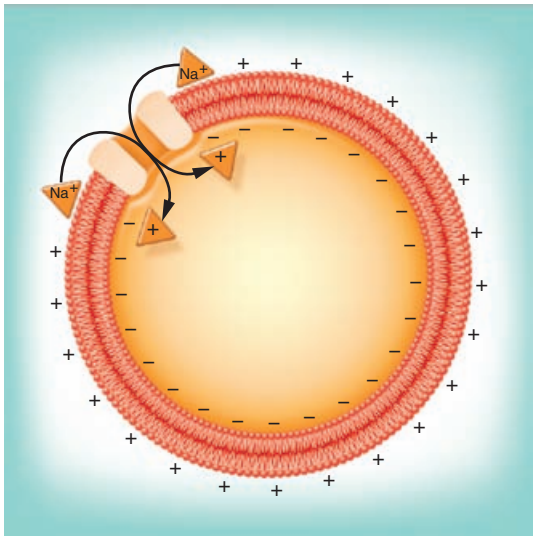
Changes in membrane potential can be classified as one of three types, according to their effect on the strength of the electrical gradient (Fig. 4.10):

- *Depolarization.* A change that *reduces* the strength of the electrical gradient—that makes the cell's interior less negative—is called **depolarization.** For example, a change of the electrical charge from –70 mV to –40 mV is partial depolarization; and a change from –70 mV to 0 mV is complete depolarization. In the transmission of electrical signals across the cell membrane, the depolarization process actually "overshoots" a bit and the interior of the cell becomes positively charged for an instant. In this case the cell interior may go from –70 mV to +30 mV, but the process is still described as depolarization.
- *Hyperpolarization.* Conversely, a change that makes the cell's interior even more negative is called **hyperpolarization.** That is, it is a change that *increases* the strength of the electrical gradient. For example, a change from –70 mV to –80 mV is hyperpolarization.
- *Repolarization.* Finally, a change in the electrical gradient that returns a cell to its original resting membrane potential is described as **repolarization.** Again, a cell's resting state is *not* electrical neutrality (0 mV) but polarization (negative cell interior, –70 mV).

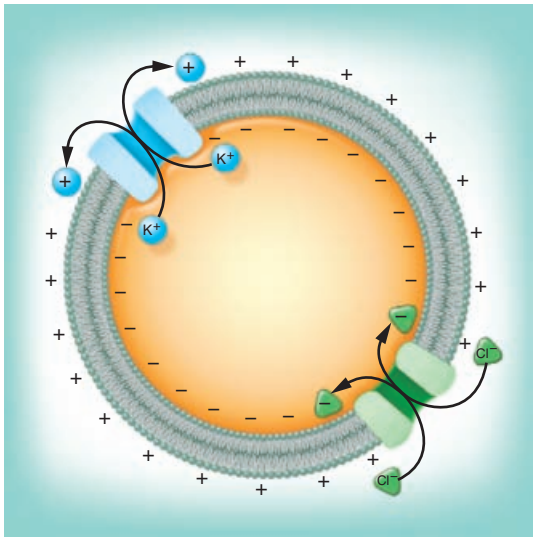
As shown in Figure 4.10A, we can use a graph to illustrate changes in membrane potential: notice that depolarization moves the voltage closer to neutral, whereas hyperpolarization moves the voltage away from neutral. After these changes, the membrane returns to the resting state by repolarization.



(a) Changes in membrane potential



(b) Depolarization



(c) Hyperpolarization

Figure 4.10. Membrane potential changes. A. Depolarization decreases the membrane potential, whereas hyperpolarization increases it. In the graph illustrated, the resting membrane potential is –70 mV. **B.** Sodium entry into the cell causes a depolarizing graded potential. **C.** Potassium exit or chloride entry causes a hyperpolarizing graded potential. *If the membrane potential moves from –70 mV to –65 mV, is the membrane hyperpolarized or depolarized?*

Case Notes

4.10. Adenosine acts on some neurons to increase the magnitude of the membrane potential. Does adenosine hyperpolarize or depolarize these neurons?

4.11. When Andy took his first gulp of caffeinated coffee, the membrane potential of certain nerve cells changed from −71 mV to −70 mV. Is this change described as hyperpolarization or depolarization?

Graded Potentials Remain Localized and Vary in Strength

Recall that neurotransmitters and paracrines work over short distances, whereas hormones are long-distance signals. In the same way, electrical signals are classified by the distance they travel. **Graded potentials** are short-lived changes in membrane potential that work locally over a small region of cell membrane or cytoplasm. They occur in most cells and are particularly important in neuronal dendrites. The most common cause of a graded potential is the opening of a ligand-gated channel. Depolarizing graded potentials, which make the cell's interior less negative, usually result from the activation of ligand-gated Na^+ channels that allow Na^+ into the cell (Fig. 4.10B). As Na^+ cations enter the cell, they match up with excess negative ions and reduce the polarity across the membrane. On the other hand, hyperpolarizing graded potentials, which make the cell's interior even more negative, result from K^+ leaving the cell through ligand-gated potassium channels (Fig. 4.10C) or from chloride (Cl^-) ions entering the cell through ligand-gated chloride channels.

The magnitude of an individual graded potential depends on how many channels in the cell membrane are open. If, for example, many sodium channels open to allow a large temporary influx of positive sodium ions, the cell will depolarize more than if fewer sodium ions entered. Conversely, a hyperpolarizing graded potential will be larger if more potassium or chloride channels are opened to let potassium out or chloride in. Graded potentials are important, for instance, in vision: the eye detects different light intensities because bright light stimulates a stronger hyperpolarizing graded potential in the retina than does dim light (➡ Chapter 9). Graded potentials, therefore, are one of the ways a cell responds to the strength of an incoming signal: the stronger the signal, the stronger the graded potential.

Many cells, neuronal dendrites in particular, experience multiple, simultaneous graded potentials. In the same way that a competitive diver's overall score reflects points gained for each successful dive and points lost for mistakes, the overall change in a cell's membrane potential depends on the sum of all individual graded potentials. For instance, let's say that a neuronal dendrite is exposed to two different ligands, one depolarizing the membrane by 10 mV and the other hyperpolarizing the membrane by 15 mV. The net result is a 5-mV hyperpolarization. The summation of graded potentials allows neurons to integrate information from many different sources.

Like any signal, a graded potential must travel to be effective. Graded potentials spread to neighboring regions of the cell membrane because negative and positive ions attract each other. The positive ions that enter the cell during an initial depolarization will attract nearby negative ions; as these negative ions leave their original position, they will leave some positive ions unpaired and thus depolarize the adjacent region. The graded potential spreads to this new region, which will depolarize adjacent new regions in the same way. That said, graded potentials travel only a very short distance. They lose strength as they travel and eventually fade to nothing, like ripples spreading out from a pebble dropped in a pond.

Case Note

4.12. Adenosine hyperpolarizes neurons. Does it increase or decrease the number of potassium ions leaving the cell?

Action Potentials Are Large Changes That Can Travel Long Distances

We've just discussed how graded potentials convey signals over very short distances—say, from the dendrite to the cell body of a neuron. In contrast, an **action potential** is a large change in membrane potential, which travels the length of the cell until it reaches the end, no matter the distance. For example, a neuron's axon can be several feet long, and action potentials travel the entire distance to communicate electrical signals. Action potentials occur only in neuronal axons, skeletal muscle cells, and a few other excitable cells.

Action Potentials Have Four Phases

As an action potential evolves at a given point on the cell membrane, we can graph the changes that occur, as shown

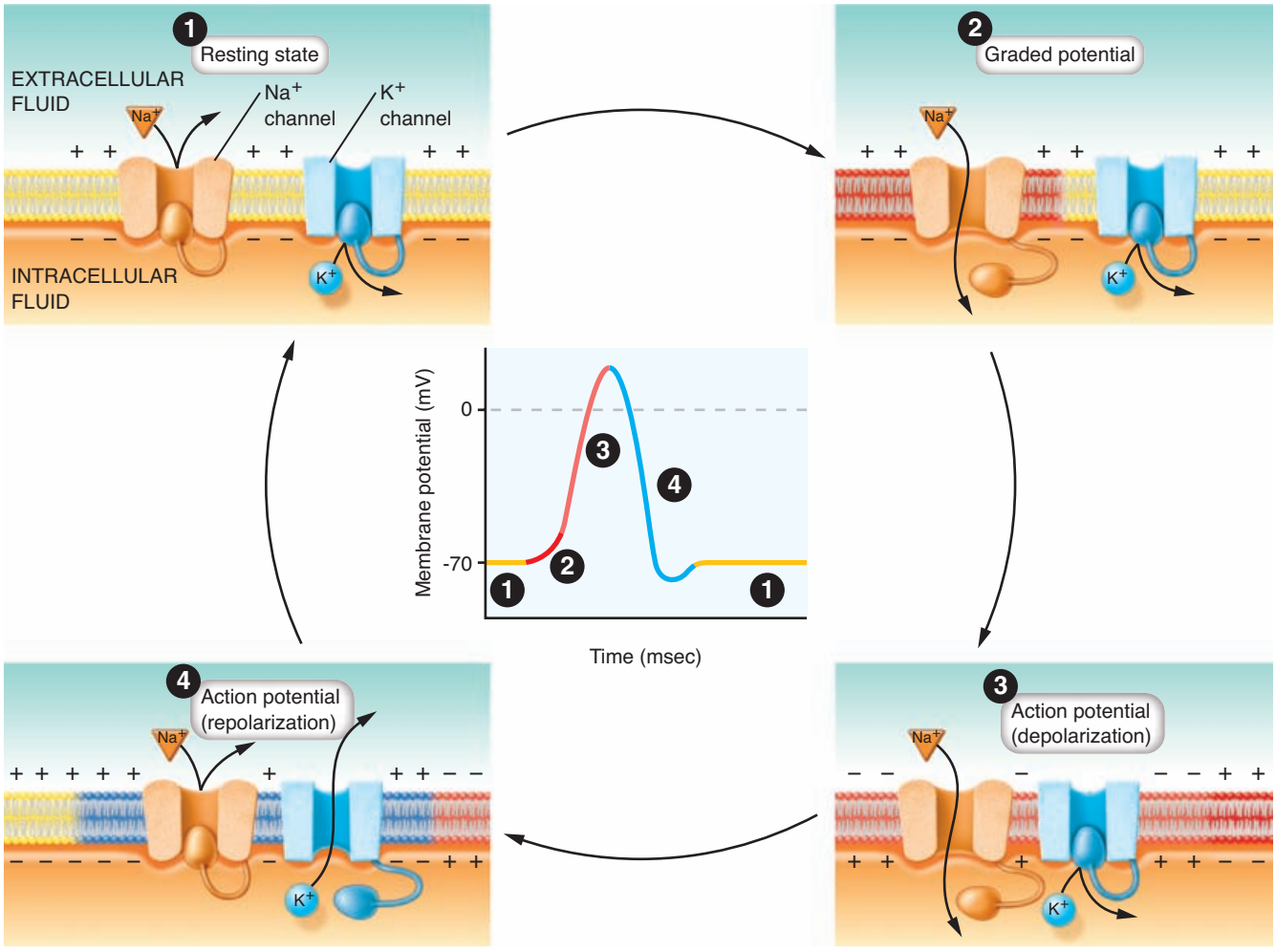


Figure 4.11. Action potential. The color of the membrane corresponds to the color on the action potential tracing. *Name the phase of the action potential when voltage-gated potassium channels are open.*

in Figure 4.11 (middle drawing). Time is plotted on the horizontal axis, the voltage of the membrane potential on the vertical axis. Notice that the events of the action potential are divided into four numbered phases, each with a corresponding color: (a) resting state; (b) graded potential; (c) depolarization; and (d) repolarization. If you study both parts of Figure 4.11 closely, you'll see that the colors for the phases on the graph in part A match the colors for the phase affecting the cell membrane in part B. For instance, red corresponds to the depolarizing phase of the action potential, so red membrane regions are depolarizing. Now let's take a closer look at the four phases of the action potential:

1. *Resting state.* The inside of the cell is negatively charged (yellow). Recall that this resting negative voltage is maintained because potassium *leak* channels are constantly open (these channels are not shown in the figure). In contrast, also recall that voltage-gated channels are special membrane channels that open only in response to changes in membrane potential. During the resting state, voltage-gated channels for both Na^+ and K^+ are closed, as shown (Fig. 4.11, phase 1).
2. *Development of a graded potential.* Action potentials begin as graded potentials. Depolarization of a nearby membrane segment (say, a signal initiated by a touch) causes a few sodium channels to open. Sodium ions enter (down their concentration and electrical gradients), depolarizing the cell slightly (dark red, phase 2). Notice that, as the cell becomes a bit less negative, the tracing on the graph rises slightly toward neutrality (zero). Voltage-gated potassium channels are still closed.
3. *Depolarization.* As the graded potential depolarizes the membrane, more voltage-gated sodium channels open and more sodium rushes into the cell. Although

only one voltage-gated sodium channel is depicted in phase 3, the actual number that open depends on the magnitude of the depolarization—larger depolarizations open more channels. So many sodium ions enter that, at its peak, depolarization causes the inside of the cell temporarily to become positively charged (light red). Notice that the curve of the graph rises above zero. As depolarization peaks, voltage-gated potassium channels finally begin to open—they are much slower to respond to depolarization than voltage-gated Na^+ channels—and Na^+ channels close. The opening of K^+ channels and closure of Na^+ channels stops depolarization.

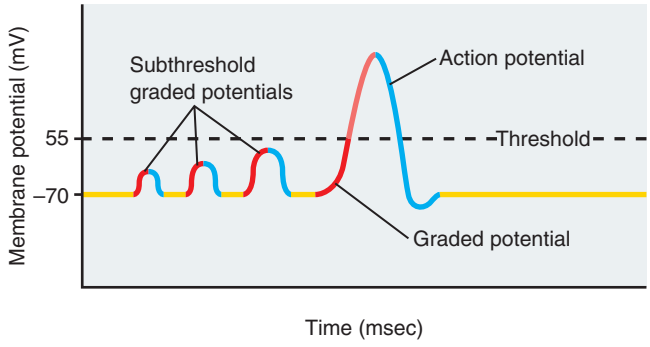
4. *Repolarization.* When the voltage-gated potassium channels open, positively charged potassium ions flood out of the cell and down their concentration and electrical gradients (blue); the cell membrane now returns to resting membrane potential (–70 mV; yellow). This lag time for potassium channels gives sodium a chance to flood in and completely depolarize the membrane before potassium floods out to repolarize the membrane back to the resting state.

Remember This! **Sodium ions entering the cell cause depolarization; potassium ions exiting the cell cause repolarization.**

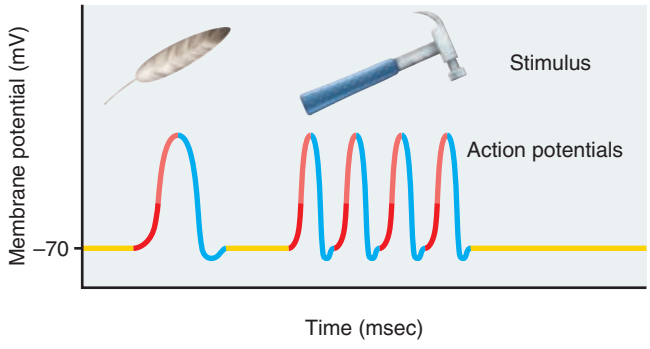
Action Potentials Are "All or Nothing"

Upon depressing the flush lever of a toilet, water begins to swirl around the bowl and, if the lever is depressed far enough, a full flush ensues. So it is with an action potential: it is all or nothing and requires a stimulus, in the form of a depolarizing graded potential, of sufficient strength to push it over the edge, so to speak. This critical electrical point that must be crossed is called the *threshold*. In most cells, the threshold is about 15 to 20 mV above resting membrane potential. If the graded potential remains subthreshold, it does not open enough voltage-gated sodium channels and an action potential will not develop (Fig. 4.12A). The graded potential will die out somewhat like a failed attempt to flush causes only a temporary swirl of water. The greater the difference between the resting membrane potential and the threshold, the more difficult it will be for the neuron to fire an action potential. It follows, therefore, that anything that hyperpolarizes the cell (i.e., makes the resting potential more negative) will make it more difficult to initiate an action potential.

Returning momentarily to toilet mechanics, pushing harder on the lever doesn't increase the magnitude of the flush—all successful flushes are of the same magnitude. Similarly, all action potentials are identical, regardless of the strength of the initiating stimulus. Action potentials are thus described as all or nothing. Because the strength of the signal—its *amplitude*—is uniform, the message it carries says, in effect, "Do it," for whatever "it" is. The signal cannot say, "Do a little" or "Do a lot" (that's only for graded potentials). For example, if "it" is activation of a motor neuron, the neuron fires or it doesn't; there is no partial firing. This does not mean, however, that the target cell's *response* is all or nothing. Although a single action potential cannot invoke a graded or variable response, a series of action potentials can. The more frequent the signal, the greater the response (Fig. 4.12B). For action potentials, intensity is encoded in their *frequency*—stronger sensory input (such as stronger touch or more intense smells) will be signaled by very frequent action potentials, while weaker stimuli will be signaled by infrequent action potentials.



(a) Action potential thresholds



(b) Action potential frequency

Figure 4.12. Characteristics of action potentials. A. Graded potentials sufficiently large to reach the threshold will initiate an action potential. **B.** Stimulus intensity is encoded in the frequency of action potentials, not in the size of individual action potentials. The touch of a feather (*left*) might initiate a single action potential, whereas the whack of a hammer (*right*) would initiate many. *If the membrane is depolarized to –50 mV, will an action potential result?*

Case Note

4.13. Remember that adenosine hyperpolarizes neurons, and caffeine antagonizes adenosine. Will caffeine make it easier or harder for neurons to fire action potentials? Explain.

Action Potentials Are Self-Regenerating

Action potentials feed upon themselves like a row of falling dominoes, so that they become self-regenerating and travel to the physical "end of the line," whatever that may be. Theoretically, a signal encoded by action potentials can be transmitted over an infinite distance without any loss in the strength or clarity of the signal, much the way that a very long line of dominoes will continue to fall after the first one is pushed over. This amazing feat is possible because action potentials are continually regenerated as they are transmitted.

Here's how. An action potential in one region of the membrane will depolarize neighboring sections, thereby opening voltage-gated sodium channels. Sodium entry through these channels will depolarize the region further (to the threshold) and propel the action potential, which depolarizes additional membrane, and on and on until the signal reaches the end of the axon or other cell region (Fig. 4.13A). Small neurons, muscle cells, and other excitable cells employ this method of transmission.

Action Potentials Travel Faster via Saltatory Conduction

Some neurons have an even faster method of transmitting an action potential—**saltatory conduction** (Latin *saltare* = "to jump from place to place"). As mentioned earlier, some axons (called *myelinated axons*) are covered by myelin sheaths. Myelinated axons look a bit like a row of sausages on a stick, the sausage representing the myelin cell's wrapping and the stick representing the axon. The minute collar of unwrapped space between adjacent cells (or sausages), where the axon is "naked," is called a **node of Ranvier** (Figs. 4.7 and 4.13).

The myelin sheath prevents sodium ions from crossing the membrane and causing action potentials. Thus,

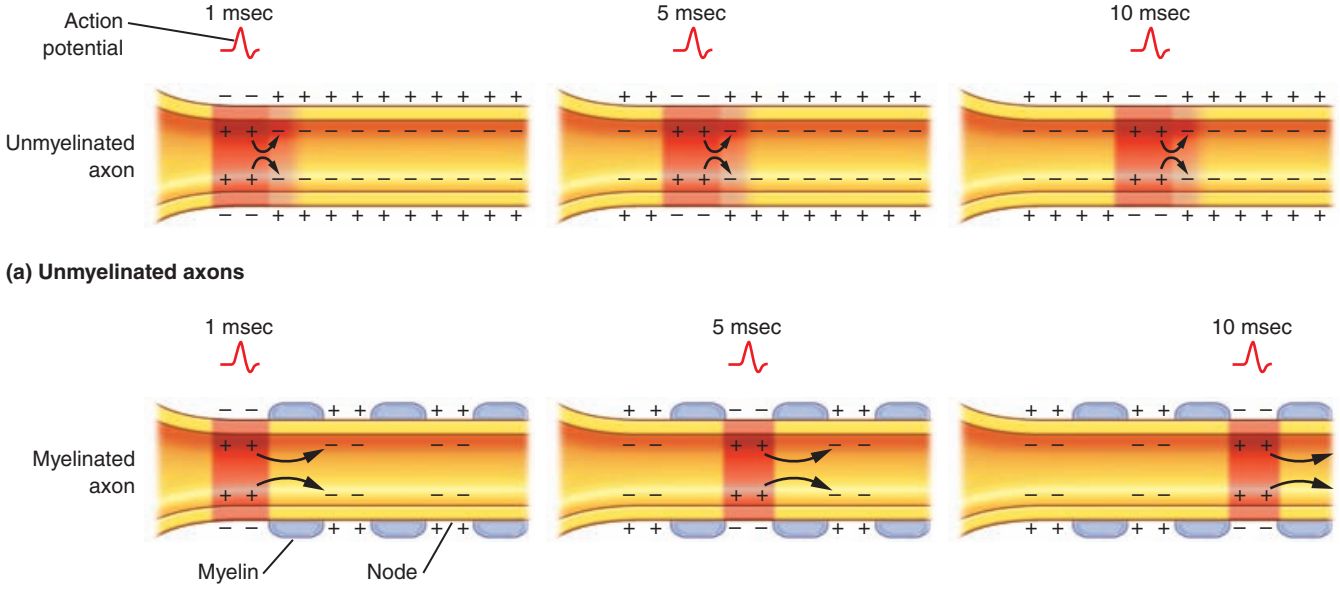


Figure 4.13. Action potential propagation. A. Action potential propagation for unmyelinated neurons. The dark red region of the membrane indicates where voltage-gated sodium channels are open and the action potential is occurring. At 1 ms, the action potential has started to move down the axon; at 5 ms, the action potential has moved a short distance; and at 10 ms, the action potential has moved slightly farther. **B.** Action potential propagation for myelinated neurons. The position of the action potential is indicated at 1 ms, 5 ms, and 10 ms. Note that the action potential has moved much farther in the myelinated neuron than in the unmyelinated neuron at 5 and 10 ms. In real neurons, the signal travels up to 200 times faster in a myelinated neuron than in an unmyelinated neuron. *Which channels are open in the depolarized (red) regions of the membrane?*

action potentials occur only in the exposed collars of membrane located at the nodes. The electrical disturbance caused by an action potential at one node jumps to the next node at the speed of light, as a spark of static electricity jumps between your finger and a metal object. At the node, it initiates a new action potential, which travels the very short distance down the exposed collar of axon before jumping again.

As shown in Figure 4.13B, this process is much faster than action potential conduction in unmyelinated nerve membranes. An action potential takes a certain amount of time—say, 5 milliseconds (ms)—to complete, whereas depolarization can spread from node to node virtually instantaneously. In the unmyelinated axon of Figure 4.13A, the action potential in the far left portion of the neuron is completed by 5 ms. It invokes a second action potential in the adjacent membrane section, consuming an additional 5 ms, which subsequently invokes a third action potential in the next membrane region. The action potential has traveled only a short distance down the axon during 15 ms. During this same time period, three action potentials have also occurred in the myelinated neuron (part B). However, since action potentials occur only at the nodes, the signal has spread much further down the axon.

Diseases in which the myelin sheath is damaged or missing, such as multiple sclerosis, result in abnormally slow impulse transmission in nerves supplying skeletal muscles. Muscle movements are correspondingly slow, or do not occur at all.

Synapses Transmit Electrical Signals between Cells

Remember that chemical signals use blood and extracellular fluid as their medium and travel through body fluids to affect other cells near and far. However, what happens to an electrical signal when it reaches the end of the cell? The answer is that it reaches a **synapse,** a site where an electrical signal passes from one cell to the next. The cell that is transmitting the signal is called the *presynaptic cell*; the receiver is the *postsynaptic cell.* Examples of synapses include the junction between a neuron and a skeletal muscle cell, between two cardiac muscle cells, or between two spinal cord neurons. In each case, the electrical signal must bridge the physical gap between the two cells.

Two options exist for a signal to traverse this physical barrier. *Electrical synapses* bridge the gap directly by *gap junctions*. *Chemical synapses,* conversely, use a chemical messenger—a *neurotransmitter*—to convey the message between the two cells.

Electrical Synapses Convey Signals through Gap Junctions

Gap junctions (↩ Chapter 3) are watery protein tunnels that permit ions and other small chemicals to pass from one cell to another. In an electrical synapse, ions pass from the presynaptic to the postsynaptic cell through the gap junction to propagate the action potential (Fig. 4.14). That is to say, the postsynaptic cell depolarizes when positive ions flow from the presynaptic cell to the postsynaptic cell, and negative ions flow in the opposite direction.

Electrical synapses are quick and efficient because the action potential spreads between neighboring cells as easily as from one membrane region to another. Electrical synapses link muscle cells in the heart, uterus, and intestines, so that all of the neighboring cells are activated and contract at essentially the same time. They also occur between some brain regions, so that all of the neurons fire at the same time.

Chemical Synapses Convert Electrical Signals into Chemical Ones

In contrast to cells linked by electrical synapses, cells participating in a chemical synapse are not physically linked; instead, they are separated by an exceedingly thin *synaptic cleft*. Electrical signals cannot directly cross this cleft; instead, neurotransmitters carry the signal across the synaptic cleft between the presynaptic and postsynaptic cells (Fig. 4.15). Familiar examples of neurotransmitters include acetylcholine, norepinephrine, and glutamate. See ↪ Chapter 8 for more information.

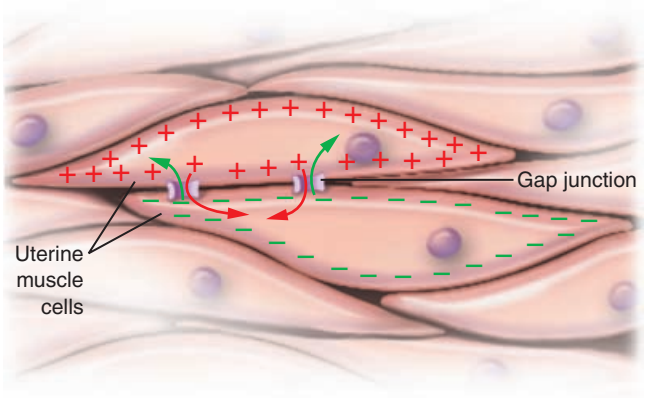


Figure 4.14. Electrical synapse. Gap junctions between two adjacent muscle cells in the uterus enable the action potential to pass directly from the upper cell into the lower cell. *Where is the action potential occurring—in the top cell or the bottom cell?*

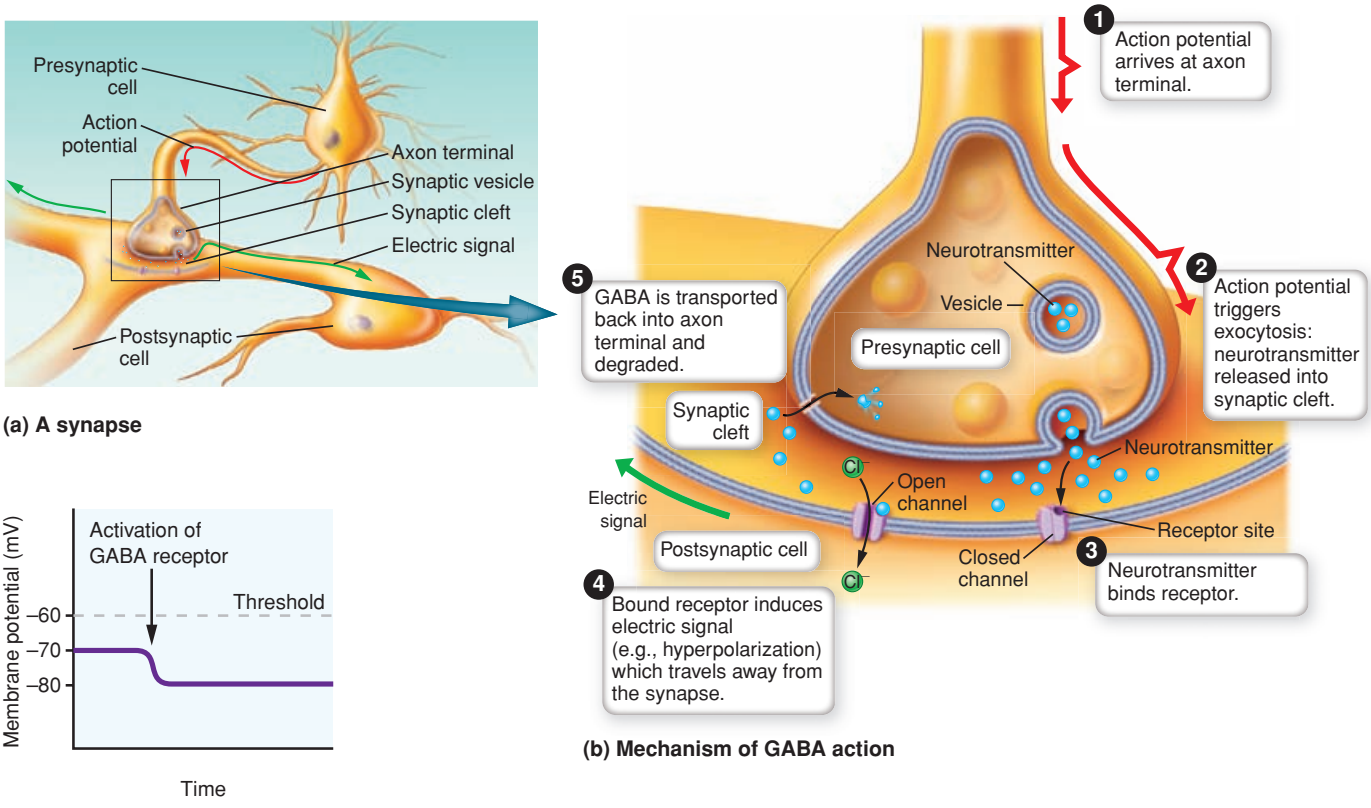


Figure 4.15. Chemical synapses. A. The parts of a chemical synapse. **B.** The events at a chemical synapse. This example uses GABA, which is an inhibitory neurotransmitter that hyperpolarizes the postsynaptic cell. **C.** Changes in membrane potential resulting from the activation of a GABA receptor. *Is the fluid in the synaptic cleft extracellular or intracellular fluid?*

Chemical synapses carry signals between two neurons or between a neuron and a target cell—usually a gland cell or a muscle cell. The end of the presynaptic neuron, the **axon terminal,** contains many **synaptic vesicles,** which are packed with neurotransmitters. On the other side of the synaptic cleft, the cell membrane of the postsynaptic cell contains numerous protein receptors that bind the neurotransmitter. The signal is transmitted from the presynaptic to the postsynaptic cell as follows (Fig. 4.15B):

1. The action potential arrives at the axon terminal.
2. The action potential induces exocytosis of synaptic vesicles; that is, the synaptic vesicles fuse with the cell membrane and the neurotransmitter molecules are released into the synaptic cleft. The neurotransmitter diffuses across the synaptic cleft.
3. The neurotransmitter binds receptors on the postsynaptic cell membrane.
4. The bound receptors induce a change in the postsynaptic cell (usually a graded potential, either hyperpolarizing or depolarizing). The signal travels away from the synapse.
5. The neurotransmitter is rapidly removed from the synaptic cleft (into neurons or other nearby cells) and recycled or destroyed.

Upon binding with a receptor in the postsynaptic membrane, most neurotransmitters induce an electrical signal, either directly or via a second messenger (such as cAMP). For instance, Figure 4.15B illustrates the particular chloride channel receptor for the neurotransmitter GABA (a modified amino acid). The chloride channel is open only when GABA is bound to the channel receptor. Chloride is more concentrated outside the cell, so the open channels permit negative chloride ions to enter the cell, making the cell's interior even more negative than before. In this condition the cell membrane is hyperpolarized (Fig. 4.15C) and the resting membrane potential is farther away from the threshold required to produce an action potential. The cell is inhibited and it will take a greater depolarization to get this cell to fire. It's as if the GABA were saying, "Relax! Stop firing so many action potentials!" GABA acts at many points in the brain to slow down brain cell activity (see the Clinical Snapshot for more information).

Many other neurotransmitters—acetylcholine, norepinephrine, and glutamate, for example—exert the opposite effect from GABA on the postsynaptic cell. These so-called *excitatory* neurotransmitters depolarize the postsynaptic cell, increasing the chance that it will fire an action potential.

Case Note

4.14. One action of adenosine is to reduce the release of excitatory neurotransmitters such as glutamate and norepinephrine. Do you think it binds the presynaptic cell or the postsynaptic cell to exert this effect?

If the postsynaptic cell is not a neuron, the signal will alter the cell's activity in a different way. For example, if the postsynaptic cell is a gland cell, the signal could stimulate or inhibit hormone secretion from a gland. If it's a muscle cell, it could stimulate or inhibit contraction.

4.9. Calcium ions are positively charged. Assuming that they can cross the membrane, will they be pulled into or pushed out of a resting cell?

4.10. If sodium moves down its concentration gradient, is it moving into the cell or out of the cell?

4.11. Name three types of ion channels.

4.12. Which sort of change—depolarization or hyperpolarization—is occurring if the membrane potential changes from –70 mV to –40 mV?

4.13. Does sodium entry into the cell result in depolarization or hyperpolarization?

4.14. In a single action potential, which event occurs first—depolarization or repolarization?

4.15. Which type of electrical signal can vary in amplitude: action potentials or graded potentials?

4.16. Which neuron would transmit a signal faster—a myelinated neuron or an unmyelinated neuron?

4.17. Which type of synapse relies on a physical bridge between the cells—chemical or electrical?

4.18. What is the space between the presynaptic and postsynaptic cells called?

Case Discussion

Caffeine and Communication: The Case of Andy M.

Let's return to our case.

Recall that Andy, who drinks five or six big (16-oz) mugs of coffee a day, has just learned that during the past few days his mother-in-law has been brewing only decaffeinated coffee. As a result, Andy has been experiencing headaches, fatigue, and an inability to concentrate. So, what, exactly, does caffeine do that explains this case?

To understand the effect of caffeine we must first understand adenosine. As illustrated in Figure 4.16, adenosine is an endogenous chemical signal (ligand) that binds to a family of G-protein–coupled receptors. Depending on the receptor type, adenosine can either inhibit (type 1 receptors) or stimulate (type 2 receptors) cAMP production.

1. Adenosine modifies electrical signaling in the brain by acting synapses (Fig. 4.16, left). It binds to type 1 receptors on the presynaptic cell and reduces the release of neurotransmitters such as acetylcholine, dopamine, and glutamate. These are excitatory neurotransmitters that increase the chance that the postsynaptic cell will fire action potentials. It also binds to type I receptors on the postsynaptic cell to increase potassium influx, resulting in hyperpolarization. The resting membrane potential is now farther away from the threshold, so the neuron fires fewer action potentials. The net result of these two actions is less synaptic transmission, less communication, and decreased arousal. Moreover, dopamine normally stimulates a feeling of well-being and enhances locomotor abilities. Thus, *adenosine induces drowsiness, reduces the natural "high" associated with feelings of well-being, and interferes with locomotion.*
2. Adenosine binds type 2 receptors on blood vessel cells everywhere, including the brain (Fig. 4.16, right side). When adenosine binds to these receptors, the muscle cells controlling vessel diameter relax and the vessel widens. Thus, *adenosine induces blood vessels to swell and become congested with blood.*

In short, adenosine promotes rest and relaxation. Caffeine is an exogenous chemical antagonist that binds to adenosine receptors in brain neurons and blood vessels and blocks adenosine from exerting its normal

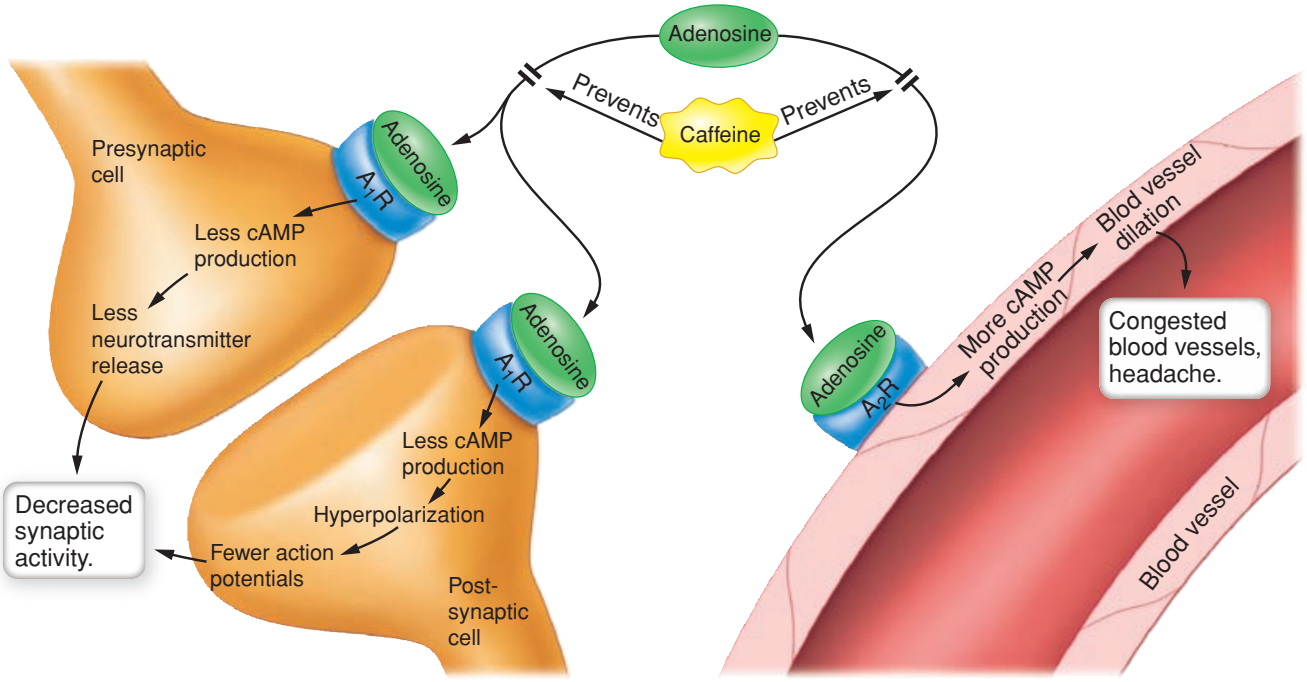


Figure 4.16. Caffeine withdrawal and Andy M. Adenosine binds to type 1 receptors (A1R) on neurons, resulting in decreased synaptic activity. Adenosine binds to type 2 receptors (A2R) on blood vessels, resulting in blood vessel widening. Caffeine antagonizes both effects. *How does adenosine decrease synaptic activity at the postsynaptic cell?*

functions. By interfering with adenosine binding, caffeine invokes the opposite of rest and relaxation. It enhances synaptic transmission and constricts blood vessels, resulting in increased alertness, increased locomotor ability, blood vessel constriction, and feelings of well-being.

Over time, Andy's body compensated for the presence of caffeine by increasing the number and sensitivity of adenosine receptors. This adaptation limits the effect of caffeine in people who drink a lot of it. Thus, in people like Andy, if caffeine is suddenly withdrawn, the brain goes into adenosine overload because all of those extra receptors are free to soak up adenosine.

So, when Andy's brain was suddenly deprived of its adenosine antagonist (caffeine) and went into adenosine overload, here is what he experienced:

- Brain alertness signals declined dramatically: Andy felt tired and was unable to concentrate normally.
- Blood vessels dilated excessively, increasing intracranial pressure: Andy got a pulsing headache.
- Dopamine synthesis fell sharply: Andy lost his sense of well-being, felt fatigued and clumsy, and couldn't compete well in an athletic event.

In the absence of caffeine, it takes about 5 to 7 days for adenosine receptor levels to return to normal and for caffeine withdrawal symptoms to cease. If you want to reduce your dependence on caffeine but avoid the unpleasant symptoms Andy experienced, reduce your intake gradually. And remember, coffee isn't the only thing containing caffeine—many sodas are loaded with it, and it is present in many other foods and drinks, including chocolate and tea.

Case Notes

4.15. By blocking adenosine's action, how does caffeine alter the resting membrane potential of the postsynaptic cell?

4.16. By blocking adenosine's action, how does caffeine alter the release of excitatory neurotransmitters?

4.17. By blocking adenosine's action, how does caffeine change the size of blood vessels and the amount of blood flow in the brain?

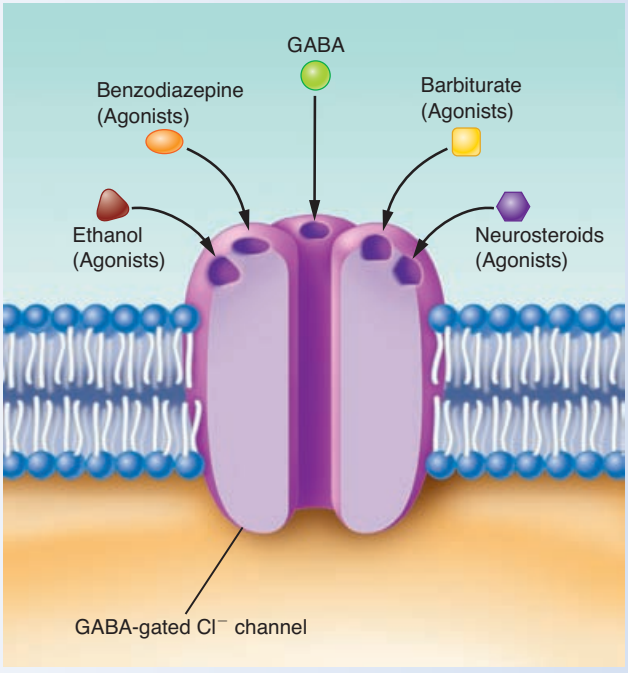
CLINICAL SNAPSHOT

Relaxing with GABA

Brain cell activity—that is, action potentials racing this way and that from cell to cell—is a good thing; it is the most important attribute of life. Epinephrine is an important stimulant of brain activity. It works by increasing the firing rate of action potentials in certain neurons. Excess brain cell activity is, however, not so desirable. For example, cocaine stimulates the activity of certain brain cells whose action potentials are normally associated with feelings of well-being and happiness, and overstimulation produces an unnatural euphoria. Overstimulation of other cells can provoke seizures; and stimulation of still other cells can induce panic or heightened anxiety.

Given that the whole of human physiology is a delicate balance of homeostatic forces, it should come as no surprise that, just as the body synthesizes neurotransmitters like epinephrine that *stimulate* action potentials, it also synthesizes neurotransmitters that *inhibit* action potentials. These inhibitory neurotransmitters include gamma aminobutyric acid, or **GABA**. A chemical ligand, GABA exerts its influence by binding to a certain type of GABA receptor (there are several) that controls flow of chloride (Cl^-) ions into brain neurons. When GABA binds to this particular type of GABA receptor, negatively charged ions flood into the cell and change the resting membrane potential from, say, –70 mV to –80 mV. This increased negativity makes the cell harder to stimulate. Thus, the ability of the cell to initiate action potentials is reduced and the cell generates fewer of them. So, if the cell sends signals that create anxiety (a normal emotion in certain situations, such as just before an important exam), GABA is going to suppress cell activity—and anxiety goes away.

The GABA receptor also has binding sites for other substances, including ethanol (found in alcoholic beverages), barbiturates, and benzodiazepines (members of a group of drugs commonly called tranquilizers). These substances cannot open the chloride channel themselves, but they augment the ability of GABA to keep the channel open; they are receptor agonists. Thus, alcohol, barbiturates, and benzodiazepines work (at least in part) by increasing the movement of chloride through GABA receptors and thereby reducing the activity (i.e., action potentials) in certain neurons. For example, if you are anxious about something, you can be sure that somewhere in your brain neurons are firing action potentials to cause the feeling. So how about a little extra intracellular chloride (courtesy of GABA) to make those bad feelings go away?



The GABA receptor. The chloride channel opens when GABA binds to it, resulting in chloride influx and hyperpolarization. Thus, GABA makes it harder for neurons to fire action potentials. GABA agonists (such as ethanol) increase this effect.

The existence of such binding sites raises an important question: Why did they evolve? Surely it was not for Neanderthals to stop at a Stone Age pharmacy for a quick pick-me-up to relieve the anxiety caused by saber-toothed tigers lurking in the bush. The most likely explanation is that they exist to bind to naturally occurring (endogenous) relaxers. The parts of the GABA receptor that bind pharmaceutical tranquilizers, for instance, also bind several substances synthesized in the brain—neurosteroids and cannabinoids. Cannabinoids, incidentally, are also the active ingredient in marijuana, which has a well-known relaxing effect. Naturally made relaxers like endocannabinoids and neurosteroids protect neurons from excessive stimulation.

Word Parts		
Latin/Greek Word Parts	**English Equivalents**	**Examples**
Ant-/i-	Against	Antagonist: works against the agonist
-crine	Secretion	Endocrine: secreted within the body
De-	Remove	Depolarize: remove the polarization
Endo-	Within	Endogenous: generated inside the body
Exo-	Outside	Exogenous: generated outside the body
Neur-/o-	Neuron, nerve, nervous tissue	Neurocrine: secreted from a neuron
Para-	Beside	Paracrine: secreted to cells beside
Post-	After	Postsynaptic cell: cell after the synapse
Pre-	Before	Presynaptic cell: cell before the synapse
Re-	Again, back	Repolarize: polarize again

Chapter Challenge

CHAPTER RECALL

1. **Chemical signals that travel through the bloodstream are described as**
   a. paracrine factors.
   b. histamines.
   c. neurotransmitters.
   d. hormones.

2. **The response of a cell to a particular hormone depends on**
   a. the quantity of ligand.
   b. the quantity of receptors.
   c. the type of receptors.
   d. all of the above.

3. **Hormone receptors in the nucleus**
   a. bind hydrophilic ligands.
   b. interact directly with DNA.
   c. activate second messengers.
   d. usually bind protein hormones.

4. **Ligand-gated ion channels**
   a. are found in the nucleus.
   b. bind hydrophilic ligands.
   c. interact directly with DNA.
   d. usually bind steroid hormones.

5. **An example of a second messenger is**
   a. a steroid hormone.
   b. cAMP.
   c. a graded potential.
   d. a protein hormone.

6. **G proteins are**
   a. components of enzyme-linked receptors.
   b. components of ligand-gated ion channels.
   c. linked to the intracellular portion of some receptors.
   d. none of the above.

7. **Receptor agonists**
   a. can amplify the signal of the endogenous ligand.
   b. can activate receptors in the absence of the endogenous ligand.
   c. can bind a different part of the receptor than the endogenous ligand.
   d. all of the above.

8. **The part of the neuron that usually receives signals is the**
   a. cell body.
   b. axon.
   c. dendrite.
   d. myelin sheath.

9. **In living cells,**
   a. sodium is more concentrated inside the cell and potassium is more concentrated outside the cell.
   b. concentration gradients for sodium and potassium change significantly because of action potentials.
   c. potassium is more concentrated inside the cell, and sodium is more concentrated outside the cell.
   d. the sodium–potassium ATPase pump transports sodium into the cell and potassium out of the cell.

10. **If the inside of the cell contains an excess of negative charges,**
    a. the membrane potential will be positive.
    b. positive ions will be drawn into the cell (if they can cross the membrane).
    c. negative ions will be drawn into the cell (if they can cross the membrane).
    d. there is no electrical gradient.

11. **Graded pot entials**
    a. do not change the membrane potential.
    b. do not appreciably change the concentration gradients for sodium and potassium.
    c. are used to transmit signals over large distances.
    d. none of the above.

12. **The depolarizing phase of the action potential results from**
    a. potassium ions entering the cell.
    b. potassium ions exiting the cell.
    c. sodium ions entering the cell.
    d. sodium ions exiting the cell.

13. **Subthreshold graded potentials**
    a. sometimes invoke an action potential.
    b. always invoke an action potential.
    c. never invoke an action potential.
    d. hyperpolarize the membrane.

14. ***Saltatory conduction* refers to**
    a. the transmission of graded potentials down a dendrite.
    b. the transmission of action potentials down myelinated axons.
    c. the transmission of action potentials down unmyelinated neurons.
    d. the "jumping" of an electrical signal from one cell to another.

15. **Which of the following components would not be found in an electrical synapse?**
    a. neurotransmitter
    b. presynaptic cell
    c. postsynaptic cell
    d. action potential

16. **Neurotransmitter receptors**
    a. are always ligand-gated ion channels.
    b. can induce depolarization or hyperpolarization of the postsynaptic cell.
    c. are floating in the synaptic cleft.
    d. are found in the nucleus of the postsynaptic cell.

CONCEPTUAL UNDERSTANDING

17. **List the steps involved when glucagon stimulates glucose production. Identify which steps amplify the signal.**

18. **Compare and contrast G protein–linked receptors and enzyme-linked receptors.**

19. **List the steps involved in an action potential. For each step, describe:**
    a. which channels are open and which are closed.
    b. which ions are moving and in which direction.

APPLICATION

20. For each of the following examples, identify the type of signal (paracrine factor, hormone, or neurotransmitter).

a. A brain cell signaling a stomach cell to secrete acid.

b. A stomach cell signaling the neighboring cell to secrete acid.

21. In a cell with a membrane potential of +50 mV, which of the following statements would be true? Explain why or why not for each statement.

a. There would be a relative excess of negative charges outside the cell.

b. Sodium ions would be drawn out of the cell down the electrical gradient.

c. The sodium concentration gradient would be reversed, and sodium would be more abundant inside than outside the cell.

22. During the action potential, sodium entry through voltage-gated sodium channels depolarizes the cell membrane, which opens more voltage-gated sodium channels. Is this an example of negative feedback or positive feedback? Explain why, using a diagram similar to Figure 1.7 (for negative feedback) or Figure 1.9 (for positive feedback).

23. A hormone called *growth hormone* stimulates growth. What are some of the different ways that the body can increase growth induced by this particular chemical signal?

You can find the answers to these questions on the student Web site at **http://thepoint.lww.com/McConnellandHull**