CONCEPT 5.6

The plasma membrane plays a key role in most cell signaling

In a multicellular organism, whether a human being or an oak tree, it is cell-to-cell communication that allows the trillions of cells of the body to coordinate their activities, and the communication process usually involves the cells' plasma membranes. In fact, communication between cells is also essential for many unicellular organisms, including prokaryotes. However, here we will focus on cell signaling in animals and plants. We'll describe the main mechanisms by which cells receive, process, and respond to chemical signals sent from other cells.

Local and Long-Distance Signaling

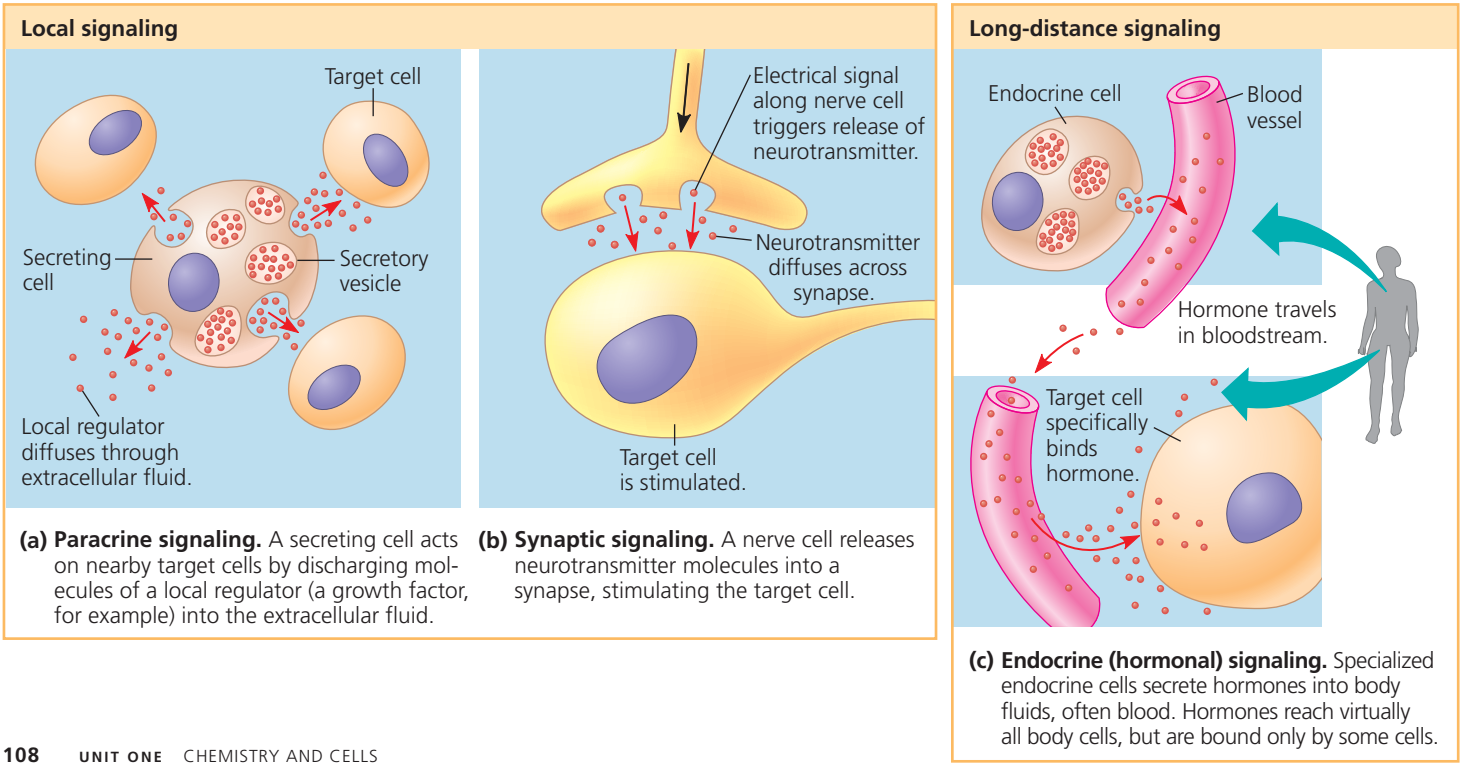
The chemical messages sent out from cells are targeted for other cells that may or may not be immediately adjacent. As discussed earlier in this chapter and in Chapter 4, eukaryotic cells may communicate by direct contact, a type of local signaling. Both animals and plants have cell junctions that, where present, directly connect the cytoplasms of adjacent cells; in animals, these are gap junctions (see Figure 4.27), and in plants, plasmodesmata (see Figure 4.25). In these cases, signaling substances dissolved in the cytosol can pass freely between adjacent cells. Also, animal cells may communicate via direct contact between membrane-bound cell-surface molecules in cell-cell recognition (see Figure 5.7d). This sort of local signaling is important in embryonic development and in the immune response.

In many other cases of local signaling, the signaling cell secretes messenger molecules. Some of these, which are called **local regulators**, travel only short distances. One class of local regulators in animals, *growth factors*, consists of compounds that stimulate nearby target cells to grow and divide. Numerous cells can simultaneously receive and respond to the molecules of growth factor produced by a nearby cell. This type of local signaling in animals is called *paracrine signaling* **(Figure 5.19a)**. (Local signaling in plants is discussed in Chapter 31.)

A more specialized type of local signaling called *synaptic signaling* occurs in the animal nervous system **(Figure 5.19b)**. An electrical signal moving along a nerve cell triggers the secretion of neurotransmitter molecules carrying a chemical signal. These molecules diffuse across the synapse, the narrow space between the nerve cell and its target cell (often another nerve cell), triggering a response in the target cell.

Both animals and plants use chemicals called **hormones** for long-distance signaling. In hormonal signaling in animals, also known as *endocrine signaling*, specialized cells release hormone molecules, which travel via the circulatory system to other parts of the body, where they reach target cells that can recognize and respond to the hormones **(Figure 5.19c)**. Most plant hormones (see Chapter 31) reach distant targets via plant vascular tissues (xylem or phloem; see Chapter 28), but some travel through the air as a gas. Hormones vary widely in molecular size and type, as do local regulators. For instance, the plant hormone ethylene, a gas that promotes fruit ripening, is a hydrocarbon of only six atoms (C_2H_4). In contrast, the mammalian hormone insulin, which regulates sugar levels in the blood, is a protein with thousands of atoms.

▼ **Figure 5.19 Local and long-distance cell signaling by secreted molecules in animals.** In both local and long-distance signaling, only specific target cells that can recognize a given signaling molecule will respond to it.



(a) Paracrine signaling. A secreting cell acts on nearby target cells by discharging molecules of a local regulator (a growth factor, for example) into the extracellular fluid.

(b) Synaptic signaling. A nerve cell releases neurotransmitter molecules into a synapse, stimulating the target cell.

(c) Endocrine (hormonal) signaling. Specialized endocrine cells secrete hormones into body fluids, often blood. Hormones reach virtually all body cells, but are bound only by some cells.

The transmission of an electrical signal along the length of a single nerve cell can also be long-distance signaling, because nerve cells can be quite long. Jumping from cell to cell via synapses, a nerve signal can quickly travel great distances—from your brain to your big toe, for example. (This type of long-distance signaling is covered in detail in Chapter 37.)

What happens when a cell encounters a secreted signaling molecule? We will now consider this question, beginning with a bit of historical background.

The Three Stages of Cell Signaling: *A Preview*

Our current understanding of how chemical messengers act on cells had its origins in the pioneering work of the American Earl W. Sutherland about a half-century ago. He was investigating how the animal hormone epinephrine (also called adrenaline) stimulates the breakdown of the storage polysaccharide glycogen within liver cells and skeletal muscle cells. (This breakdown yields glucose molecules for use by the body.)

Sutherland's research team discovered that epinephrine never actually enters the glycogen-containing cells, and this discovery provided two insights. First, epinephrine does not interact directly with the enzyme responsible for glycogen breakdown; an intermediate step or series of steps must be occurring inside the cell. Second, the plasma membrane must somehow be involved in transmitting the signal. Sutherland's research suggested that the process going on at the receiving end of a cell-to-cell message can be divided into three stages: reception, transduction, and response **(Figure 5.20)**: **1 Reception** is the target cell's detection of a signaling molecule coming from outside the cell. A chemical signal is "detected" when the signaling molecule binds to a receptor protein located at the cell's surface or, in some cases, inside the cell. **2 Transduction** is a step or series of steps that converts the signal to a form that can bring about a specific cellular response. Transduction usually requires a sequence of changes in a series of different molecules—a **signal transduction pathway**. The molecules in the pathway are often called relay molecules. **3** In the third stage of cell signaling, the transduced signal finally triggers a specific cellular **response**. The response may be almost any imaginable cellular activity—such as catalysis by an enzyme (for example, the enzyme that breaks down glycogen), rearrangement of the cytoskeleton, or activation of specific genes in the nucleus. The cell-signaling process helps ensure that crucial activities like these occur in the right cells, at the right time, and in proper coordination with the activities of other cells of the organism. We'll now explore the mechanisms of cell signaling in more detail.

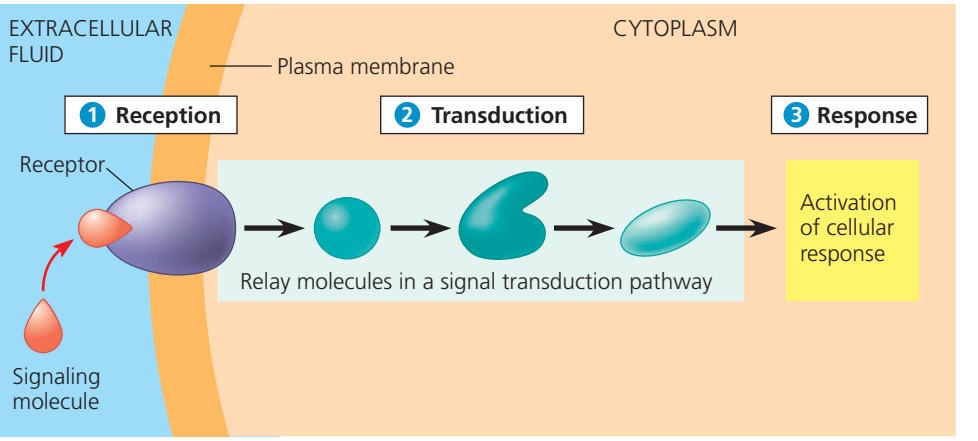
Reception, the Binding of a Signaling Molecule to a Receptor Protein

A radio station broadcasts its signal indiscriminately, but it can be picked up only by radios tuned to the right wavelength; reception of the signal depends on the receiver. Similarly, in the case of epinephrine, the hormone encounters many types of cells as it circulates in the blood, but only certain target cells detect and react to the hormone molecule. A receptor protein on or in the target cell allows the cell to detect the signal and respond to it. The signaling molecule is complementary in shape to a specific site on the receptor and attaches there, like a key in a lock. The signaling molecule behaves as a **ligand**, a molecule that specifically binds to another molecule, often a larger one. (LDLs, mentioned in Concept 5.5, act as ligands when they bind to their receptors, as do the molecules that bind to enzymes; see Figure 3.16.) Ligand binding generally causes a receptor protein to undergo a change in shape. For many receptors, this shape change directly activates the receptor, enabling it to interact with other cellular molecules.

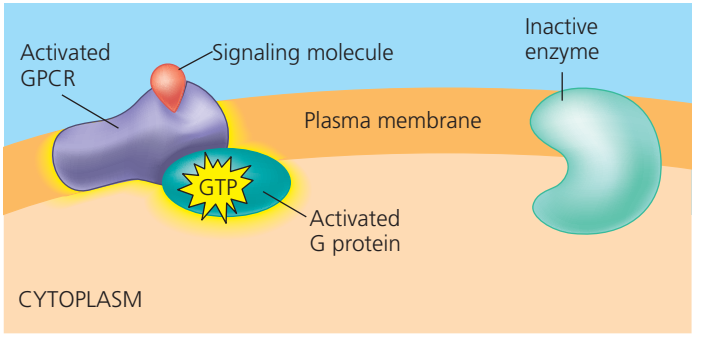
Most signal receptors are plasma membrane proteins. Their ligands are water-soluble and generally too large to pass freely through the plasma membrane. Other signal receptors, however, are located inside the cell. We discuss both of these types next.

Receptors in the Plasma Membrane

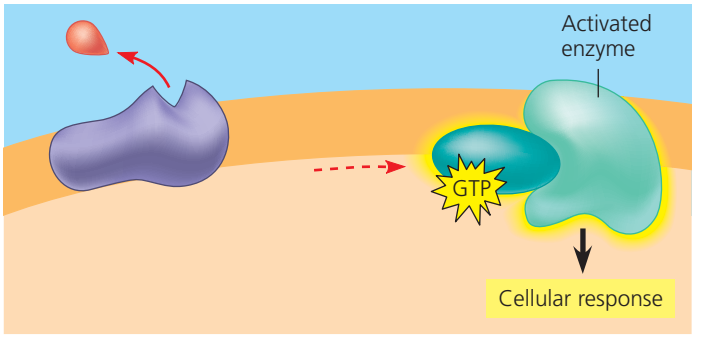
Most water-soluble signaling molecules bind to specific sites on receptor proteins that span the cell's plasma membrane. Such a transmembrane receptor transmits information from the extracellular environment to the inside of the cell by changing shape when a specific ligand binds to it. We can see how transmembrane receptors work by looking at two major types: G protein-coupled receptors and ligand-gated ion channels.



▲ Figure 5.20 Overview of cell signaling. From the perspective of the cell receiving the message, cell signaling can be divided into three stages: signal reception, signal transduction, and cellular response. When reception occurs at the plasma membrane, as shown here, the transduction stage is usually a pathway of several steps, with each relay molecule in the pathway bringing about a change in the next molecule. The final molecule in the pathway triggers the cell's response. The three stages are explained in more detail in the text.



1 When the appropriate signaling molecule binds to the extracellular side of the receptor, the receptor is activated and changes shape. Its cytoplasmic side then binds and activates a G protein. The activated G protein carries a GTP molecule.



2 The activated G protein leaves the receptor, diffuses along the membrane, and then binds to an enzyme, altering the enzyme's shape and activity. Once activated, the enzyme can trigger the next step leading to a cellular response. Binding of signaling molecules is reversible.The activating change in the GPCR, as well as the changes in the G protein and enzyme, are only temporary; these molecules soon become available for reuse.

▲ Figure 5.21 A G protein-coupled receptor (GPCR) in action.

Figure 5.21 shows the functioning of a **G protein-coupled receptor (GPCR)**. A GPCR is a cell-surface transmembrane receptor that works with the help of a **G protein**, a protein that binds the energy-rich molecule GTP, which is similar to ATP (see end of Concept 3.1). Many signaling molecules, including epinephrine, many other hormones, and neurotransmitters, use GPCRs. These receptors vary in the binding sites for their signaling molecules and for different types of G proteins inside the cell. Nevertheless, all GPCRs and many G proteins are remarkably similar in structure, suggesting that these signaling systems evolved very early in the history of life.

The nearly 1,000 GPCRs examined to date make up the largest family of cell-surface receptors in mammals. GPCR pathways are extremely diverse in their functions, which include roles in embryonic development and the senses of smell and taste. They are also involved in many human diseases. For example, cholera, pertussis (whooping cough), and botulism are caused by bacterial toxins that interfere with G protein function. Up to 60% of all medicines used today exert their effects by influencing G protein pathways.

A **ligand-gated ion channel** is a membrane receptor that has a region that can act as a "gate" for ions when the receptor assumes a certain shape **(Figure 5.22)**. When a signaling molecule binds as a ligand to the receptor protein, the gate opens or closes, allowing or blocking the diffusion of specific ions, such as Na^+ or Ca^{2+}, through a channel in the protein. Like other membrane receptors, these proteins bind the ligand at a specific site on their extracellular side.

Ligand-gated ion channels are very important in the nervous system. For example, the neurotransmitter molecules released at a synapse between two nerve cells (see Figure 5.19b) bind as ligands to ion channels on the receiving cell, causing the channels to open. The diffusion of ions through the open channels may trigger an electrical signal that propagates down the length of the receiving cell. (You'll learn more about ion channels in Chapter 37.)

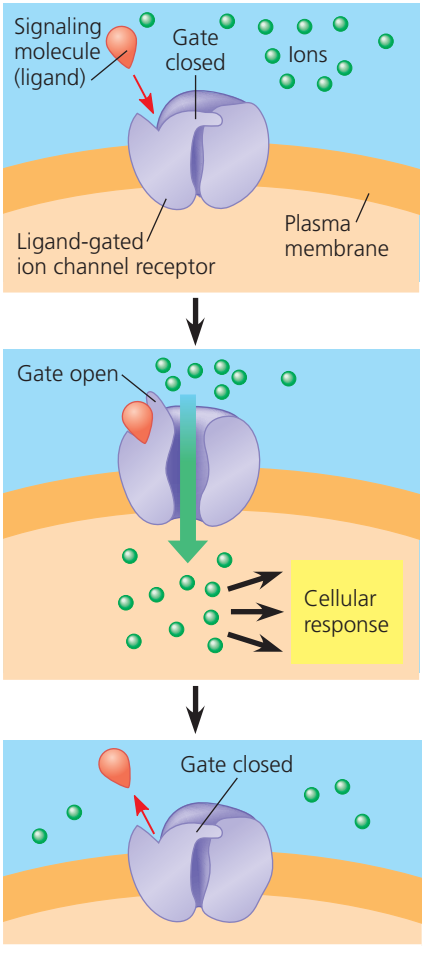
Intracellular Receptors

Intracellular receptor proteins are found in either the cytoplasm or nucleus of target cells. To reach such a receptor, a chemical messenger passes through the target cell's plasma membrane. A

1 Here we show a ligand-gated ion channel receptor in which the gate remains closed until a ligand binds to the receptor.

2 When the ligand binds to the receptor and the gate opens, specific ions can flow through the channel and rapidly change the concentration of that particular ion inside the cell. This change may directly affect the activity of the cell in some way.

3 When the ligand dissociates from this receptor, the gate closes and ions no longer enter the cell.



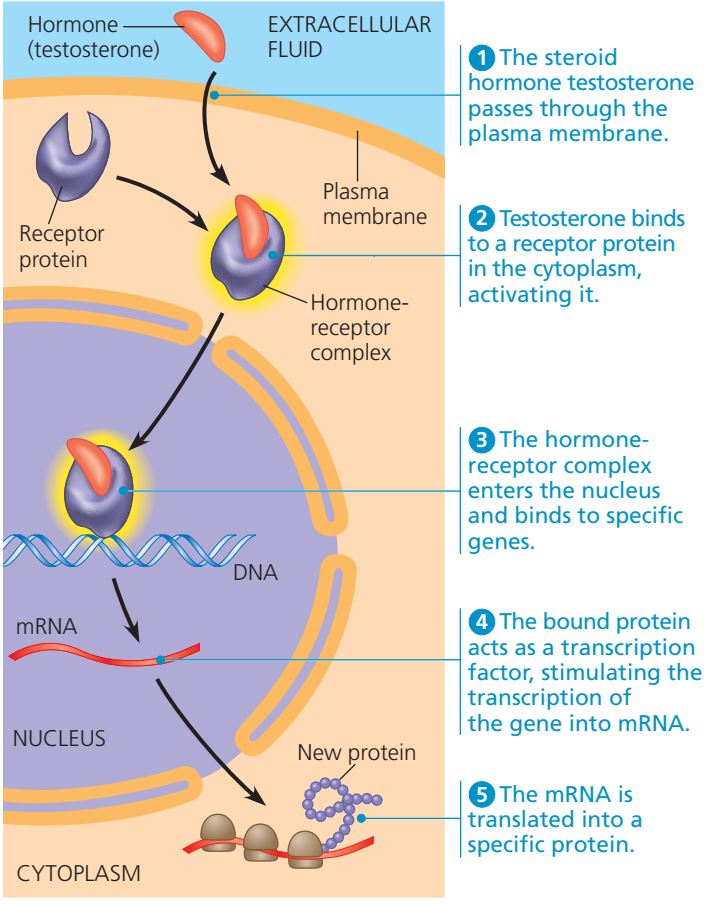
▲ Figure 5.22 Ion channel receptor. This is a ligand-gated ion channel, a type of receptor protein that regulates the passage of specific ions across the membrane. Whether the channel is open or closed depends on whether a specific ligand is bound to the protein.

number of important signaling molecules can do this because they are hydrophobic enough to cross the hydrophobic interior of the membrane. Such hydrophobic chemical messengers include the steroid hormones and thyroid hormones of animals. In both animals and plants, another chemical signaling molecule with an intracellular receptor is nitric oxide (NO), a gas; its very small, hydrophobic molecules can easily pass between the membrane phospholipids.

The behavior of testosterone is representative of steroid hormones. In males, the hormone is secreted by cells of the testes. It then travels through the blood and enters cells all over the body. However, only cells that contain receptors for testosterone respond. In these cells, the hormone binds to the receptor protein, activating it **(Figure 5.23)**. With the hormone attached, the active form of the receptor protein then enters the nucleus and turns on specific genes that control male sex characteristics.

How does the activated hormone-receptor complex turn on genes? Recall that the genes in a cell's DNA function by being transcribed and processed into messenger RNA (mRNA), which leaves the nucleus and is translated into a specific protein by ribosomes in the cytoplasm. Special proteins called *transcription factors* control which genes are turned on—that is, which genes are transcribed into mRNA—in a particular cell at a particular time. The testosterone receptor, when activated, acts as a transcription factor that turns on specific genes.

By acting as a transcription factor, the testosterone receptor itself carries out the complete transduction of the signal. Most other intracellular receptors function in the same way, although many of them, such as the thyroid hormone receptor, are already in the nucleus before the signaling molecule reaches them. Interestingly, many of these intracellular receptor proteins are structurally similar, suggesting an evolutionary kinship.



▲ Figure 5.23 Steroid hormone interacting with an intracellular receptor.

? *Why is a cell-surface receptor protein not required for this steroid hormone to enter the cell?*

Transduction by Cascades of Molecular Interactions

When receptors for signaling molecules are plasma membrane proteins, like most of those we have discussed, the transduction stage of cell signaling is usually a multistep pathway. Steps often include activation of proteins by addition or removal of phosphate groups or release of other small molecules or ions that act as messengers. One benefit of multiple steps is the possibility of greatly amplifying a signal. If some of the molecules in a pathway transmit the signal to numerous molecules at the next step in the series, the result can be a large number of activated molecules at the end of the pathway. Moreover, multistep pathways provide more opportunities for coordination and regulation than simpler systems do.

The binding of a specific signaling molecule to a receptor in the plasma membrane triggers the first step in the chain of molecular interactions—the signal transduction pathway—that leads to a particular response within the cell. Like falling dominoes, the signal-activated receptor activates another molecule, which activates yet another molecule, and so on, until the protein that produces the final cellular response is activated. The molecules that relay a signal from receptor to response, which we call relay molecules in this book, are often proteins. The interaction of proteins is a major theme of cell signaling.

Keep in mind that the original signaling molecule is not physically passed along a signaling pathway; in most cases, it never even enters the cell. When we say that the signal is relayed along a pathway, we mean that certain information is passed on. At each step, the signal is transduced into a different form, commonly via a shape change in a protein. Very often, the shape change is brought about by phosphorylation, the addition of phosphate groups to a protein (see Figure 3.5).

Protein Phosphorylation and Dephosphorylation

The phosphorylation of proteins and its reverse, dephosphorylation, are a widespread cellular mechanism for regulating protein activity. An enzyme that transfers phosphate groups from ATP to a protein is known as a **protein kinase**. Such enzymes are widely involved in signaling pathways in animals, plants, and fungi.

Many of the relay molecules in signal transduction pathways are protein kinases, and they often act on other protein kinases in the pathway. A hypothetical pathway containing

two different protein kinases that form a short "phosphorylation cascade" is depicted in **Figure 5.24**. The sequence shown is similar to many known pathways, although typically three protein kinases are involved. The signal is transmitted by a cascade of protein phosphorylations, each bringing with it a shape change. Each such shape change results from the interaction of the newly added phosphate groups with charged or polar amino acids (see Figure 3.17). The addition of phosphate groups often changes the form of a protein from inactive to active.

The importance of protein kinases can hardly be overstated. About 2% of our own genes are thought to code for protein kinases. A single cell may have hundreds of different kinds, each specific for a different protein. Together, they probably regulate a large proportion of the thousands of proteins in a cell. Among these are most of the proteins that, in turn, regulate cell division. Abnormal activity of such a kinase can cause abnormal cell growth and contribute to the development of cancer.

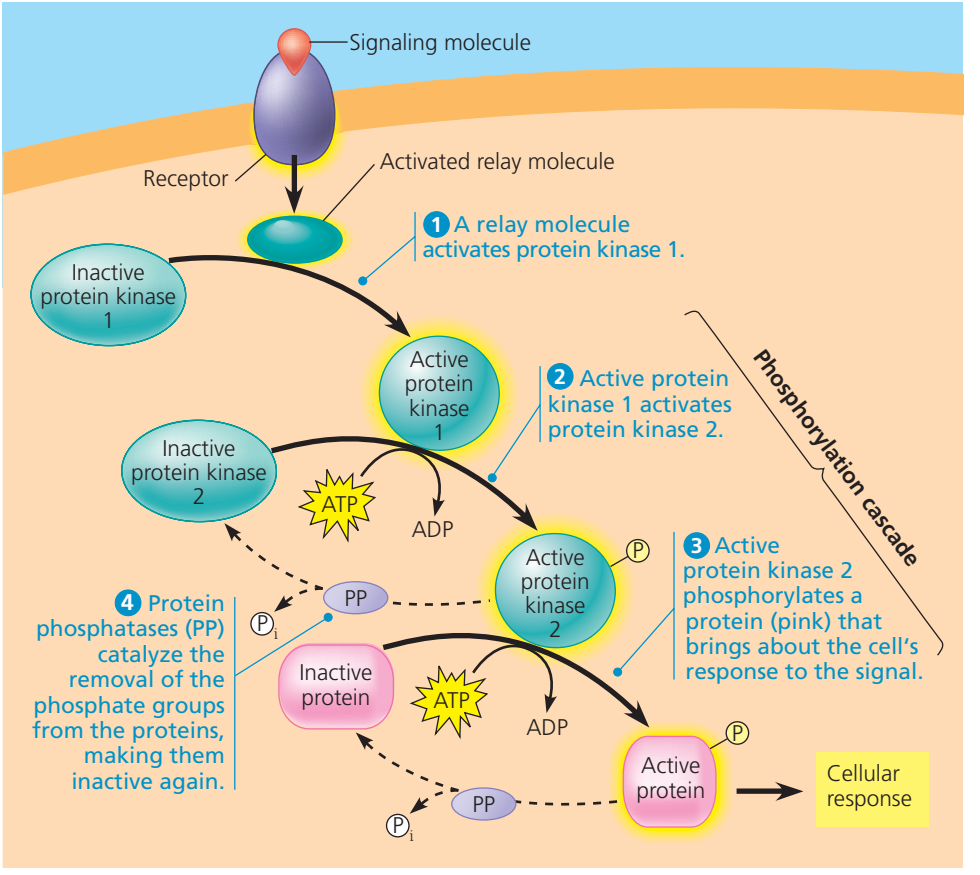
Equally important in the phosphorylation cascade are the **protein phosphatases**, enzymes that can rapidly remove phosphate groups from proteins, a process called dephosphorylation. By dephosphorylating and thus inactivating protein kinases, phosphatases provide the mechanism for turning off the signal transduction pathway when the initial signal is no longer present. Phosphatases also make the protein kinases available for reuse, enabling the cell to respond again to an extracellular signal. A phosphorylation-dephosphorylation system acts as a molecular switch in the cell, turning an activity on or off, or up or down, as required. At any given moment, the activity of a protein regulated by phosphorylation depends on the balance in the cell between active kinase molecules and active phosphatase molecules.

Small Molecules and Ions as Second Messengers

Not all components of signal transduction pathways are proteins. Many signaling pathways also involve small, nonprotein, water-soluble molecules or ions called **second messengers**. (The pathway's "first messenger" is considered to be the extracellular signaling molecule that binds to the membrane receptor.) Because they are small, second messengers can readily spread throughout the cell by diffusion. The two most common second messengers are cyclic AMP and calcium ions, Ca^{2+}. Here we'll limit our discussion to cyclic AMP.

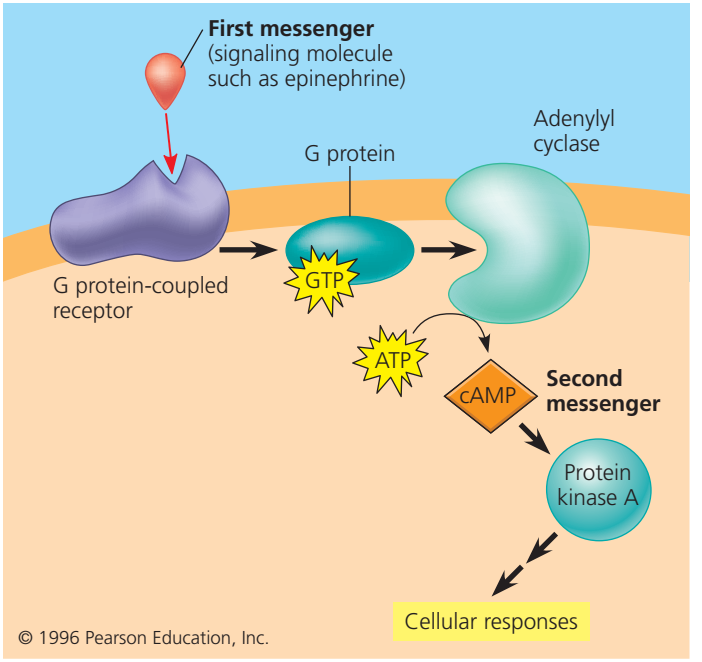
In his research on epinephrine, Earl Sutherland discovered that the binding of epinephrine to the plasma membrane of a liver cell elevates the cytosolic concentration of **cyclic AMP (cAMP)** (cyclic adenosine monophosphate). The binding of epinephrine to a specific receptor protein leads to activation of adenylyl cyclase, an enzyme embedded in the plasma membrane that converts ATP to cAMP **(Figure 5.25)**. Each molecule of adenylyl cyclase can catalyze the synthesis of many molecules of cAMP. In this way, the normal cellular concentration of cAMP can be boosted 20-fold in a matter of seconds. The cAMP broadcasts the signal to the cytoplasm. It does not persist for long in the absence of the hormone because another enzyme converts cAMP to AMP. Another surge of epinephrine is needed to boost the cytosolic concentration of cAMP again.

Subsequent research has revealed that epinephrine is only one of many hormones and other signaling molecules that trigger the formation of cAMP. It has also brought to light the other components of many cAMP pathways, including G proteins, G protein-coupled receptors, and protein kinases. The immediate effect of cAMP is usually the activation of a protein kinase called *protein kinase A*. The activated protein kinase A then phosphorylates various other proteins.



▲ Figure 5.24 A phosphorylation cascade. In a phosphorylation cascade, a series of different molecules in a pathway are phosphorylated in turn, each molecule adding a phosphate group to the next one in line. Dephosphorylation returns the molecule to its inactive form.

? *Which protein is responsible for activation of protein kinase 2?*



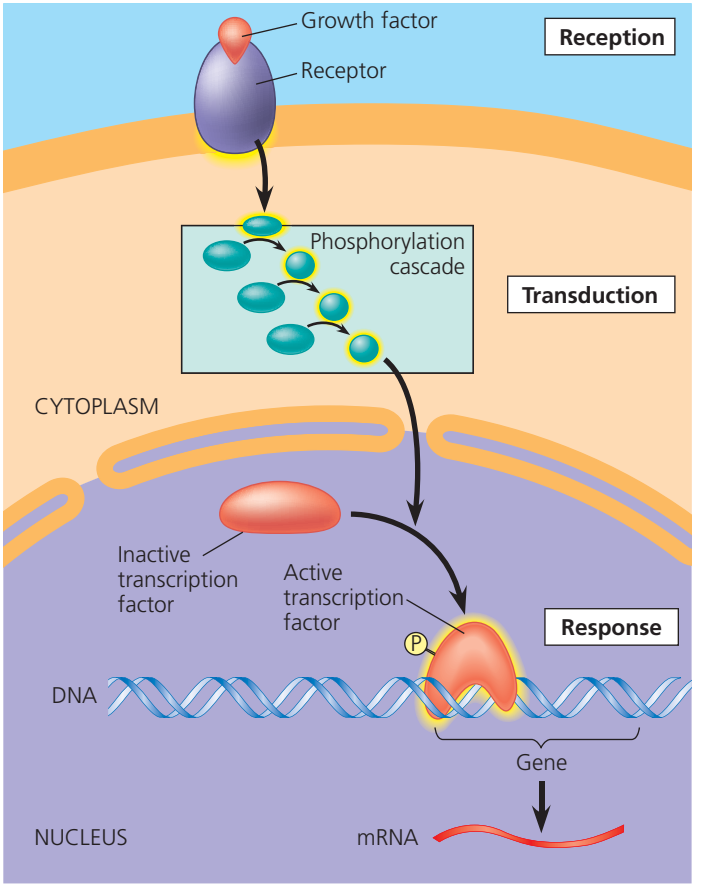
▲ Figure 5.25 cAMP as a second messenger in a G protein signaling pathway. The first messenger activates a G protein-coupled receptor, which activates a specific G protein. In turn, the G protein activates adenylyl cyclase, which catalyzes the conversion of ATP to cAMP. The cAMP then acts as a second messenger and activates another protein, usually protein kinase A, leading to cellular responses.

Response: Regulation of Transcription or Cytoplasmic Activities

What is the nature of the final step in a signaling pathway—the *response* to an external signal? Ultimately, a signal transduction pathway leads to the regulation of one or more cellular activities. The response may occur in the nucleus of the cell or in the cytoplasm.

Many signaling pathways ultimately regulate protein synthesis, usually by turning specific genes on or off in the nucleus. Like an activated steroid receptor (see Figure 5.23), the final activated molecule in a signaling pathway may function as a transcription factor. **Figure 5.26** shows an example in which a signaling pathway activates a transcription factor that turns a gene on: The response to the growth factor signal is transcription, the synthesis of mRNA, which will be translated in the cytoplasm into a specific protein. In other cases, the transcription factor might regulate a gene by turning it off. Often a transcription factor regulates several different genes.

Sometimes a signaling pathway may regulate the *activity* of a protein rather than its synthesis, directly affecting a cellular activity outside the nucleus. For example, a signal may cause the opening or closing of an ion channel in the plasma membrane or a change in cell metabolism. As we have discussed, the response of cells to the hormone epinephrine helps regulate cellular energy metabolism by affecting the activity of an enzyme: The final step in the signaling pathway that begins with epinephrine binding activates the enzyme that catalyzes the breakdown of glycogen.



▲ Figure 5.26 Nuclear response to a signal: the activation of a specific gene by a growth factor. This diagram shows a typical signaling pathway that leads to the regulation of gene activity in the cell nucleus. The initial signaling molecule, a local regulator called a growth factor, triggers a phosphorylation cascade. (The ATP molecules and phosphate groups are not shown.) Once phosphorylated, the last kinase in the sequence enters the nucleus and activates a transcription factor, which stimulates transcription of a specific gene. The resulting mRNA then directs the synthesis of a particular protein in the cytoplasm.

The Evolution of Cell Signaling

EVOLUTION In studying how cells signal to each other and how they interpret the signals they receive, biologists have discovered some universal mechanisms of cellular regulation, additional evidence for the evolutionary relatedness of all life. The same small set of cell-signaling mechanisms shows up again and again in diverse species, in biological processes ranging from hormone action to embryonic development to cancer. Scientists think that early versions of today's cell-signaling mechanisms evolved well before the first multicellular creatures appeared on Earth.

CONCEPT CHECK 5.6

1. Explain how nerve cells provide examples of both local and long-distance signaling.
2. When a signal transduction pathway involves a phosphorylation cascade, what turns off the cell's response?
3. **WHAT IF?** How can a target cell's response to a single hormone molecule result in a response that affects a million other molecules?

For suggested answers, see Appendix A.