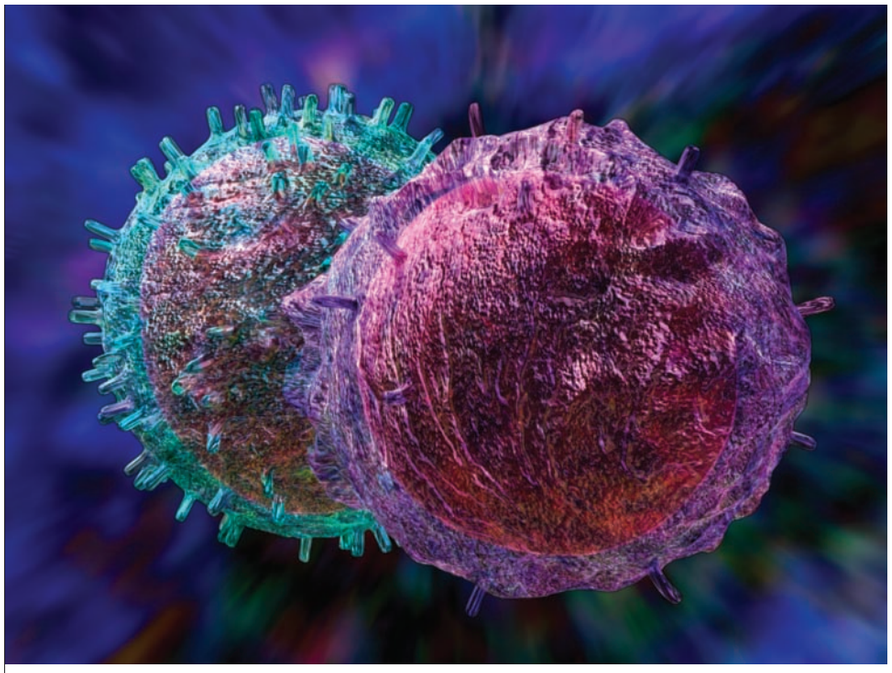


A B cell and a T cell communicating by direct contact in the human immune system (computer image). Cell communication coordinates the cellular defense against disease.

7 Cell Communication

Study Plan

7.1 Cell Communication: An Overview

7.2 Characteristics of Cell Communication Systems with Surface Receptors

Peptide hormones and neurotransmitters are extracellular signal molecules recognized by surface receptors in animals

Surface receptors are integral membrane glycoproteins

The signaling molecule bound by a surface receptor triggers response pathways within the cell

7.3 Surface Receptors with Built-In Protein Kinase Activity: Receptor Tyrosine Kinases

7.4 G-Protein–Coupled Receptors

G proteins are key molecular switches in second-messenger pathways

Two major G-protein–coupled receptor–response pathways involve different second messengers

7.5 Pathways Triggered by Internal Receptors: Steroid Hormone Receptors

Steroid hormones have widely different effects that depend on relatively small chemical differences

The response of a cell to steroid hormones depends on its internal receptors and the genes they activate

7.6 Integration of Cell Communication Pathways

Why It Matters

Hundreds of aircraft, ranging from small private planes to huge passenger jets, approach and leave airports in Southern California. In addition to the large terminals in Los Angeles and San Diego, dozens of smaller airports are located in the vicinity. The aircraft that approach these airports are traveling at various speeds, entering from all points of the compass, and flying at different altitudes. Airplanes are also leaving the same airports with routes distributed over the same directions, speeds, and altitudes. A wrong turn, ascent, or descent by any one of the hundreds of planes could lead to disaster. Yet, disasters are extremely rare. How are all these aircraft kept separate, and routed to and from their airports safely and efficiently? The answer lies in a highly organized system of controllers, signals, and receivers.

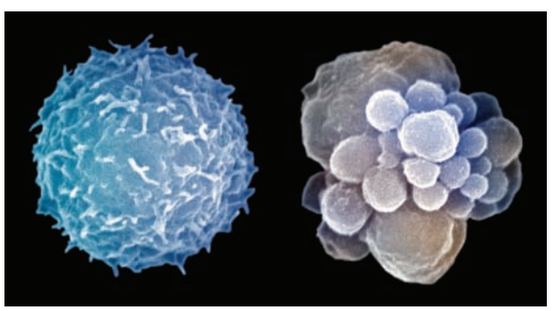
As the aircraft thread their way along the various approach and departure routes, they follow directions issued by air traffic controllers. Each aircraft has a radio receiver tuned to a frequency that has been assigned by the controllers. By speaking on a transmitter tuned to the frequency assigned to Piper 4879Z, a slow-moving two-seater headed for Montgomery Field near San Diego, and using its identifier

("seven niner Zulu"), controllers can keep this plane's path separate from that of "five-two heavy," a passenger jet, leaving the main San Diego air terminal. The flow of directing signals, followed individually by each aircraft in the vicinity, keeps the traffic unscrambled and moving safely.

The principle of the air control system is nothing new. An equivalent system of signals and tuned receivers evolved hundreds of millions of years ago, as one of the developments that made multicellular life possible. Within a multicellular organism, the activities of individual cells are directed by molecular signals, such as hormones, that are released by controlling cells. Although the controlling cells release many signals, each receiving cell has receptors that are "tuned" to recognize only one or a few of the many signal molecules that circulate in its vicinity; other signals pass by without effect because the cell has no receptors for them.

When a cell binds a signal molecule, it modifies its internal activities in accordance with the signal, coordinating its functions with the activities of other cells of the organism. The responses of the receiving cell may include changes in gene activity, protein synthesis, transport of molecules across the plasma membrane, metabolic reactions, secretion, movement, and division. In some cases, the response to a signal may be "suicide"—that is, the programmed death of the receiving cell **(Figure 7.1).** As part of its response, a cell may itself become a controller and thus contribute to the organizational network by releasing signal molecules that modify the activity of other cell types. The total network of signals and responses allows multicellular organisms to grow, develop, reproduce, and compensate for environmental changes in an internally coordinated fashion.

This chapter describes the major pathways that form parts of the cell communication system based on both surface and internal receptors, including the links that tie the different response pathways into fully integrated networks. (Communication pathways based on neurons—nerve cells—in animals are discussed in Chapter 37.) This chapter concentrates primarily on the systems working in animals, particularly in mammals, from which most of our knowledge of cell communication has been developed. Nonetheless, the principles of cell communication illustrated by these pathways apply to most multicellular eukaryotic organisms, including plants, protists, and fungi, and to single-celled eukaryotic organisms such as yeast. (The plant communication and control systems are described in more detail in Chapter 35.) This discussion begins with a few fundamental principles that underlie the often complex networks of cell communication.



Visuals Unlimited

Figure 7.1
A normal cell (left) and a cell undergoing apoptosis (programmed cell death) (right).

7.1 Cell Communication: An Overview

Communication is critical for the function and survival of cells that compose a multicellular animal. For example, the ability of cells to communicate with one another in a regulated way is responsible for the controlled growth and development of an animal, as well as the integrated activities of its tissues and organs.

Cells communicate with one another in three ways. Adjacent cells use direct channels of communication. In this rapid means of communication, small molecules and ions exchange directly between the two cytoplasms. In animal cells, the direct channels of communication are *gap junctions,* the specialized connections between the cytoplasms of adjacent cells (see Section 5.5 for a detailed discussion of gap junctions). The main role of gap junctions is to synchronize metabolic activities or electronic signals between cells in a tissue. For example, gap junctions play a key role in the spread of electrical signals from one cell to the next in cardiac muscle. In plant cells, the direct channels of communication are plasmodesmata (see discussion in Section 5.4). Small molecules moving between adjacent cells in plants include plant hormones that regulate growth. In this way, responses triggered by plant hormones are spread to other cells.

Cells also communicate through *specific contact between cells*. Certain cells have molecules on their surfaces that allow them to interact directly with other cells. For example, some cells of a mammal's immune system use their surface molecules to recognize particular molecules on the surfaces of invading pathogens that signal them as foreign. The host cell then engulfs the invader. Cells also have on their surfaces *cell adhesion molecules,* integral membrane proteins that allow the cells to bind to other cells or to the extracellular matrix. There are many important functions of cell adhesion molecules, including roles in coordinating tissue and organ formation as an embryo develops.

Finally, cells communicate through *intercellular ("between cell") chemical messengers*. This method is the most common means of cell communication. Here, one cell, the *controlling cell,* synthesizes a specific molecule that acts as a *signaling molecule* to affect the activity of another cell, the *target cell*. The target cell is not in contact with the cell that synthesizes the signaling molecule; rather, it is either nearby or at a distance away in the organism.

Insights from the Molecular Revolution

Surviving Something Bad by Taking a Risk

Programmed cell death, called *apoptosis,* is a natural part of many developmental pathways. For example, human embryos initially have webbed fingers and toes; as the embryo develops, cells in the webbing die and the fingers and toes become fully separated. The instructions for apoptosis are transmitted to the condemned cells by extracellular signal molecules and executed by internal response pathways. The pathways activate enzymes that break down DNA and proteins, fragmenting the chromosomes and destroying vital cellular processes. The cell quickly dies and disintegrates.

Programmed cell death also occurs as the brain develops. Nerve cells that fail to make normal connections are marked for death and cleared from the brain. Apoptosis in neurons occurs via a surface-receptor–regulated signal transduction pathway that activates a death protein called BAD, which sets off the killing reactions. Not all of the marked neurons die; some survive if a signal molecule called *BDNF* (*b*rain-*d*erived *n*eurotrophic *f*actor) is bound by its receptor on the cell surface. Molecular research by Michael E. Greenberg and his coworkers at Harvard Medical School, Cambridge, Massachusetts, has shown how BDNF counteracts the BAD effects and rescues cells marked for death.

Greenberg and his colleagues set out to discover the signal transduction pathway that starts with the BDNF signal and ends with inactivation of BAD. In their experiments, they activated this pathway in nerve cells, then broke open the cells and identified the activated signal transduction pathway proteins. To identify the proteins, they used specific marker proteins that bound to BDNF pathway proteins only if they were in their activated, phosphorylated state.

Using this method, Greenberg and his colleagues discovered that BDNF-triggered cell rescue occurred by activating a Ras G protein, which, in turn, activated a phosphorylation cascade that involved MAP kinases (see Figure 7.13). The phosphorylation cascade activates another protein kinase called Rsk, which then phosphorylates (inactivates) BAD and saves the cell.

To test this hypothesis, Greenberg and coworkers introduced genes that encode MAP kinase, Rsk, and BAD into cultures of a cell type unrelated to neurons. After activation of MAP kinase, the cells were broken open and tested with the antibody that reacts with inactivated BAD. The antibody reacted positively, showing that the death protein was inactivated. However, if a gene encoding a mutant form of Rsk, unable to phosphorylate BAD, was introduced into the cells instead of the normal form, BAD remained unphosphorylated. These results supported their hypothesis. In summary, Greenberg's laboratory had evidence for the following model for the cellular response pathway that saves neurons from apoptosis:

BDNF → receptor → unknown steps → Ras → MAP kinase series → Rsk → inactive BAD

Therefore, preventing BAD things does indeed involve some Rsk.

For example, in response to stress, cells of a mammal's adrenal glands (located on top of the kidneys)—the controlling cells—secrete the hormone epinephrine into the bloodstream. Epinephrine acts on target cells to increase the amount of glucose in the blood.

Cell communication through intercellular chemical messengers is the focus of this chapter, and the epinephrine example is used to illustrate the principles involved. In the 1950s, Earl Sutherland and his research team at Case Western Reserve University, Cleveland, Ohio, began investigating this cell communication system. Sutherland discovered that the hormone epinephrine acts by activating an enzyme, glycogen phosphorylase, which catalyzes the production of glucose from glycogen. That is, the result of the secretion of epinephrine into the blood by adrenal gland cells is an increase in the amount of glucose in the blood. Sutherland's experiments showed that enzyme activation did not involve epinephrine directly but did require an unknown (at the time) cellular substance. Sutherland called the hormone the *first messenger* in the system and the unknown cellular substance the *second messenger.* He proposed that the following chain of reactions was involved: epinephrine (the first messenger) leads to the formation of the second messenger, which activates the enzyme for conversion of glycogen to glucose.

Sutherland's work was the foundation for research that developed our current understanding of this type of cell communication. In brief, a controlling cell releases a signal molecule that causes a response (affects the function) of target cells. Target cells process the signal in the following three sequential steps **(Figure 7.2):**

1. **Reception.** Reception is the binding of a signal molecule with a specific receptor of target cells. Target cells have receptors that are specific for the signal molecule, which distinguishes them from cells that do not respond to the signal molecule. The signals themselves may be polar (charged, hydrophilic) molecules or nonpolar (hydrophobic) molecules, and their receptors are shaped to recognize and bind them specifically **(Figure 7.3).** Receptors for polar signal molecules are embedded in the plasma membrane with a binding site for the signal molecule on the cell surface (see Figures 7.2 and 7.3a). Epinephrine, the first messenger in Sutherland's research, is a peptide hormone, a polar molecule that is recognized by a surface recep-

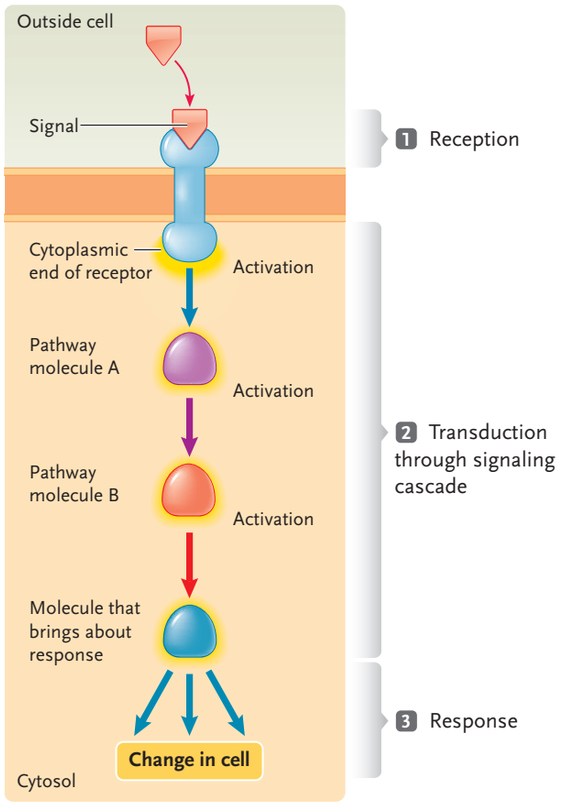


Figure 7.2
The three stages of signal transduction: reception, transduction, and response (shown for a system using a surface receptor).

tor on target cells. Receptors for nonpolar molecules are located within the cell (see Figure 7.3b). In this case, the nonpolar signal molecule passes freely through the plasma membrane and interacts with its receptor within the cell. Steroid hormones such as testosterone and estrogen are examples of nonpolar signal molecules.

2. **Transduction.** Transduction is the process of changing the signal into the form necessary to cause the cellular response (see Figure 7.2). In other words, the binding of a signal molecule to its receptor is not directly responsible for the response. Transduction may occur in a single step, although more often it involves a cascade of reactions that include several different molecules, often referred to as a *signaling cascade*. For example, in Sutherland's work, after epinephrine bound to its surface receptor, the signal was transmitted through the plasma membrane into the cell, where transduction by a signaling cascade activated a molecule that triggered a cellular response. This molecule was Sutherland's *second messenger.*
3. **Response.** In the third and last stage, the transduced signal causes a specific cellular response. That response depends on the signal and the receptors on the target cell. In Sutherland's work, the response was the activation of the enzyme glycogen phosphorylase; the active enzyme catalyzed the conversion of stored glycogen to glucose.

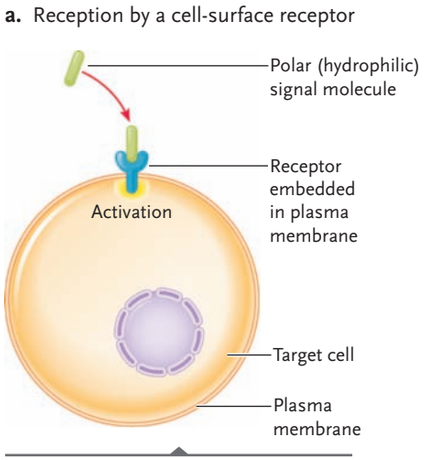


Figure 7.3
Reception **(a)** of a polar (hydrophilic) signal molecule by a receptor on the cell surface and **(b)** of a nonpolar (hydrophobic) signal molecule by a receptor in the cell.

The whole series of events from reception to response is called **signal transduction.** As explained in subsequent sections, signal transduction occurs by different mechanisms, depending on the receptor type. Earl Sutherland was awarded a Nobel Prize in 1971 for his research on the mechanisms of action of hormones.

Study Break

What accounts for the specificity of a cellular response in signal transduction?

7.2 Characteristics of Cell Communication Systems with Surface Receptors

Cell communication systems based on surface receptors have three components: (1) the extracellular signal molecules released by controlling cells, (2) the surface receptors on target cells that receive the signals, and (3) the internal response pathways triggered when receptors bind a signal.

Peptide Hormones and Neurotransmitters Are Extracellular Signal Molecules Recognized by Surface Receptors in Animals

Surface receptors in mammals and other vertebrates recognize and bind two major types of extracellular signal molecules: *peptide hormones* and *neurotransmitters*. These signal molecules are polar, water-soluble molecules that are released by control cells and enter the fluids that surround cells, including the blood circulation in animals with a circulatory system.

Peptide hormones are small proteins with a few to more than 200 amino acids. As a group, they affect all body systems. For example, they regulate sugar levels in blood, pigmentation, and ovulation. A special class of peptide hormones, the *growth factors,* affects cell growth, division, and differentiation.

Cells that release peptide hormones are called gland cells. They may form part of distinct, individual organs such as the thyroid or pituitary gland, or they may be distributed among the cells of organs with other functions, such as the stomach and intestines, heart, brain, liver, and kidneys in humans and other mammals. For example, gland cells scattered through the lining of the human stomach and small intestine secrete peptide hormones that regulate digestive functions. (Peptide hormones and growth factors are discussed in further detail in Chapter 40.)

Neurotransmitters are molecules released by neurons that trigger activity in other neurons or other cells in the body; they include small peptides, individual amino acids or their derivatives, and other chemical substances. Some neurotransmitters affect only one or a few cells in the immediate vicinity of the neuron that releases the signal molecule, whereas others are released into the body circulation and act essentially as hormones, affecting many types of tissues. (Neurotransmitters are discussed in further detail in Chapter 37.)

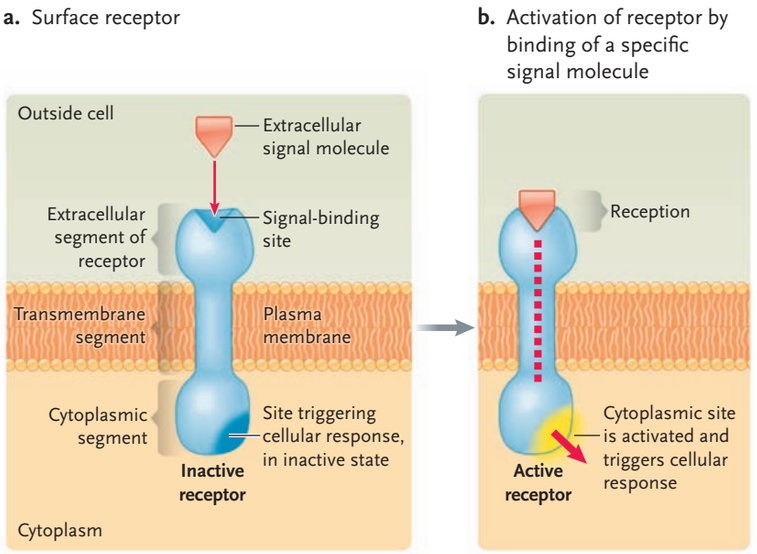
Once signal molecules are released into the body's circulation, they remain for only a certain time. They are either broken down at a steady rate by enzymes in their target cells or in organs such as the liver, or they are excreted by the kidneys. The removal process ensures that the signal molecules are active only as long as controlling cells are secreting them.

Surface Receptors Are Integral Membrane Glycoproteins

The surface receptors that recognize and bind signal molecules are all glycoproteins—proteins with attached carbohydrate chains (see Section 3.5). They are integral membrane proteins that extend entirely through the plasma membrane **(Figure 7.4).** The signal-binding site of the receptor, which extends from the outer membrane surface, is folded in a way that closely fits the signal molecule. The fit, similar to the fit of an enzyme to its substrate, is specific, so a particular receptor binds only one type of signal molecule or a closely related group of signal molecules.

A signal molecule brings about specific changes in cells to which it binds. When a signal molecule binds to a surface receptor, the molecular structure of that receptor is changed so that it transmits the signal through the plasma membrane, activating the cytoplasmic end of the receptor. The activated receptor then initiates the first step in a cascade of molecular events—the signal transduction pathway—that triggers the cellular response (see Figure 7.2).

Animal cells typically have hundreds to thousands of surface receptors that represent many receptor types. Receptors for a specific peptide hormone may number from 500 to as many as 100,000 or more per cell. Different cell types contain distinct combinations of receptors, allowing them to react individually to the



A surface receptor has an extracellular segment with a site that recognizes and binds a particular signal molecule.

When the signal molecule is bound, a conformational change is transmitted through the transmembrane segment that activates a site on the cytoplasmic segment of receptor. The activation triggers a reaction pathway that results in the cellular response.

Figure 7.4
The mechanism by which a surface receptor responds when it binds a signal molecule.

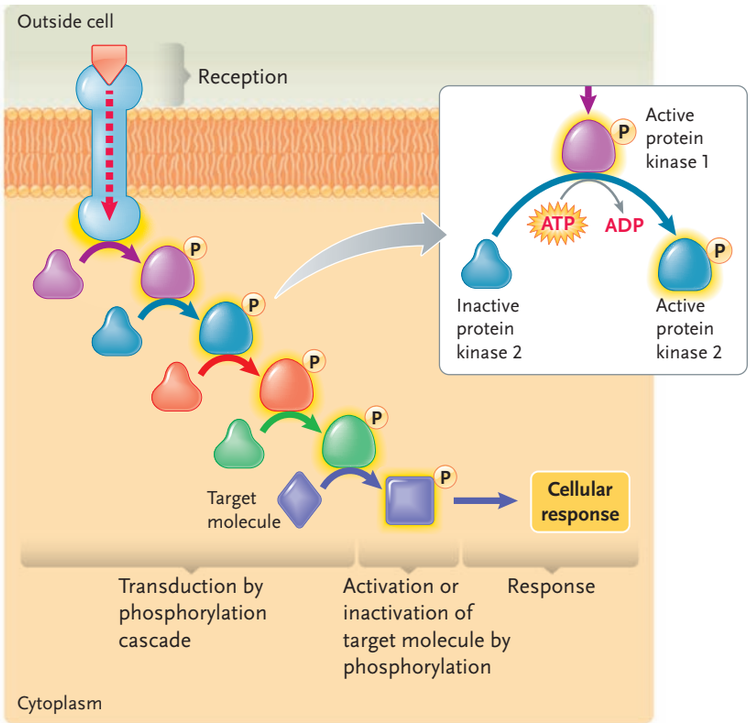


Figure 7.5
Phosphorylation, a key reaction in many signaling pathways.

hormones and growth factors circulating in the extracellular fluids. The combination of surface receptors on particular cell types is not fixed but rather changes as cells develop. Changes also occur as normal cells are transformed into cancer cells.

The Signaling Molecule Bound by a Surface Receptor Triggers Response Pathways within the Cell

Signal transduction pathways triggered by surface receptors are common to all animal cells. At least parts of the pathways are also found in protists, fungi, and plants. In all cases, binding of a signal molecule to a surface receptor is sufficient to trigger the cellular response—the signal molecule does not have to enter the cell. For example, experiments have shown that (1) a signal molecule produces no response if it is injected directly into the cytoplasm, and (2) unrelated molecules that mimic the structure of the normal extracellular signal molecule can trigger a full cellular response as long as they can bind to the recognition site of the receptor.

Another typical characteristic of signal transduction is that the signal is relayed inside the cell by **protein kinases**, enzymes that transfer a phosphate group from ATP to one or more sites on particular proteins (**Figure 7.5;** see Section 4.5). These phosphorylated proteins are known as *target proteins* because they are the proteins modified by signaling pathways. The added phosphate groups either stimulate or inhibit the activity of the target proteins; the change in the target proteins' activity leads directly or indirectly to the cellular response. Often, protein kinases act in a chain, called a *protein kinase cascade,* to pass along a signal. The first kinase catalyzes phosphorylation of the second, which then becomes active and phosphorylates the third kinase, and so on. The proteins that bring about the cellular response may be parts of the reaction pathways, enzymes of other cellular reactions, end targets of the signal transduction pathways (such as transport proteins), or at the most fundamental level, proteins that regulate gene transcription.

The effects of protein kinases in the signal transduction pathways are balanced or reversed by another group of enzymes called **protein phosphatases**, which remove phosphate groups from target proteins. Unlike the protein kinases, which are active only when a surface receptor binds a signal molecule, most of the protein phosphatases are continuously active in cells. By continually removing phosphate groups from target proteins, the protein phosphatases quickly shut off a signal transduction pathway if its signal molecule is no longer bound at the cell surface.

Two scientists, Edwin Krebs and Edmond Fischer at the University of Washington, Seattle, first discovered that protein kinases add phosphate groups to control the activities of key proteins in cells and provided evidence showing that protein phosphatases reverse these phosphorylations. Krebs and Fischer, who began their experiments in the 1950s, received a Nobel Prize in 1992 for their discoveries concerning reversible protein phosphorylation.

A third characteristic of signal transduction pathways involving surface receptors is **amplification**—an increase in the magnitude of each step as a signal transduction pathway proceeds **(Figure 7.6).** Amplification occurs because many of the proteins that carry out individual steps in the pathways, including the protein kinases, are enzymes. Once activated, each enzyme can activate hundreds of proteins, including other enzymes, that enter the next step in the pathway. Generally, the more enzyme-catalyzed steps in a response pathway, the greater the amplification. As a result, just a few extracellular signal molecules binding to their receptors can produce a full internal response. For similar reasons, amplification also occurs for signal transduction pathways that involve internal receptors.

As signal transduction runs its course, the receptors and their bound signal molecules are removed from the cell surface by endocytosis. Both the receptor and its bound signal molecule may be degraded in lysosomes after entering the cell. Alternatively, the

receptors may be separated from the signal molecules and recycled to the cell surface, whereas only the signal molecules are degraded. Thus, surface receptors participate in an extremely lively cellular "conversation" with moment-to-moment shifts in the information.

The next two sections discuss two large families of surface receptors: the receptor tyrosine kinases and the G-protein–coupled receptors.

Study Break

1. What are protein kinases, and how are they involved in signal transduction pathways?
2. How is amplification accomplished in a signal transduction pathway?

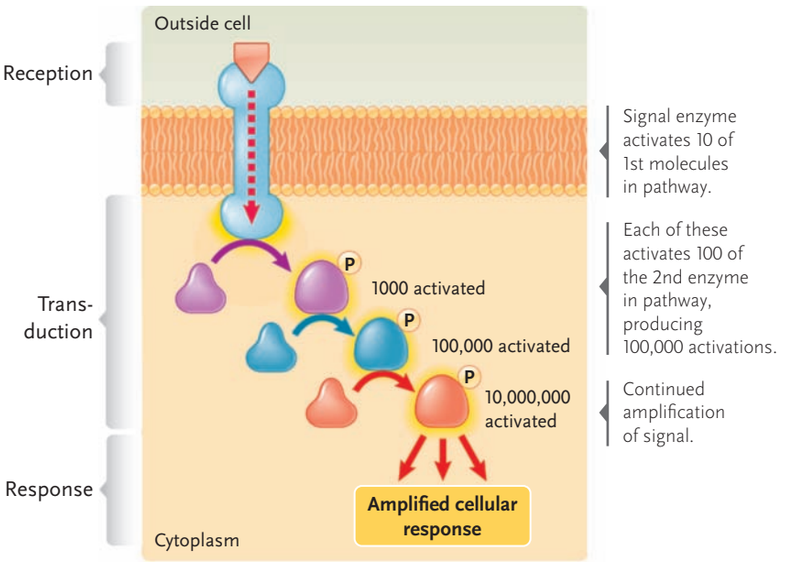


Figure 7.6
Amplification in signal transduction.

7.3 Surface Receptors with Built-in Protein Kinase Activity: Receptor Tyrosine Kinases

In the simplest form of signal transduction, the receptor itself has a protein kinase site at its cytoplasmic end. For this type of receptor, initiation of transduction occurs when two receptor molecules each bind a signal molecule in the reception step, move together in the membrane, and assemble into a pair called a *dimer* **(Figure 7.7).** Dimer assembly activates the receptor's protein kinase, which adds phosphate groups to sites on the receptor itself, a process known as *autophosphorylation*. Target proteins recognize and bind to the phosphorylated sites on the receptor and are then activated by being phosphorylated themselves. The total effect of the phosphorylations is to initiate the signal transduction pathway controlled by the receptor.

In autophosphorylation, the phosphate groups are added to tyrosine amino acids on the receptor. The protein kinase activity of the activated receptors also adds phosphate groups to tyrosines in the amino acid chains of target proteins. Because of this specificity of phosphorylation, the receptors in this group are called **receptor tyrosine kinases**. More than 50 receptor tyrosine kinases are known. In mammals, receptor tyrosine kinases fall into 14 different families, all related to one another in structure and amino acid sequence. Relatives of the mammalian receptors have been discovered in yeasts, *Drosophila,* and higher plants, indicating that the origin of the receptor tyrosine kinases is a single ancestral type that must have appeared before the evolutionary splits that led to the fungi, plants, and animals.

The cellular responses triggered by receptor tyrosine kinases are among the most important processes of animal cells. For example, the receptor tyrosine kinases binding the peptide hormone *insulin,* a regulator of carbohydrate metabolism, triggers diverse cellular responses, including effects on glucose uptake, the rates of many metabolic reactions, and cell growth and division. (The insulin receptor is exceptional because it is permanently in the dimer form.) Other receptor tyrosine kinases bind growth factors, including *epidermal growth factor, platelet-derived growth factor,* and *nerve growth factor,* which are all important peptide hormones that regulate cell growth and division in higher animals.

Hereditary defects in the insulin receptor are responsible for some forms of *diabetes,* a disease in which glucose accumulates in the blood because it cannot be absorbed in sufficient quantity by body cells. The inherited defects may impair the ability of the receptor to bind insulin or block its ability to trigger a cellular response. In either case, the cell is unresponsive to insulin and does not add sufficient glucose transporters to take up glucose. (The role of insulin in glucose metabolism and diabetes is discussed further in Chapter 40.)

Study Break

1. How does a receptor tyrosine kinase become activated?
2. How is the insulin receptor different from general receptor tyrosine kinases?

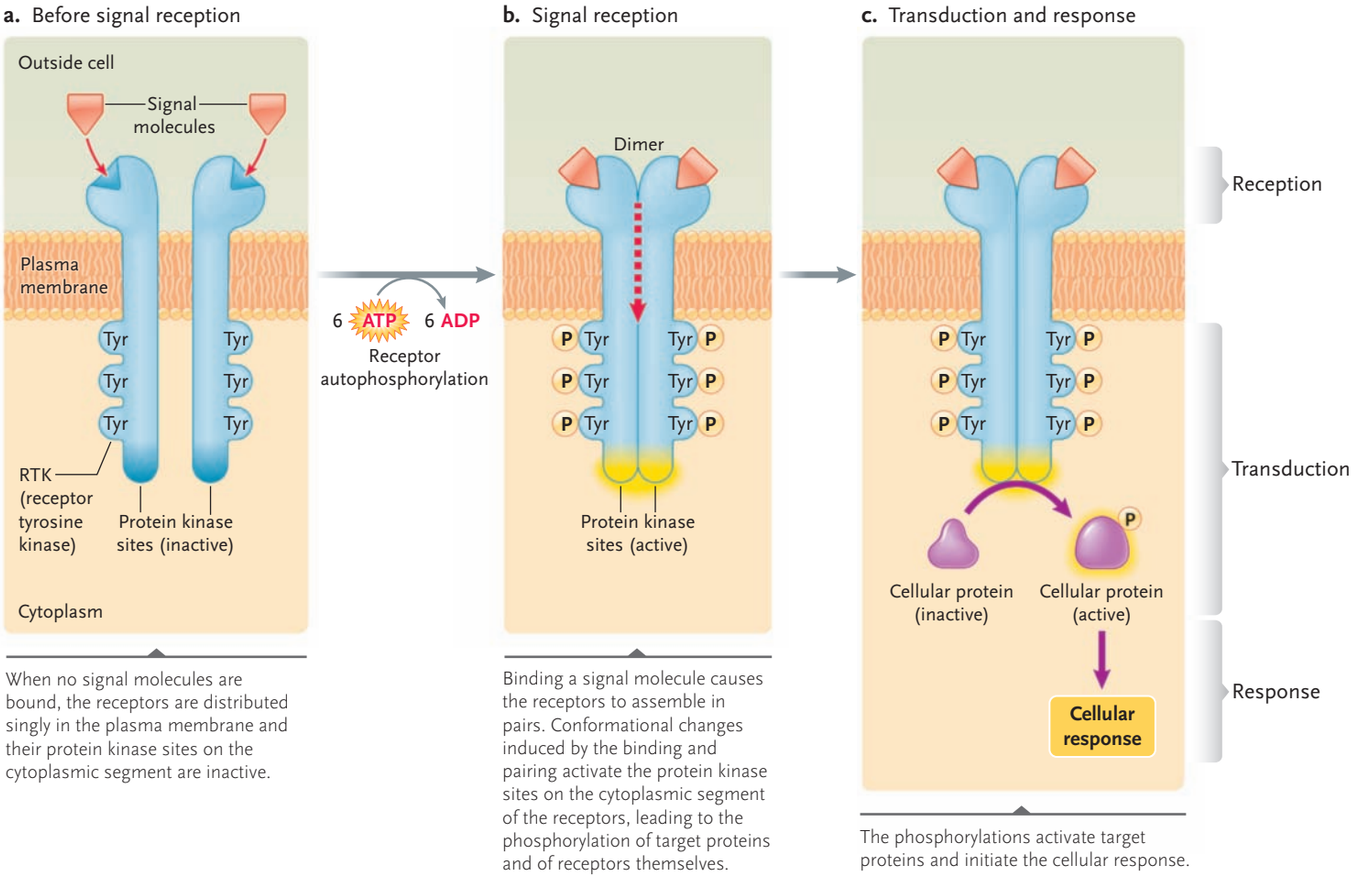


Figure 7.7
The action of receptors with built-in protein kinase activity leading to the phosphorylation of the receptors themselves and the subsequent phosphorylation of target proteins. These receptors are called receptor tyrosine kinases because they add phosphate groups to tyrosines in target proteins. These receptors combine into pairs (dimers) when they bind signal molecules; the assembly into a dimer transmits the signal that activates the cytoplasmic end of the receptors.

7.4 G-Protein–Coupled Receptors

A second large family of surface receptors, known as the **G-protein–coupled receptors**, respond to a signal by activating an inner membrane protein called a G protein, which is closely associated with the cytoplasmic end of the receptor. About 1000 different G-protein–coupled receptors have been identified in mammals; several hundred types are involved in recognizing and binding odor molecules as part of the mammalian sense of smell. Almost all of the receptors of this group are large glycoproteins built up from a single polypeptide chain anchored in the plasma membrane by seven segments of the amino acid chain that zigzag back and forth across the membrane seven times **(Figure 7.8).**

Unlike receptor tyrosine kinases, these receptors lack built-in protein kinase activity.

G Proteins Are Key Molecular Switches in Second-Messenger Pathways

The extracellular signal molecule in signal transduction pathways controlled by G-protein–coupled receptors is termed the **first messenger.** Binding the first messenger by the receptor activates a site on the cytoplasmic end of the receptor (**Figure 7.9,** step 1). The active site of the receptor then activates the G protein next to it by inducing the G protein to bind GTP, replacing the GDP that was bound to it (step 2). The G protein is an example of a *molecular switch* protein because it changes between inactive and active states. If GDP is bound to the G protein, the G protein is inactive, whereas if GTP is bound, it is active. In fact, G proteins are named because they use GDP and GTP to control their activities. The role of a switched-on G protein is to activate a plasma membrane–associated enzyme called the **effector** (step 3). In turn, the effector generates one or

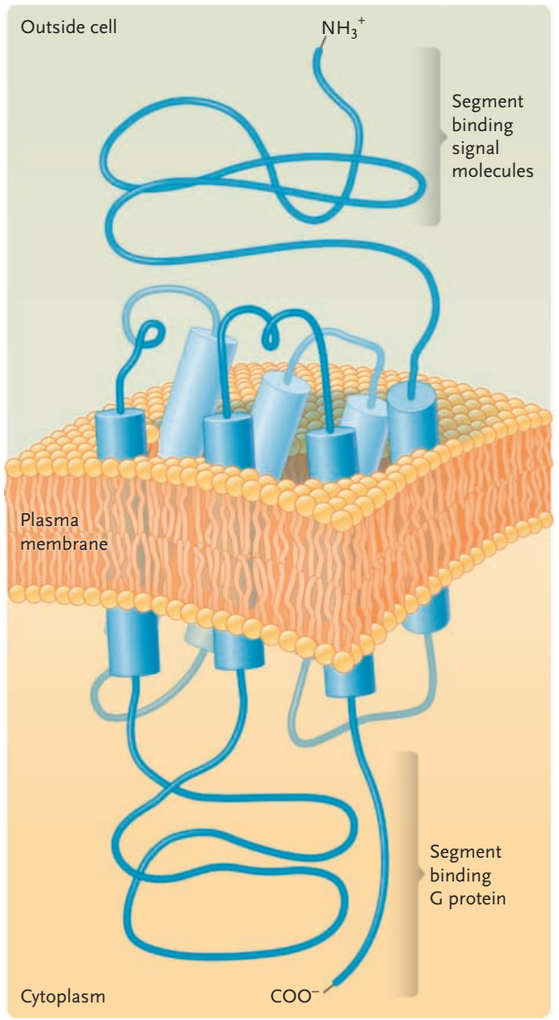


Figure 7.8
Structure of the G-protein–coupled receptors, which activate separate protein kinases. These receptors have seven transmembrane α-helical segments (shown as cylinders) that zigzag across the plasma membrane. Binding of a signal molecule at the cell surface, by inducing changes in the positions of some of the helices, activates the cytoplasmic end of the receptor.

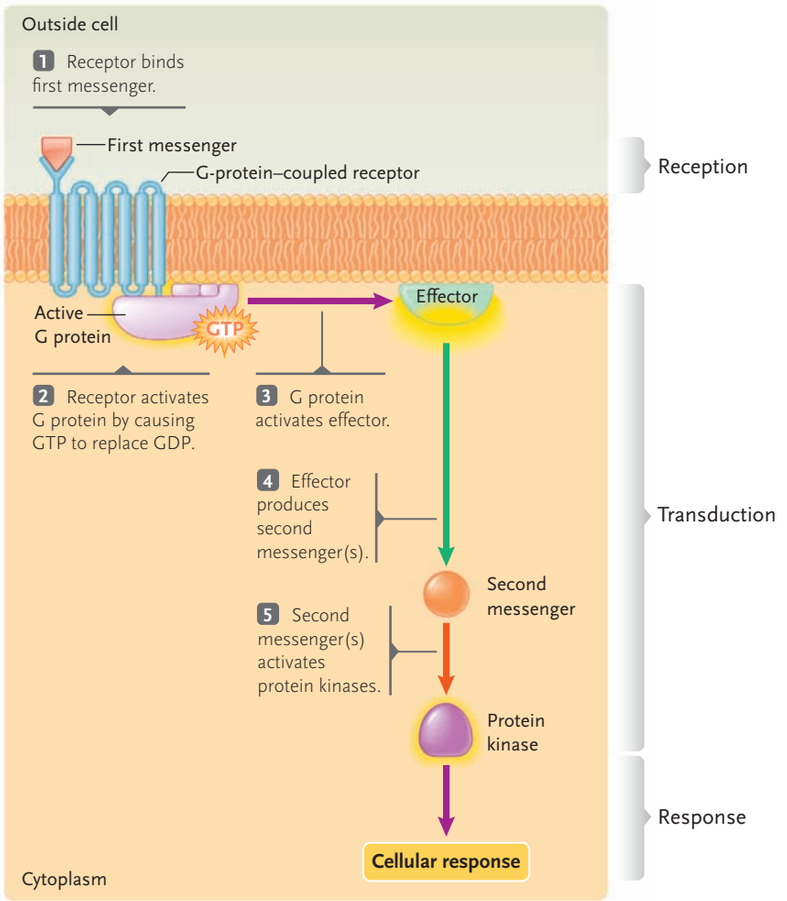


Figure 7.9
Response pathways activated by G-protein–coupled receptors, in which protein kinase activity is separate from the receptor. The signal molecule is called the first messenger; the effector is an enzyme that generates one or more internal signal molecules called second messengers. The second messengers directly or indirectly activate the protein kinases of the pathway, leading to the cellular response.

more internal, nonprotein signal molecules called **second messengers** (step 4). The second messengers directly or indirectly activate protein kinases, which elicit the cellular response by adding phosphate groups to specific target proteins (step 5). Thus, the entire control pathway operates through the following sequence:

first messenger → receptor → G proteins → effector → protein kinases → target proteins

The separate protein kinases of these pathways all add phosphate groups to serine or threonine amino acids in their target proteins, which are typically:

- Enzymes catalyzing steps in metabolic pathways
- Ion channels in the plasma and other membranes
- Regulatory proteins that control gene activity and cell division

The pathway from first messengers to target proteins is common to all G-protein–coupled receptors.

As long as a G-protein–coupled receptor is bound to a first messenger, the receptor keeps the G protein active. The activated G protein, in turn, keeps the effector active in generating second messengers. If the first messenger is released from the receptor, or if the receptor is taken into the cell by endocytosis, GTP is hydrolyzed to GDP, which inactivates the G protein. As a result, the effector becomes inactive, turning "off" the response pathway.

Cells can make a variety of G proteins, with each type activating a different cellular response. Alfred G. Gilman at the University of Virginia, Charlottesville, and Martin Rodbell at the National Institutes of Health,

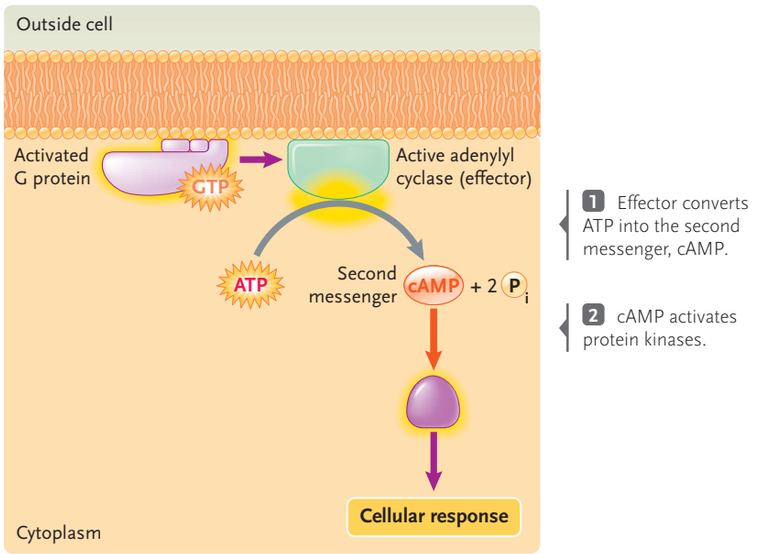


Figure 7.10
The operation of cAMP receptor–response pathways. The second messenger of the pathway, cAMP, activates one or more cAMP-dependent protein kinases, which add phosphate groups to target proteins to initiate the cellular response.

Bethesda, Maryland, received a Nobel Prize in 1994 for their discovery of G proteins and their role in signal transduction in cells.

The importance of G proteins to cellular metabolism is underscored by the fact that they are targets of toxins released by some infecting bacteria. The cholera toxin produced by *Vibrio cholerae,* the pertussis toxin that causes whooping cough produced by *Bordetella pertussis,* and a toxin produced by a disease-causing form of *Escherichia coli* are all enzymes that modify the G proteins, making them continuously active and keeping their response pathways turned "on" at high levels. For example, the cholera toxin prevents a G protein from hydrolyzing GTP, keeping the G protein switched on and the pathway in a permanently active state. Among other effects, the pathway opens ion channels in intestinal cells, causing severe diarrhea through a massive release of salt and water from the body into the intestinal tract. Unless the resulting dehydration of the body is relieved, death can result quickly. The *E. coli* toxin, which has similar but milder effects, is the cause of many cases of traveler's diarrhea.

Two Major G-Protein–Coupled Receptor–Response Pathways Involve Different Second Messengers

Activated G proteins bring about a cellular response through two major receptor–response pathways in which different effectors generate different second messengers. One pathway involves the second messenger **cyclic AMP (cAMP),** a relatively small, water-soluble molecule derived from ATP **(Figure 7.10).** The effector that produces cAMP is the enzyme *adenylyl cyclase,* which converts ATP to cAMP **(Figure 7.11).** cAMP diffuses through the cytoplasm and activates protein kinases that add phosphate groups to target proteins. The other pathway involves two second messengers: **inositol triphosphate (IP_3)** and **diacylglycerol (DAG).** The effector of this pathway, an enzyme called *phospholipase C,* produces both of these second messengers by breaking down a membrane phospholipid **(Figure 7.12).** IP_3 is a small, water-soluble molecule that diffuses rapidly through the cytoplasm. DAG is hydrophobic; it remains and functions in the plasma membrane.

The primary effect of IP_3 in animal cells is to activate transport proteins in the endoplasmic reticulum (ER), which release Ca^{2+} stored in the ER into the cytoplasm. The released Ca^{2+}, either alone or in combination with DAG, activates a protein kinase cascade that brings about the cellular effect. Techniques designed to detect Ca^{2+} release inside cells are among the most important tools of researchers studying cell signaling (see the *Focus on Research* for a description of two of these techniques.)

Both major G-protein–coupled receptor–response pathways are balanced by reactions that constantly eliminate their second messengers. For example, cAMP is quickly degraded by *phosphodiesterase,* an enzyme that is continuously active in the cytoplasm (see Figure 7.11). The rapid elimination of the second messengers provides another highly effective off switch for the pathways, ensuring that protein kinases are inactivated quickly if the receptor becomes inactive. Still another off switch is provided by protein phosphatases that remove the phosphate groups added to proteins by the protein kinases.

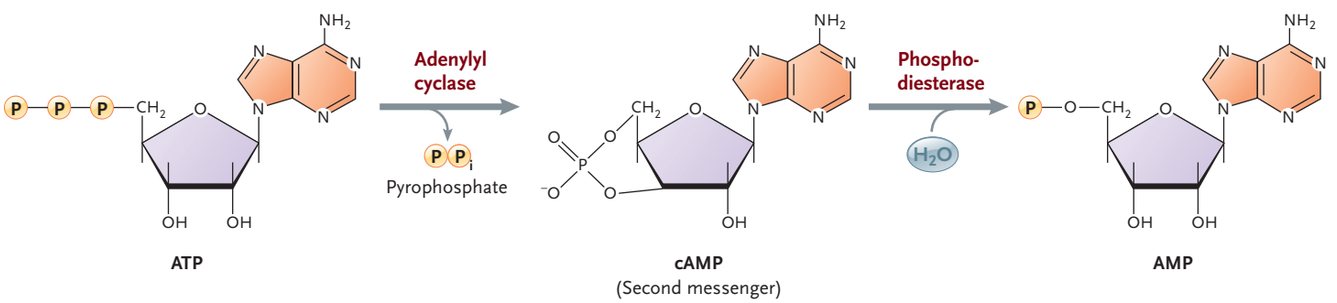


Figure 7.11
cAMP. The second messenger, cAMP, is made from ATP by adenylyl cyclase and is broken down to AMP by phosphodiesterase.

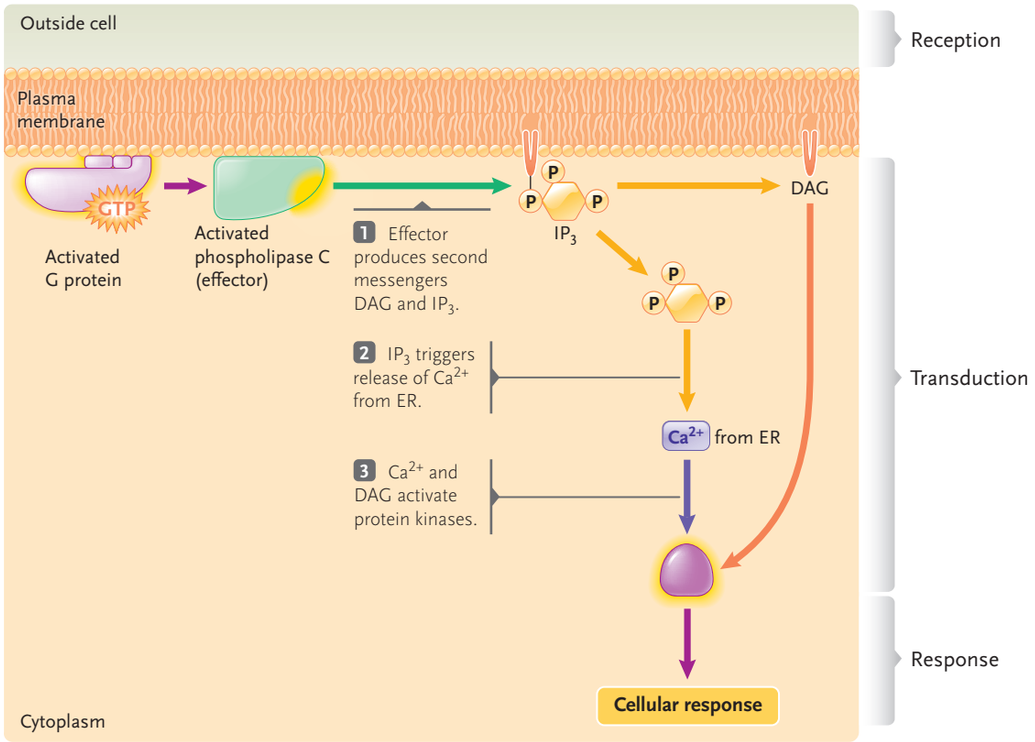


Figure 7.12
The operation of IP_3/DAG receptor–response pathways. Two second messengers, IP_3 and DAG, are produced by the pathway. IP_3 opens Ca^{2+} channels in ER membranes, releasing the ion into the cytoplasm. The Ca^{2+}, with DAG in some cases, directly or indirectly activates the protein kinases of the pathway, which add phosphate groups to target proteins to initiate the cellular response.

As in the receptor tyrosine kinase pathways, the activities of the pathways controlled by cAMP and IP_3/DAG second messengers are also stopped by endocytosis of receptors and their bound extracellular signals. As with all cell signaling pathways, cells vary in their response to cAMP or IP_3/DAG pathways depending on the type of G-protein–coupled receptors on the cell surface and the kinds of protein kinases present in the cytoplasm.

The cAMP pathway is limited to animals and some fungi. The IP_3/DAG pathway is universally distributed among eukaryotic organisms, including both vertebrate and invertebrate animals, fungi, and plants. In plants, IP_3 releases Ca^{2+} primarily from the large central vacuole rather than from the ER.

Specific Examples of Cyclic AMP Pathways. Many peptide hormones act as first messengers for cAMP pathways in mammals and other vertebrates. The receptors that bind these hormones control such varied cellular responses as the uptake and oxidation of glucose, glycogen breakdown or synthesis, ion transport, the transport of amino acids into cells, and cell division.

For example, a cAMP pathway is involved in the regulation of the level of glucose, the fundamental fuel of cells. When the level of blood glucose falls too low in mammals, cells in the pancreas release the peptide hormone glucagon. Binding of the hormone by a G-protein–coupled glucagon receptor on the surface of liver cells triggers the cAMP receptor–response pathway (see Figure 7.10). The cAMP produced activates a protein kinase cascade that amplifies the effects of the pathway at each step. Two enzymes are end targets of the protein kinase cascades. One enzyme is *glycogen phosphorylase,* which catalyzes the breakdown of glycogen into glucose units that pass from the liver cells into the bloodstream and increase the glucose level in the blood; it is activated by the cascades. The other enzyme is *glycogen synthase,* which adds glucose units to glycogen; it is inactivated by the cascades, ensuring that glucose is not converted back into glycogen in the liver cells.

Specific Examples of IP_3/DAG Pathways. The IP_3/DAG-response–pathways are also activated by a large number of peptide hormones (including growth factors) and neurotransmitters, leading to responses as varied as sugar and ion transport, glucose oxidation, cell growth and division, and movements such as smooth muscle contraction.

Among the mammalian hormones that activate the pathways are vasopressin, angiotensin, and norepinephrine. Vasopressin, also known as antidiuretic hormone, helps the body conserve water by reducing the output of urine. Angiotensin helps maintain blood volume and pressure. Norepinephrine, together with epinephrine, brings about the fight-or-flight response in threatening or stressful situations.

Many growth factors operate through IP_3/DAG pathways. Defects in the receptors or other parts of the pathways that lead to higher-than-normal levels of DAG in response to growth factors are often associated with the progression of some forms of cancer. This is

Focus on Research

Basic Research: Detecting Calcium Release in Cells

Because calcium ions are used as a control element in all eukaryotic cells, it was important to develop techniques for detecting Ca^{2+} when it is released into the cytosol. One of the most interesting techniques uses substances that release a burst of light when they bind the ion. One of these substances is *aequorin*, a protein produced by jellyfish, ctenophores, and many other luminescent organisms. Aequorin is injected into the cytoplasm of cells using microscopic needles, and it releases light when IP_3 opens Ca^{2+} channels in the ER, causing an increase in cytosolic Ca^{2+} concentration.

Artificially made, water-soluble molecules called *fura-2* and *quin-2* are also used as indicators of Ca^{2+} release. These molecules fluoresce (emit light) when exposed to ultraviolet (UV) light. The wavelength of UV light that causes the fluorescence is different depending on whether the molecules are bound to or free of Ca^{2+}. Therefore, the amount of Ca^{2+} released into the cytosol can be quantified by measuring how much fluorescence occurs at each of the two wavelengths. Rather than injecting fura-2 or quin-2 into cells, investigators combine them with a hydrophobic organic molecule that allows them to pass directly through the plasma membrane. After fura-2 or quin-2 are inside the cell, enzymes normally found in the cytoplasm remove the added organic group, releasing the Ca^{2+} indicators into the cytosol. This approach sidesteps injection by microneedles, which is a technically demanding technique that can damage the cells being studied.

In a typical experiment designed to follow steps in the IP_3/DAG pathway, an investigator might want to know whether a given hormone triggers the pathway in a group of cells. The investigator first adds aequorin or quin-2 to the cells, and then the hormone. If the cells emit a bright flash of light after they are exposed to the hormone, it is a good indication that the hormone triggers the IP_3/DAG pathway.

Other techniques allow investigators to study the effects of Ca^{2+} in cells independently, without complications introduced by the addition of hormones or other first messengers. One commonly used technique involves adding substances called *calcium ionophores* to the plasma membrane. The ionophores are open Ca^{2+} channels, produced naturally as antibiotics by some microorganisms, that can bury themselves in the plasma membrane of targeted cells. In the membrane, they allow Ca^{2+} to flow into the cytoplasm from the outside. After adding an ionophore to cells in a calcium-free medium, an investigator can detect any cellular activities controlled by Ca^{2+} simply by adding the ion to the medium.

Experiments using these methods have revealed the many cellular processes controlled by Ca^{2+} concentration inside cells, including cellular response pathways, cell movements, assembly and disassembly of the cytoskeleton, secretion, and endocytosis.

because DAG, in turn, causes an overactivity of the protein kinases responsible for stimulating cell growth and division. Also, plant substances in a group called *phorbol esters* resemble DAG so closely that they can promote cancer in animals by activating the same protein kinases.

IP_3/DAG pathways have also been linked to mental disease, particularly *bipolar disorder* (previously called *manic depression*), in which patients experience periodic changes in mood. Lithium has been used for many years as a therapeutic agent for bipolar disorder. Recent research has shown that lithium reduces the activity of IP_3/DAG pathways that release neurotransmitters, among them some that take part in brain function. Lithium also relieves cluster headaches and premenstrual tension, suggesting that they may be related to IP_3/DAG pathways as well.

In plants, IP_3/DAG pathways control responses to conditions such as water loss and changes in light intensity or salinity. Plant hormones—relatively small, nonprotein molecules such as *auxin* (a derivative of the amino acid tryptophan) and the *cytokinins* (derivatives of the nucleotide base adenine)—act as first messengers activating some of the IP_3/DAG pathways of these organisms.

Example of a Signaling Pathway That Combines a Receptor Tyrosine Kinase with a G Protein. Some pathways important in gene regulation link certain receptor tyrosine kinases to a specific type of G protein called Ras. When the receptor tyrosine kinase receives a signal (**Figure 7.13,** step 1), it activates by autophosphorylation (step 2). Adapter proteins then bind to the phosphorylated receptor and bridge to Ras, stimulating the activation of Ras (step 3). Like other G proteins, Ras is activated by binding GTP. The activated Ras sets in motion a phosphorylation cascade that involves a series of three enzymes known as *mitogen-activated protein kinases* (MAP kinases; step 4). The last MAP kinase in the cascade, when activated, enters the nucleus (step 5) and phosphorylates other proteins, which then change the expression of certain genes, particularly activating those involved in cell division (step 6). (A *mitogen* is a substance that controls cell division, hence the name of the kinases.) Changes in gene expression can have far-reaching effects on the cell, such as determining whether a cell divides or how frequently it divides. The Ras proteins are of major interest to investigators because of their role in linking receptor tyrosine kinases to gene regulation, as well as their major roles in the development of many types of cancer when their function is altered.

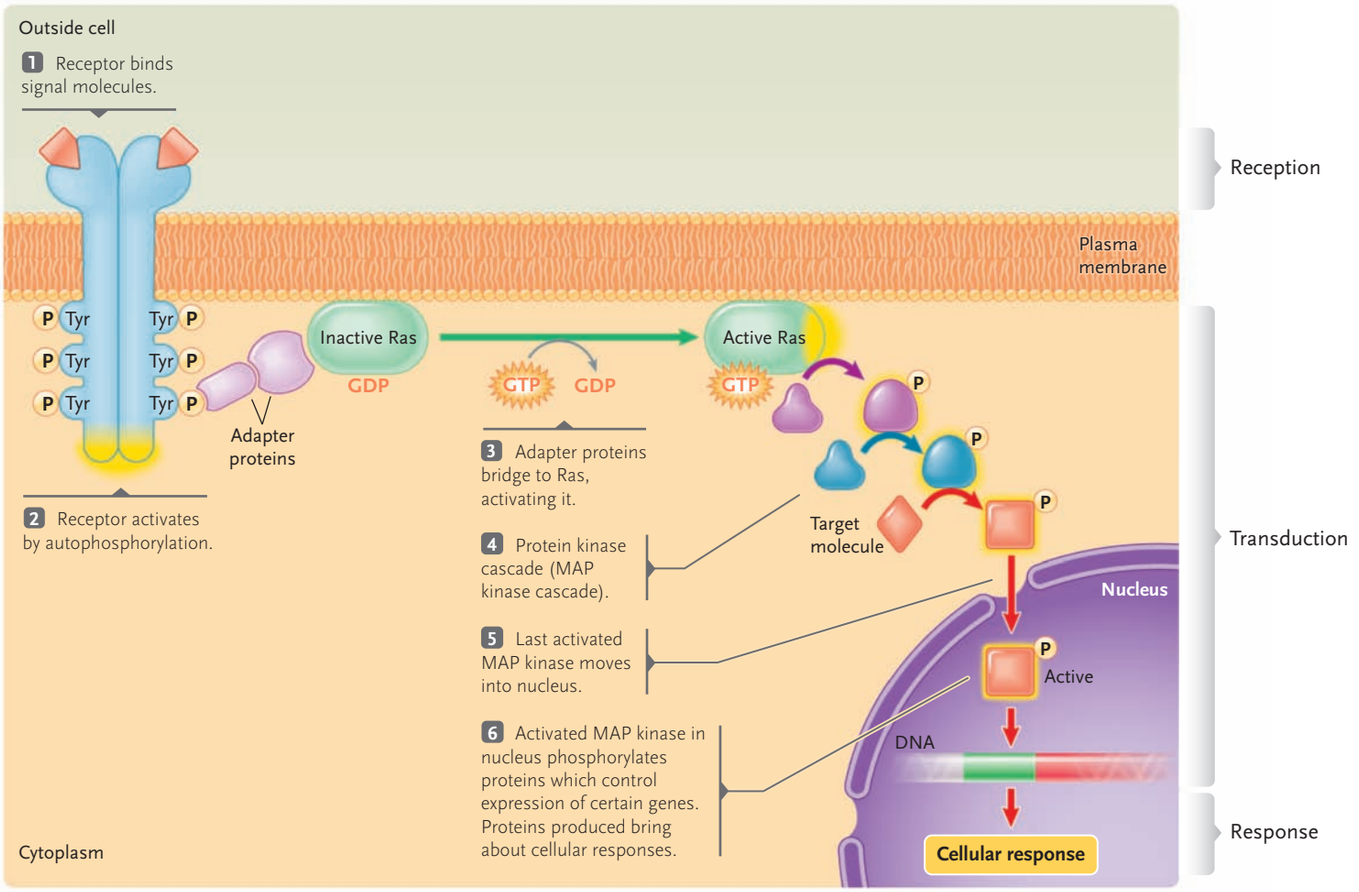


Figure 7.13
The pathway from receptor tyrosine kinases to gene regulation, including the G protein, Ras, and MAP kinase.

In this section, we have surveyed major response pathways linked to surface receptors that bind peptide hormones, growth factors, and neurotransmitters. We now turn to the other major type of signal receptor: the internal receptors binding signal molecules—primarily steroid hormones—that penetrate through the plasma membrane.

Study Break

1. What is the role of the first messenger in a G-protein–coupled receptor-controlled pathway?
2. What is the role of the effector?
3. For a cAMP second-messenger pathway, how is the pathway turned off if no more signal molecules are present in the extracellular fluids?

7.5 Pathways Triggered by Internal Receptors: Steroid Hormone Receptors

Cells of many types have internal receptors that respond to signals arriving from the cell exterior. Unlike the signal molecules that bind to surface receptors, these signals, primarily steroid hormones, penetrate through the plasma membrane to trigger response pathways inside the cells. The internal receptors, called **steroid hormone receptors**, are typically control proteins that turn on specific genes when they are activated by binding a signal molecule.

Steroid Hormones Have Widely Different Effects That Depend on Relatively Small Chemical Differences

Steroid hormones are relatively small, nonpolar molecules derived from cholesterol, with a chemical structure based on four carbon rings (see Figure 3.14). Steroid hormones combine with hydrophilic carrier proteins that mask their hydrophobic groups and hold them in solution in the blood and extracellular fluids. When a steroid hormone–carrier protein complex collides with the surface of a cell, the hormone is released and penetrates directly through the nonpolar part of the plasma membrane. On the cytoplasmic side, the hormone binds to its internal receptor.

The various steroid hormones differ only in the side groups attached to their carbon rings. Although the differences are small, they are responsible for highly distinctive effects. For example, the male and

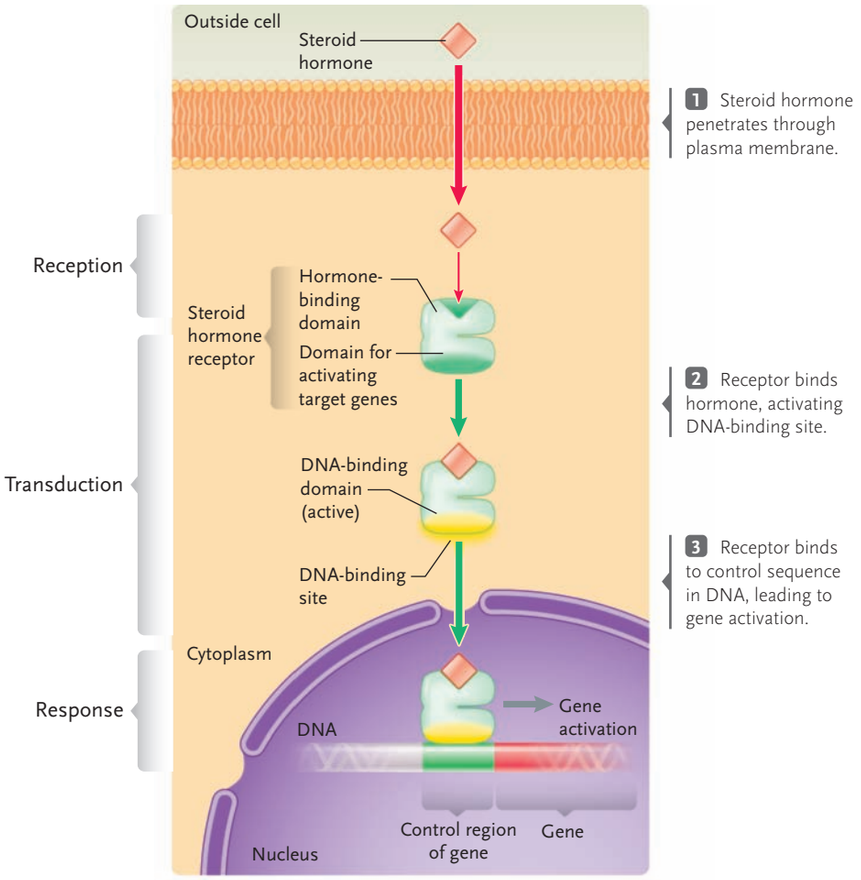


Figure 7.14 Pathway of gene activation by steroid hormone

female sex hormones of mammals, testosterone and estrogen, respectively, which are responsible for many of the structural and behavioral differences between male and female mammals, differ only in minor substitutions in side groups at two positions (see Figure 3.14). The differences cause the hormones to be recognized by different receptors, which activate specific group of genes leading to development of individuals as males or females.

The Response of a Cell to Steroid Hormones Depends on Its Internal Receptors and the Genes They Activate

Steroid hormone receptors are proteins with two major domains **(Figure 7.14).** One domain recognizes and binds a specific steroid hormone. The other domain interacts with the regions of target genes that control their expression. When a steroid hormone combines with the hormone-binding domain, the gene activation domain changes shape, thus enabling the complex to bind to the control regions of the target genes that the hormone affects. For most steroid hormone receptors, binding of the activated receptor to a gene control region activates that gene.

Steroid hormones, like peptide hormones, are released by cells in one part of an organism and are carried by the organism's circulation to other cells. Whether a cell responds to a steroid hormone depends on whether it has an internal receptor for the hormone within the cell. The type of response depends on the genes that are recognized and turned on by an activated receptor. Depending on the receptor type and the particular genes it recognizes, even the same steroid hormone can have highly varied effects on different cells. (The effects of steroid hormones are described in more detail in Chapter 40.)

Taken together, the various types of receptor tyrosine kinases, G-protein–coupled receptors, and steroid hormone receptors prime cells to respond to a stream of specific signals that continuously fine-tune their function. How are the signals integrated within the cell and organism to produce harmony rather than chaos? The next section shows how the various signal pathways are integrated into a coordinated response.

Study Break

1. What distinguishes a steroid receptor from an receptor tyrosine kinase receptor or a G-protein–coupled receptor?
2. By what means does a specific steroid hormone result in a specific cellular response?

7.6 Integration of Cell Communication Pathways

Cells are under the continual influence of many simultaneous signal molecules. The cell signaling pathways may communicate with one another to integrate their responses to cellular signals. The interpathway interaction is called **cross-talk**; a conceptual example that involves two second-messenger pathways is shown in **Figure 7.15.** For example, a protein kinase in one pathway might phosphorylate a site on a target protein in another signal transduction pathway, activating or inhibiting that protein, depending on the site of the phosphorylation. The cross-talk can be extensive, resulting in a complex network of interactions between cell communication pathways.

Cross-talk often leads to modifications of the cellular responses controlled by the pathways. Such modi-

fications fine-tune the effects of combinations of signal molecules binding to the receptors of a cell. For example, cross-talk between second-messenger pathways is involved in particular types of olfactory (smell) signal transduction in rats, and probably in many animals. The two pathways involved are activated upon stimulation with distinct odors. One pathway involves cAMP as the second messenger, and the other involves IP_3. However, the two olfactory second-messenger pathways do not work independently; rather, they operate in an antagonistic way. That is, experimentally blocking key enzymes of one signal transduction cascade inhibits that pathway, while simultaneously augmenting the activity of the other pathway. The cross-talk may be a way to refine the animal's olfactory sensory perception by helping discriminate different odor molecules more effectively.

Cross-talk networks may also involve inputs from other cellular response systems, such as those triggered by cell adhesion molecules as a result of specific contact between cells. Cell adhesion molecules are receptor-like glycoproteins in plasma membranes; they link cells together or bind them to molecules of the extracellular matrix. Many of these surface molecules also trigger cellular responses. For example, when the surface molecule *integrin* binds to another cell or to a molecule of the extracellular matrix, such as collagen, it triggers a cellular response, often including cross-talk steps that link the reactions to the cAMP and IP_3/DAG pathways. The responses triggered by the cell adhesion molecules include changes in the rate of cell division and gene activity and alterations in cell motility, development, and differentiation.

Direct channels of communication may also be involved in a cross-talk network. For example, gap junctions between the cytoplasms of adjacent cells admit ions and small molecules, including the Ca^{2+}, cAMP, and IP_3 second messengers released by the receptor–response pathways. (Gap junctions are discussed in further detail in Section 5.5.) Thus, one cell that receives a signal through its surface receptors can transmit the signal to other cells in the same tissue via the connecting gap junctions, thereby coordinating the functions of those cells. For instance, cardiac muscle cells are connected by gap junctions, and the Ca^{2+} flow regulates coordinated muscle fiber contractions.

The entire system integrating cellular response mechanisms, tied together by many avenues of cross-talk between individual pathways, creates a sensitively balanced control mechanism that regulates and coordinates the activities of individual cells into the working unit of the organism.

In this chapter you have seen that proteins in the plasma membrane play an important role in many aspects of cell communication. The next two chapters take up another vital role of membranes in cells of all kinds—their participation in fundamentally important reactions of energy metabolism.

Study Break

What cell communication pathways might be integrated in a cross-talk network?

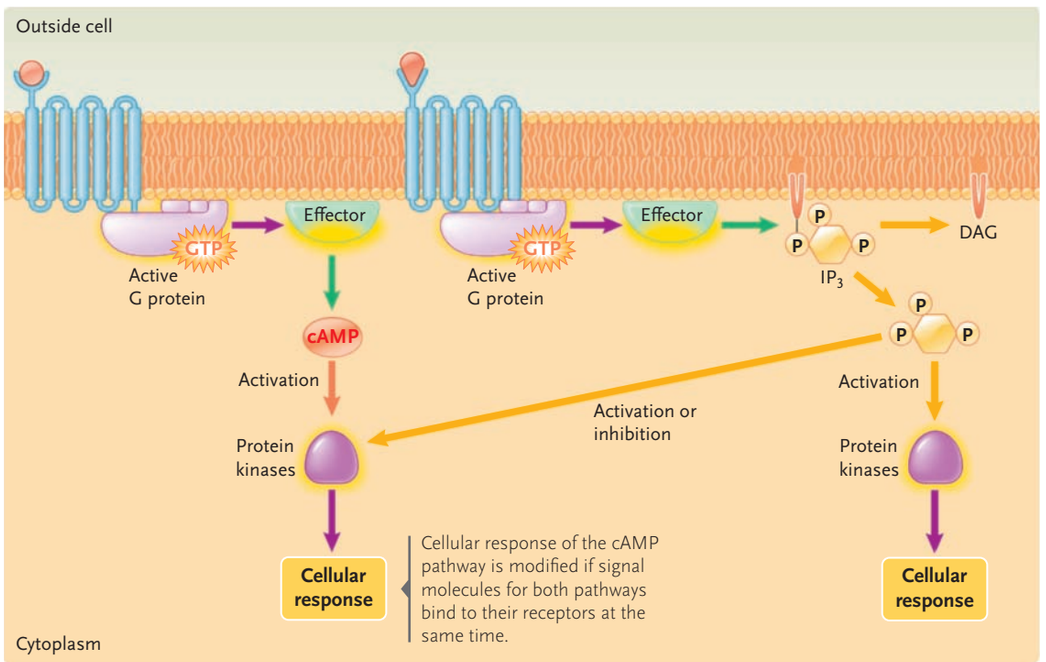


Figure 7.15
Cross-talk, the interaction between cell communication pathways to integrate the responses to signal molecules.

Unanswered Questions

Intercellular signal molecules control many cellular activities; therefore, it is not surprising that many laboratories are researching extensively the mechanisms involved. Experimental goals include determining the molecular details of the receptor structures and how they interact with and change when a signal molecular binds, identifying and characterizing all of the components of the transduction steps, detailing how the final activated component of the transduction steps triggers the cellular responses, and understanding the regulation of signal transduction pathways.

What are the prospects for treating human diseases caused by signal transduction pathway malfunctions?

Receptor tyrosine kinase–mediated signaling is critical for cell growth, division, differentiation, and development. Some human diseases and developmental abnormalities result from mutations in the genes for receptor tyrosine kinases and from overexpression of those genes. Examples are dwarfism, heritable cancer susceptibility, vein malformations, and piebaldism. Researchers are determining the exact nature of the receptor gene mutations in order explore how the mutations cause the malfunctions of the signal transduction pathways. They have found that some mutations affect the ability of the receptor to form a dimer when the signal molecule binds, and others affect the kinase activity of the cytoplasmic side of the receptor. In fact, there are a surprisingly large number of different mutations that affect receptor tyrosine kinases, meaning that there are many ways that their functions can be affected. In terms of treating human diseases resulting from receptor tyrosine kinase mutations, research is at a relatively early stage. Prospects for therapeutic approaches to treat these diseases include developing anti-tyrosine kinase drugs. Clearly an increased understanding of receptor tyrosine kinases' signaling and function is crucial for progress to be made in diagnosis and treatment of human diseases resulting from mutations that cause abnormal regulation of receptor tyrosine kinase function.

How do steroid hormones act in the brain to modify brain function and behavior?

Research is being done on the cellular processes by which steroid hormones involved in mammalian reproductive behavior act in neurons. During the estrous cycle of female rats, estradiol and progesterone (ovarian hormones) regulate the expression of reproductive behaviors by binding to steroid hormone receptors in neurons.

The model presented in this chapter is that a steroid receptor becomes activated when the steroid hormone binds to it. However, several groups have now shown that neurotransmitters can activate steroid hormone receptors in the absence of hormone. In addition, experiments have demonstrated that when a male rat mates with a female rat, the mating stimulates the female's neural steroid hormone receptors. This activation causes neuronal changes in the brain, which result in changes in behavior and physiology. These changes are similar to those induced by steroid hormones. That is, how a male behaves toward a female alters neurotransmitters in her brain and creates events, many of which are the same as those caused by hormone secretion from the female's ovaries. Jeffrey Blaustein's research group at the University of Massachusetts (Amherst) is studying a number of questions in this area: How does the hormone-independent steroid hormone receptor activation occur? In which neurons do these events occur? What regulates the process? The results will give valuable insights into the mechanisms of steroid hormone action in the brain.

Peter J. Russell

Review

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7.1 Cell Communication: An Overview

- Cells communicate with one another through direct channels of communication, specific contact between cells, and intercellular chemical messengers.
- In communication that involves an intercellular chemical messenger, a controlling cell releases a signal molecule that causes a response of target cells. The target cell processes the signal in three steps: reception, transduction, and response. The series of events from reception to response is called signal transduction (Figures 7.2 and 7.3).

7.2 Characteristics of Cell Communication Systems with Surface Receptors

- Cell communication systems based on surface receptors have three components: (1) extracellular signal molecules, (2) surface receptors that receive the signals, and (3) internal response pathways triggered when receptors bind a signal.
- The systems based on surface receptors respond to peptide hormones and neurotransmitters.
- Peptide hormones are small proteins. A special class of peptide hormones is the growth factors, which affect cell growth, division, and differentiation. Neurotransmitters include small peptides, individual amino acids or their derivatives, and other chemical substances.
- Surface receptors are integral membrane proteins that extend entirely through the plasma membrane. Binding a signal molecule induces a molecular change in the receptor that activates its cytoplasmic end (Figure 7.4).
- Cellular response pathways operate by activating protein kinases. Phosphate groups added by the protein kinases stimulate or inhibit the activities of the target proteins, thereby accomplishing the cellular response. The response is reversed by protein phosphatases that remove phosphate groups from target proteins. In addition, receptors are removed by endocytosis when signal transduction has run its course (Figure 7.5).
- Each step of a response pathway catalyzed by an enzyme is amplified, because each enzyme can activate hundreds or thousands of proteins that enter the next step in the pathway. Amplification allows a full cellular response when a few signal molecules bind to their receptors (Figure 7.6).

Animation: Signal transduction

7.3 Surface Receptors with Built-In Protein Kinase Activity: Receptor Tyrosine Kinases

- When receptor tyrosine kinases bind a signal molecule, the protein kinase site becomes active and adds phosphate groups to tyrosines in the receptor itself and to target proteins. The phosphate groups added to the cytoplasmic end of the receptor are recognition sites for proteins that are activated by binding to the receptor (Figure 7.7).

7.4 G-Protein–Coupled Receptors

- In the pathways activated by G-protein-coupled receptors, binding of the extracellular signal molecule (the first messenger) activates a site on the cytoplasmic end of the receptor (Figure 7.8).
- An activated receptor turns on a G protein, which acts as a molecular switch. The G protein is active when it is bound to GTP and inactive when it is bound to GDP (Figure 7.9).
- When a G protein is active, it switches on the effector of the pathway, an enzyme that generates small internal signal molecules called second messengers. The second messengers activate the protein kinases of the pathway (Figure 7.9).
- In one of the two major pathways triggered by G-protein–coupled receptors, the effector, adenylyl cyclase, generates cAMP as second messenger. cAMP activates specific protein kinases (Figures 7.10 and 7.11).
- In the other major pathway, the activated effector, phospholipase C, generates two second messengers, IP_3 and DAG. IP_3 activates transport proteins in the ER, which release stored Ca^{2+} into the cytoplasm. The released Ca^{2+}, alone or in combination with DAG, activates specific protein kinases that add phosphate groups to their target proteins (Figure 7.12).
- Both the cAMP and IP_3/DAG pathways are balanced by reactions that constantly eliminate their second messengers. Both pathways are also stopped by protein phosphatases that continually remove phosphate groups from target proteins and by endocytosis of receptors and their bound extracellular signals.
- Mutated systems can turn on the pathways permanently, contributing to the progression of some forms of cancer.
- Some pathways important in gene regulation link certain receptor tyrosine kinases to a specific G protein called Ras. When the receptor binds a signal molecule, it phosphorylates itself and adapter proteins then bind, bridging to Ras, activating it. Activated Ras turns on the MAP kinase cascade. The last MAP kinase in the cascade, when activated, phosphorylates target proteins in the nucleus, activating them to turn on specific genes. Many of those genes control cell division (Figure 7.13).

Practice: Response pathways activated by G-protein–coupled receptors

7.5 Pathways Triggered by Internal Receptors: Steroid Hormone Receptors

- Steroid hormones penetrate through the plasma membrane to bind to receptors within the cell. The internal receptors are regulatory proteins that turn on specific genes when they are activated by binding a signal molecule, thereby producing the cellular response (Figure 7.14).
- Steroid hormone receptors have a domain that recognizes and binds a specific steroid hormone and a domain that interacts with the controlling regions of target genes (Figure 7.14).
- Whether a cell responds to a steroid hormone depends on whether it has an internal receptor for the hormone; within the cell, the type of response depends on the genes that are recognized and turned on by an activated receptor.

Animation: Pathway of gene activation by steroid hormone receptors

7.6 Integration of Cell Communication Pathways

- In cross-talk, cell signaling pathways communicate with one another to integrate responses to cellular signals. Cross-talk may result a complex network of interactions between cell communication pathways (Figure 7.15).
- Cross-talk often results in modifications of the cellular responses controlled by the pathways, fine-tuning the effects of combinations of signal molecules binding to the receptors of a cell.
- In animals, inputs from other cellular response systems, including cell adhesion molecules, as well as molecules arriving through gap junctions, also can become involved in the cross-talk network.

Animation: Animal cell junctions

Questions

Self-Test Questions

1. In signal transduction, which of the following is *not* a target protein?
   a. proteins that regulate gene activity
   b. hormones that activate the receptor
   c. enzymes of pathways
   d. transport proteins
   e. enzymes of cell reactions
2. Which of the following could *not* elicit a signal transduction response?
   a. a signal molecule injected directly into the cytoplasm
   b. a virus mimicking a normal signal molecule
   c. a peptide hormone
   d. a steroid hormone
   e. a neurotransmitter
3. A cell that responds to a signal molecule is distinguished from a cell that does not respond by the fact that it has:
   a. a cell adhesion molecule.
   b. cAMP.
   c. a first messenger molecule.
   d. a receptor.
   e. a protein kinase.
4. The mechanism to activate an immune cell to make an antibody involves signal transduction using tyrosine kinases. Place in order the following series of steps to activate this function.
   (1) The activated receptor phosphorylates cytoplasmic proteins.
   (2) Conformational change occurs in the receptor tyrosine kinase.
   (3) Cytoplasmic protein crosses the nuclear membrane to activate genes.
   (4) An immune hormone signals the immune cell.
   (5) Activation of protein kinase site(s) adds phosphates to the receptor to activate it.
   a. 2, 1, 4, 3, 5
   b. 5, 3, 4, 2, 1
   c. 4, 1, 5, 2, 3
   d. 4, 2, 5, 1, 3
   e. 2, 5, 3, 4, 1

5. Which of the following is the ability of enzymes, requiring few receptors, to activate thousands of molecules in a stepwise pathway?
   a. autophosphorylation
   b. second-messenger enhancement
   c. amplification
   d. ion channel regulation
   e. G protein turn-on

6. Which of the following is *incorrect* about pathways activated by G-protein–coupled receptors?
   a. The extracellular signal is the first messenger.
   b. When activated, plasma membrane–bound G protein can switch on an effector.
   c. Second messengers enter the nucleus.
   d. ATP converts to cAMP to activate protein kinases.
   e. Protein kinases phosphorylate molecules to change cellular activity.

7. Which of the following would *not* inhibit signal transduction?
   a. Phosphate groups are removed from proteins.
   b. Endocytosis acts on receptors and their bound signals.
   c. Receptors and signals separate.
   d. Receptors and bound signals enter lysosomes.
   e. Autophosphorylation targets the cytoplasmic portion of the receptor.

8. An internal receptor binds both a signal molecule and controlling region of a gene. What type of receptor is it?
   a. protein
   b. steroid
   c. IP_3/DAG
   d. receptor tyrosine kinase
   e. switch protein

9. Place in order the following steps for the normal activity of a Ras protein.
   (1) Ras turns on the MAP kinase cascade.
   (2) Adaptor proteins connect phosphorylated tyrosine on a receptor to Ras.
   (3) GTP activates Ras by binding to it, displacing GDP.
   (4) The last MAP kinase in the cascade phosphorylates proteins in the nucleus that activate genes.
   (5) Receptor tyrosine kinase binds a signal molecule and is activated.
   a. 1, 2, 3, 4, 5
   b. 2, 3, 5, 1, 4
   c. 5, 2, 3, 1, 4
   d. 2, 3, 1, 5, 4
   e. 4, 1, 5, 3, 2

10. Cross-talk is best exemplified as:
    a. second messenger activates protein kinases.
    b. effector protein produces second messengers DAG and IP_3.
    c. an MAP kinase in a cascade that activates DNA.
    d. a protein kinase in a pathway that activates or inactivates a protein in another pathway.
    e. steroid hormones can move across the plasma membrane.

Questions for Discussion

1. Describe the possible ways in which a G-protein–coupled receptor pathway could become defective and not trigger any cellular responses.
2. Is providing extra insulin an effective cure for an individual who has diabetes caused by a hereditary defect in the insulin receptor? Why or why not?
3. There are molecules called GTP analogs that resemble GTP so closely that they can be bound by G proteins. However, they cannot be hydrolyzed by cellular GTPases. What differences in effect would you expect if you inject GTP or a nonhydrolyzable GTP analog into a liver cell that responds to glucagon?
4. Why do you suppose cells evolved internal response mechanisms using switching molecules that bind GTP instead of ATP?

Experimental Analysis

How would you set up an experiment to determine whether a hormone receptor is located on the cell surface or inside the cell?

Evolution Link

Based on their distributions among different groups of organisms, which signaling pathway is the oldest?