7

Cell-Cell Interactions

Concept Outline

7.1 Cells signal one another with chemicals.

Receptor Proteins and Signaling between Cells. Receptor proteins embedded in the plasma membrane change shape when they bind specific signal molecules, triggering a chain of events within the cell.

Types of Cell Signaling. Cell signaling can occur between adjacent cells, although chemical signals called hormones act over long distances.

7.2 Proteins in the cell and on its surface receive signals from other cells.

Intracellular Receptors. Some receptors are located within the cell cytoplasm. These receptors respond to lipid-soluble signals, such as steroid hormones.

Cell Surface Receptors. Many cell-to-cell signals are water-soluble and cannot penetrate membranes. Instead, the signals are received by transmembrane proteins protruding out from the cell surface.

7.3 Follow the journey of information into the cell.

Initiating the Intracellular Signal. Cell surface receptors often use "second messengers" to transmit a signal to the cytoplasm.

Amplifying the Signal: Protein Kinase Cascades. Surface receptors and second messengers amplify signals as they travel into the cell, often toward the cell nucleus.

7.4 Cell surface proteins mediate cell-cell interactions.

The Expression of Cell Identity. Cells possess on their surfaces a variety of tissue-specific identity markers that identify both the tissue and the individual.

Intercellular Adhesion. Cells attach themselves to one another with protein links. Some of the links are very strong, others more transient.

Tight Junctions. Adjacent cells form a sheet when connected by tight junctions, and molecules are encouraged to flow through the cells, not between them.

Anchoring Junctions. The cytoskeleton of a cell is connected by an anchoring junction to the cytoskeleton of another cell or to the extracellular matrix.

Communicating Junctions. Many adjacent cells have direct passages that link their cytoplasms, permitting the passage of ions and small molecules.

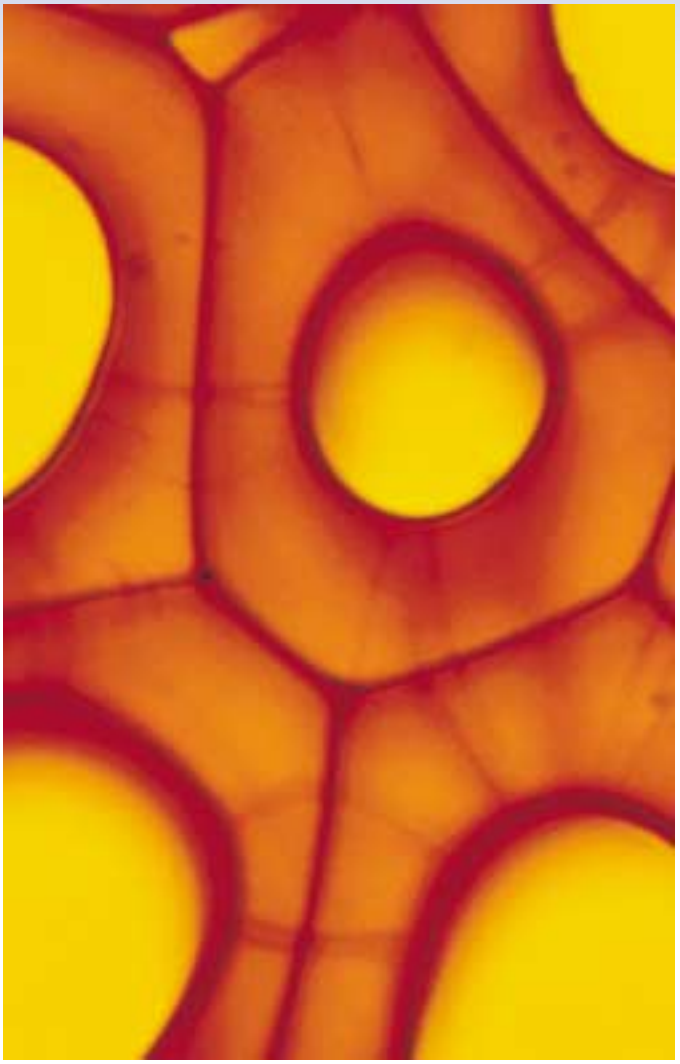


FIGURE 7.1
Persimmon cells in close contact with one another. These plant cells and all cells, no matter what their function, interact with their environment, including the cells around them.

Did you know that each of the 100 trillion cells of your body shares one key feature with the cells of tigers, bumblebees, and persimmons (figure 7.1)—a feature that most bacteria and protists lack? Your cells touch and communicate with one another. Sending and receiving a variety of chemical signals, they coordinate their behavior so that your body functions as an integrated whole, rather than as a massive collection of individual cells acting independently. The ability of cells to communicate with one another is the hallmark of multicellular organisms. In this chapter we will look in detail at how the cells of multicellular organisms interact with one another, first exploring how they signal one another with chemicals and then examining the ways in which their cell surfaces interact to organize tissues and body structures.

7.1 Cells signal one another with chemicals.

Receptor Proteins and Signaling between Cells

Communication between cells is common in nature. Cell signaling occurs in all multicellular organisms, providing an indispensable mechanism for cells to influence one another. The cells of multicellular organisms use a variety of molecules as signals, including not only peptides, but also large proteins, individual amino acids, nucleotides, steroids and other lipids.

Even dissolved gases are used as signals. Nitric oxide (NO) plays a role in mediating male erections (Viagra functions by stimulating NO release).

Some of these molecules are attached to the surface of the signaling cell; others are secreted through the plasma membrane or released by exocytosis.

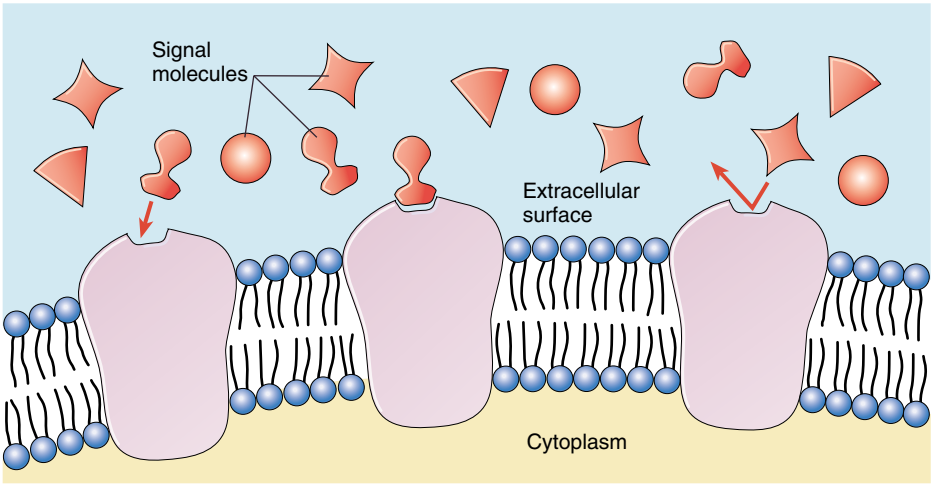


FIGURE 7.2
Cell surface receptors recognize only specific molecules. Signal molecules will bind only to those cells displaying receptor proteins with a shape into which they can fit snugly.

Cell Surface Receptors

Any given cell of a multicellular organism is exposed to a constant stream of signals. At any time, hundreds of different chemical signals may be in the environment surrounding the cell. However, each cell responds only to certain signals and ignores the rest (figure 7.2), like a person following the conversation of one or two individuals in a noisy, crowded room. How does a cell "choose" which signals to respond to? Located on or within the cell are **receptor proteins,** each with a three-dimensional shape that fits the shape of a specific signal molecule. When a signal molecule approaches a receptor protein of the right shape, the two can bind. This binding induces a change in the receptor protein's shape, ultimately producing a response in the cell. Hence, a given cell responds to the signal molecules that fit the particular set of receptor proteins it possesses, and ignores those for which it lacks receptors.

The Hunt for Receptor Proteins

The characterization of receptor proteins has presented a very difficult technical problem, because of their relative scarcity in the cell. Because these proteins may constitute less than 0.01% of the total mass of protein in a cell, purifying them is analogous to searching for a particular grain of sand in a sand dune! However, two recent techniques have enabled cell biologists to make rapid progress in this area.

Monoclonal antibodies. The first method uses *monoclonal antibodies.* An antibody is an immune system protein that, like a receptor, binds specifically to another molecule. Each individual immune system cell can make only one particular type of antibody, which can bind to only one specific target molecule. Thus, a cell-line derived from a single immune system cell (a clone) makes one specific antibody (a *monoclonal* antibody). Monoclonal antibodies that bind to particular receptor proteins can be used to isolate those proteins from the thousands of others in the cell.

Gene analysis. The study of mutants and isolation of gene sequences has had a tremendous impact on the field of receptor analysis. In chapter 19 we will present a detailed account of how this is done. These advances make it feasible to identify and isolate the many genes that encode for various receptor proteins.

Remarkably, these techniques have revealed that the enormous number of receptor proteins can be grouped into just a handful of "families" containing many related receptors. Later in this chapter we will meet some of the members of these receptor families.

Cells in a multicellular organism communicate with others by releasing signal molecules that bind to receptor proteins on the surface of the other cells. Recent advances in protein isolation have yielded a wealth of information about the structure and function of these proteins.

Types of Cell Signaling

Cells communicate through any of four basic mechanisms, depending primarily on the distance between the signaling and responding cells (figure 7.3). In addition to using these four basic mechanisms, some cells actually send signals to themselves, secreting signals that bind to specific receptors on their own plasma membranes. This process, called **autocrine signaling,** is thought to play an important role in reinforcing developmental changes.

Direct Contact

As we saw in chapter 6, the surface of a eukaryotic cell is a thicket of proteins, carbohydrates, and lipids attached to and extending outward from the plasma membrane. When cells are very close to one another, some of the molecules on the cells' plasma membranes may bind together in specific ways. Many of the important interactions between cells in early development occur by means of direct contact between cell surfaces (figure 7.3*a*). We'll examine contact-dependent interactions more closely later in this chapter.

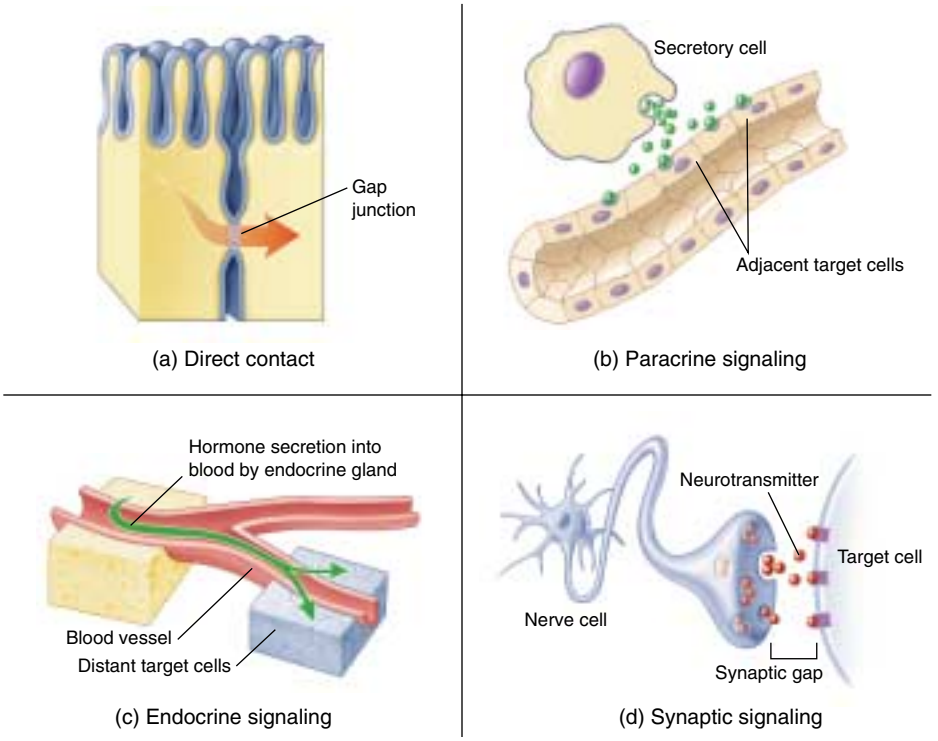


FIGURE 7.3
Four kinds of cell signaling. Cells communicate in several ways. (*a*) Two cells in *direct contact* with each other may send signals across gap junctions. (*b*) In *paracrine signaling*, secretions from one cell have an effect only on cells in the immediate area. (*c*) In *endocrine signaling*, hormones are released into the circulatory system, which carries them to the target cells. (*d*) Chemical *synaptic signaling* involves transmission of signal molecules, called neurotransmitters, from a neuron over a small synaptic gap to the target cell.

Paracrine Signaling

Signal molecules released by cells can diffuse through the extracellular fluid to other cells. If those molecules are taken up by neighboring cells, destroyed by extracellular enzymes, or quickly removed from the extracellular fluid in some other way, their influence is restricted to cells in the immediate vicinity of the releasing cell. Signals with such short-lived, local effects are called **paracrine** signals (figure 7.3*b*). Like direct contact, paracrine signaling plays an important role in early development, coordinating the activities of clusters of neighboring cells.

Endocrine Signaling

If a released signal molecule remains in the extracellular fluid, it may enter the organism's circulatory system and travel widely throughout the body. These longer lived signal molecules, which may affect cells very distant from the releasing cell, are called **hormones,** and this type of intercellular communication is known as **endocrine** signaling (figure 7.3*c*). Chapter 58 discusses endocrine signaling in detail. Both animals and plants use this signaling mechanism extensively.

Synaptic Signaling

In animals, the cells of the nervous system provide rapid communication with distant cells. Their signal molecules, **neurotransmitters,** do not travel to the distant cells through the circulatory system like hormones do. Rather, the long, fiberlike extensions of nerve cells release neurotransmitters from their tips very close to the target cells (figure 7.3*d*). The narrow gap between the two cells is called a **chemical synapse.** While paracrine signals move through the fluid between cells, neurotransmitters cross the synapse and persist only briefly. We will examine synaptic signaling more fully in chapter 54.

Adjacent cells can signal others by direct contact, while nearby cells that are not touching can communicate through paracrine signals. Two other systems mediate communication over longer distances: in endocrine signaling the blood carries hormones to distant cells, and in synaptic signaling nerve cells secrete neurotransmitters from long cellular extensions close to the responding cells.

7.2 Proteins in the cell and on its surface receive signals from other cells.

Intracellular Receptors

All cell signaling pathways share certain common elements, including a chemical signal that passes from one cell to another and a receptor that receives the signal in or on the target cell. We've looked at the sorts of signals that pass from one cell to another. Now let's consider the nature of the receptors that receive the signals. Table 7.1 summarizes the types of receptors we will discuss in this chapter.

Many cell signals are lipid-soluble or very small molecules that can readily pass across the plasma membrane of the target cell and into the cell, where they interact with a receptor. Some bind to protein receptors located in the cytoplasm; others pass across the nuclear membrane as well and bind to receptors within the nucleus. These **intracellular receptors** (figure 7.4) may trigger a variety of responses in the cell, depending on the receptor.

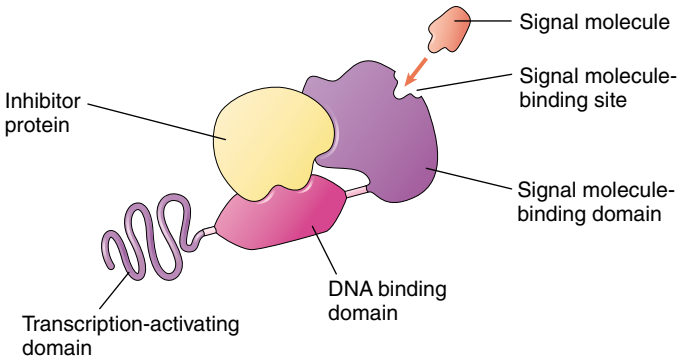


FIGURE 7.4
Basic structure of a gene-regulating intracellular receptor. These receptors are located within the cell and function in the reception of signals such as steroid hormones, vitamin D, and thyroid hormone.

Table 7.1 Cell Communicating Mechanisms

Mechanism	Structure	Function	Example
INTRACELLULAR RECEPTORS	No extracellular signal-binding site	Receives signals from lipid-soluble or noncharged, nonpolar small molecules	Receptors for NO, steroid hormone, vitamin D, and thyroid hormone
CELL SURFACE RECEPTORS			
Chemically gated ion channels	Multipass transmembrane protein forming a central pore	Molecular "gates" triggered chemically to open or close	Neurons
Enzymic receptors	Single-pass transmembrane protein	Binds signal extracellularly, catalyzes response intracellularly	Phosphorylation of protein kinases
G-protein-linked receptors	Seven-pass transmembrane protein with cytoplasmic binding site for G protein	Binding of signal to receptor causes GTP to bind a G protein; G protein, with attached GTP, detaches to deliver the signal inside the cell	Peptide hormones, rod cells in the eyes
PHYSICAL CONTACT WITH OTHER CELLS			
Surface markers	Variable; integral proteins or glycolipids in cell membrane	Identify the cell	MHC complexes, blood groups, antibodies
Tight junctions	Tightly bound, leakproof, fibrous protein "belt" that surrounds cell	Organizing junction: holds cells together such that material passes *through* but not *between* the cells	Junctions between epithelial cells in the gut
Desmosomes	Intermediate filaments of cytoskeleton linked to adjoining cells through cadherins	Anchoring junction: "buttons" cells together	Epithelium
Adherens junctions	Transmembrane fibrous proteins	Anchoring junction: "roots" extracellular matrix to cytoskeleton	Tissues with high mechanical stress, such as the skin
Gap junctions	Six transmembrane connexon proteins creating a "pipe" that connects cells	Communicating junction: allows passage of small molecules from cell to cell in a tissue	Excitable tissue such as heart muscle
Plasmodesmata	Cytoplasmic connections between gaps in adjoining plant cell walls	Communicating junction between plant cells	Plant tissues

Receptors That Act as Gene Regulators

Some intracellular receptors act as regulators of gene transcription. Among them are the receptors for steroid hormones, such as cortisol, estrogen, and progesterone, as well as the receptors for a number of other small, lipid-soluble signal molecules, such as vitamin D and thyroid hormone. All of these receptors have similar structures; the genes that code for them may well be the evolutionary descendants of a single ancestral gene. Because of their structural similarities, they are all part of the *intracellular receptor superfamily*.

Each of these receptors has a binding site for DNA. In its inactive state, the receptor typically cannot bind DNA because an inhibitor protein occupies the binding site. When the signal molecule binds to another site on the receptor, the inhibitor is released and the DNA binding site is exposed (figure 7.5). The receptor then binds to a specific nucleotide sequence on the DNA, which activates (or, in a few instances, suppresses) a particular gene, usually located adjacent to the regulatory site.

The lipid-soluble signal molecules that intracellular receptors recognize tend to persist in the blood far longer than water-soluble signals. Most water-soluble hormones break down within minutes, and neurotransmitters within seconds or even milliseconds. A steroid hormone like cortisol or estrogen, on the other hand, persists for hours.

The target cell's response to a lipid-soluble cell signal can vary enormously, depending on the nature of the cell. This is true even when different target cells have the same intracellular receptor, for two reasons: First, the binding site for the receptor on the target DNA differs from one cell type to another, so that different genes are affected when the signal-receptor complex binds to the DNA, and second, most eukaryotic genes have complex controls. We will discuss them in detail in chapter 16, but for now it is sufficient to note that several different regulatory proteins are usually involved in reading a eukaryotic gene. Thus the intracellular receptor interacts with different signals in different tissues. Depending on the cell-specific controls operating in different tissues, the effect the intracellular receptor produces when it binds with DNA will vary.

Receptors That Act as Enzymes

Other intracellular receptors act as enzymes. A very interesting example is the receptor for the signal molecule, **nitric oxide (NO).** A small gas molecule, NO diffuses readily out of the cells where it is produced and passes directly into neighboring cells, where it binds to the enzyme guanylyl cyclase. Binding of NO activates the enzyme, enabling it to catalyze the synthesis of cyclic guanosine monophosphate (GMP), an intracellular messenger molecule that produces cell-specific responses such as the relaxation of smooth muscle cells.

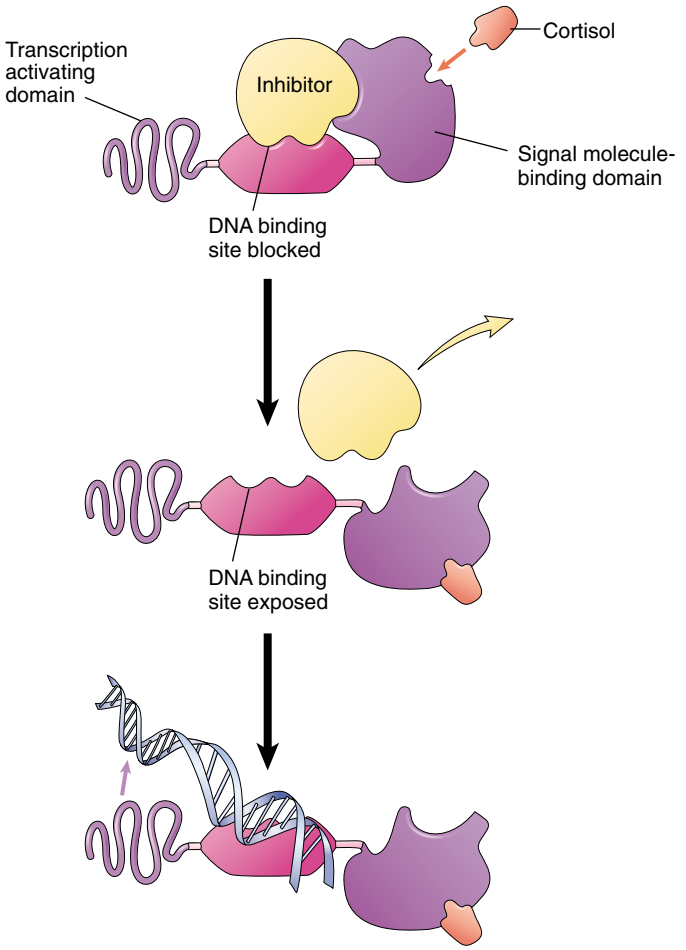


FIGURE 7.5
How intracellular receptors regulate gene transcription. In this model, the binding of the steroid hormone cortisol to a DNA regulatory protein causes it to alter its shape. The inhibitor is released, exposing the DNA binding site of the regulatory protein. The DNA binds to the site, positioning a specific nucleotide sequence over the transcription activating domain of the receptor and initiating transcription.

NO has only recently been recognized as a signal molecule in vertebrates. Already, however, a wide variety of roles have been documented. For example, when the brain sends a nerve signal relaxing the smooth muscle cells lining the walls of vertebrate blood vessels, the signal molecule acetylcholine released by the nerve near the muscle does not interact with the muscle cell directly. Instead, it causes nearby epithelial cells to produce NO, which then causes the smooth muscle to relax, allowing the vessel to expand and thereby increase blood flow.

Many target cells possess intracellular receptors, which are activated by substances that pass through the plasma membrane.

Cell Surface Receptors

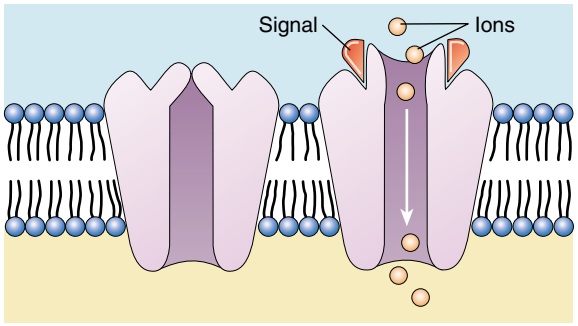
Most signal molecules are water-soluble, including neurotransmitters, peptide hormones, and the many proteins that multicellular organisms employ as "growth factors" during development. Water-soluble signals cannot diffuse through cell membranes. Therefore, to trigger responses in cells, they must bind to receptor proteins on the surface of the cell. These **cell surface receptors** (figure 7.6) convert the extracellular signal to an intracellular one, responding to the binding of the signal molecule by producing a change within the cell's cytoplasm. Most of a cell's receptors are cell surface receptors, and almost all of them belong to one of three receptor superfamilies: chemically gated ion channels, enzymic receptors, and G-protein-linked receptors.

Chemically Gated Ion Channels

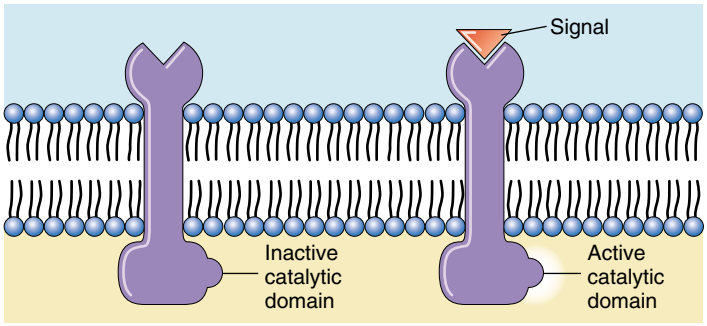
Chemically gated ion channels are receptor proteins that ions pass through. The receptor proteins that bind many neurotransmitters have the same basic structure (figure 7.6*a*). Each is a "multipass" transmembrane protein, meaning that the chain of amino acids threads back and forth across the plasma membrane several times. In the center of the protein is a pore that connects the extracellular fluid with the cytoplasm. The pore is big enough for ions to pass through, so the protein functions as an **ion channel.** The channel is said to be chemically gated because it opens when a chemical (the neurotransmitter) binds to it. The type of ion (sodium, potassium, calcium, chloride, for example) that flows across the membrane when a chemically gated ion channel opens depends on the specific three-dimensional structure of the channel.

Enzymic Receptors

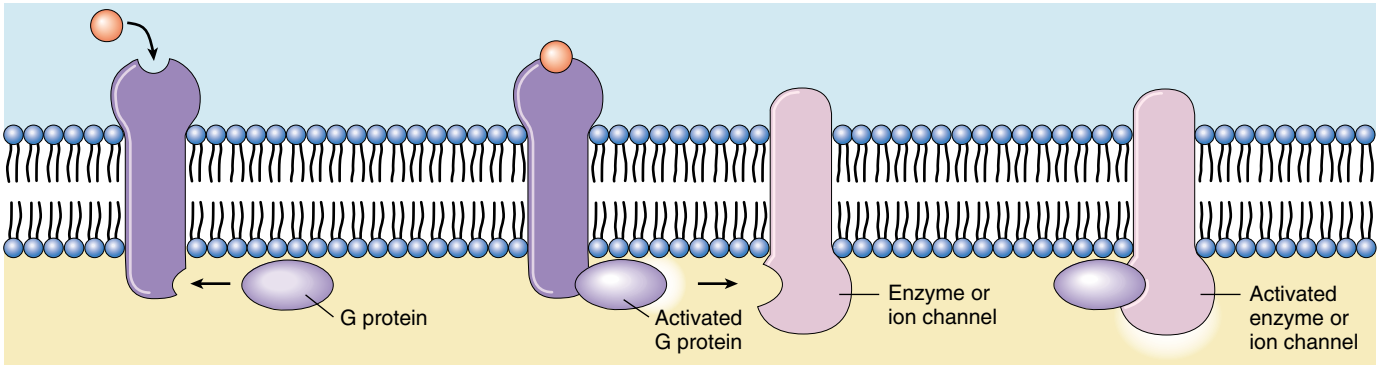
Many cell surface receptors either act as enzymes or are directly linked to enzymes (figure 7.6*b*). When a signal molecule binds to the receptor, it activates the enzyme. In almost all cases, these enzymes are **protein kinases,** enzymes that add phosphate groups to proteins. Most enzymic receptors have the same general structure. Each is a single-pass transmembrane protein (the amino acid chain passes through the plasma membrane only once); the portion that binds the signal molecule lies outside the cell, and the portion that carries out the enzyme activity is exposed to the cytoplasm.



(a) Chemically gated ion channel



(b) Enzymic receptor



(c) G-protein-linked receptor

FIGURE 7.6
Cell surface receptors. (*a*) Chemically gated ion channels are multipass transmembrane proteins that form a pore in the cell membrane. This pore is opened or closed by chemical signals. (*b*) Enzymic receptors are single-pass transmembrane proteins that bind the signal on the extracellular surface. A catalytic region on their cytoplasmic portion then initiates enzymatic activity inside the cell. (*c*) G-protein-linked receptors bind to the signal outside the cell and to G proteins inside the cell. The G protein then activates an enzyme or ion channel, mediating the passage of a signal from the cell's surface to its interior.

G-Protein-Linked Receptors

A third class of cell surface receptors acts indirectly on enzymes or ion channels in the plasma membrane with the aid of an assisting protein, called a *guanosine triphosphate* (GTP)-*binding protein*, or **G protein** (figure 7.6*c*). Receptors in this category use G proteins to mediate passage of the signal from the membrane surface into the cell interior.

How G-Protein-Linked Receptors Work. G proteins are mediators that initiate a diffusible signal in the cytoplasm. They form a transient link between the receptor on the cell surface and the signal pathway within the cytoplasm. Importantly, this signal has a relatively short life span whose active age is determined by GTP. When a signal arrives, it finds the G protein nestled into the G-protein-linked receptor on the cytoplasmic side of the plasma membrane. Once the signal molecule binds to the receptor, the G-protein-linked receptor changes shape. This change in receptor shape twists the G protein, causing it to bind GTP. The G protein can now diffuse away from the receptor. The "activated" complex of a G protein with attached GTP is then free to initiate a number of events. However, this activation is short-lived, because GTP has a relatively short life span (seconds to minutes). This elegant arrangement allows the G proteins to activate numerous pathways, but only in a transient manner. In order for a pathway to "stay on," there must be a continuous source of incoming extracellular signals. When the rate of external signal drops off, the pathway shuts down.

The Largest Family of Cell Surface Receptors. Scientists have identified more than 100 different G-protein-linked receptors, more than any other kind of cell surface receptor. They mediate an incredible range of cell signals, including peptide hormones, neurotransmitters, fatty acids, and amino acids. Despite this great variation in specificity, however, all G-protein-linked receptors whose amino acid sequences are known have a similar structure. They are almost certainly closely related in an evolutionary sense, arising from a single ancestral sequence. Each of these G-protein-linked receptors is a seven-pass transmembrane protein (figure 7.7)—a single polypeptide chain that threads back and forth across the lipid bilayer seven times, creating a channel through the membrane.

Evolutionary Origin of G-Protein-Linked Receptors. As research revealed the structure of G-protein-linked receptors, an interesting pattern emerged: the same seven-pass structural motif is seen again and again, in sensory receptors such as the light-activated rhodopsin protein in the vertebrate eye, in the light-activated bacteriorhodopsin proton pump that plays a key role in bacterial photosynthesis, in the receptor that recognizes the yeast mating factor protein discussed earlier, and in many other sensory receptors. Vertebrate rhodopsin is in fact a G-protein-linked receptor and utilizes a G protein. Bacteriorhodopsin is not. The occurrence of the seven-pass structural motif in both, and in so many other G-protein-linked receptors, suggests that this motif is a very ancient one, and that G-protein-linked receptors may have evolved from sensory receptors of single-celled ancestors.

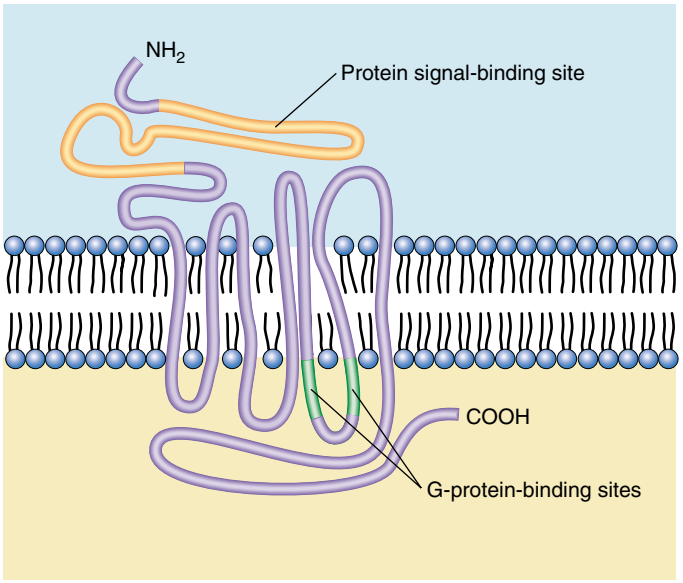


FIGURE 7.7
The G-protein-linked receptor is a seven-pass transmembrane protein.

Discovery of G Proteins. Martin Rodbell of the National Institute of Environmental Health Sciences and Alfred Gilman of the University of Texas Southwestern Medical Center received the 1994 Nobel Prize for Medicine or Physiology for their work on G proteins. Rodbell and Gilman's work has proven to have significant ramifications. G proteins are involved in the mechanism employed by over half of all medicines in use today. Studying G proteins will vastly expand our understanding of how these medicines work. Furthermore, the investigation of G proteins should help elucidate how cells communicate in general and how they contribute to the overall physiology of organisms. As Gilman says, G proteins are "involved in everything from sex in yeast to cognition in humans."

Most receptors are located on the surface of the plasma membrane. Chemically gated ion channels open or close when signal molecules bind to the channel, allowing specific ions to diffuse through. Enzyme receptors typically activate intracellular proteins by phosphorylation. G-protein-linked receptors activate an intermediary protein, which then effects the intracellular change.

7.3 Follow the journey of information into the cell.

Initiating the Intracellular Signal

Some enzymic receptors and most G-protein-linked receptors carry the signal molecule's message into the target cell by utilizing other substances to relay the message within the cytoplasm. These other substances, small molecules or ions commonly called **second messengers** or intracellular mediators, alter the behavior of particular proteins by binding to them and changing their shape. The two most widely used second messengers are cyclic adenosine monophosphate (cAMP) and calcium.

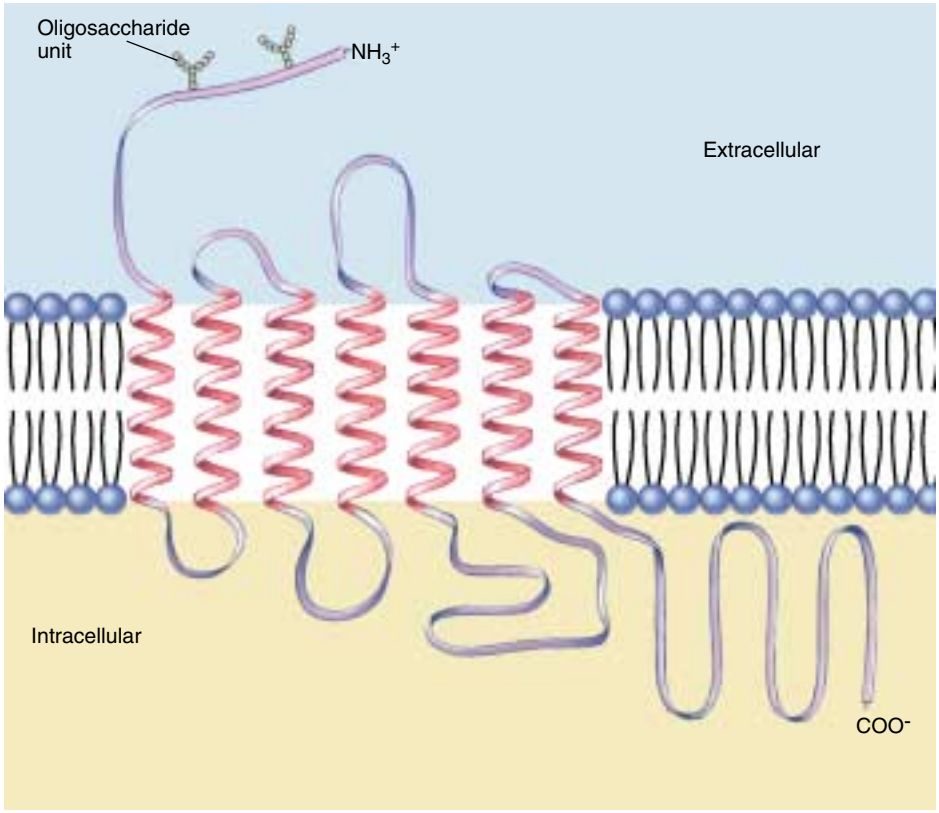


FIGURE 7.8
Structure of the β-adrenergic receptor. The receptor is a G-protein-linked molecule which, when it binds to an extracellular signal molecule, stimulates voluminous production of cAMP inside the cell, which then effects the cellular change.

cAMP

All animal cells studied thus far use **cAMP** as a second messenger (chapter 56 discusses cAMP in detail). To see how cAMP typically works as a messenger, let's examine what happens when the hormone epinephrine binds to a particular type of G-protein-linked receptor called the β-adrenergic receptor (figure 7.8). When epinephrine binds with this receptor, it activates a G protein, which then stimulates the enzyme **adenylyl cyclase** to produce large amounts of cAMP within the cell (figure 7.9*a*). The cAMP then binds to and activates the enzyme α-kinase, which adds phosphates to specific proteins in the cell. The effect this phosphorylation has on cell function depends on the identity of the cell and the proteins that are phosphorylated. In muscle cells, for example, the α-kinase phosphorylates and thereby activates enzymes that stimulate the breakdown of glycogen into glucose and inhibit the synthesis of glycogen from glucose. Glucose is then more available to the muscle cells for metabolism.

Calcium

Calcium (Ca^{++}) ions serve even more widely than cAMP as second messengers. Ca^{++} levels inside the cytoplasm of a cell are normally very low (less than 10^{-7} M), while outside the cell and in the endoplasmic reticulum Ca^{++} levels are quite high (about 10^{-3} M). Chemically gated calcium channels in the endoplasmic reticulum membrane act as switches; when they open, Ca^{++} rushes into the cytoplasm and triggers proteins sensitive to Ca^{++} to initiate a variety of activities. For example, the efflux of Ca^{++} from the endoplasmic reticulum causes skeletal muscle cells to contract and some endocrine cells to secrete hormones.

The gated Ca^{++} channels are opened by a G-protein-linked receptor. In response to signals from other cells, the receptor activates its G protein, which in turn activates the enzyme, *phospholipase C*. This enzyme catalyzes the production of *inositol trisphosphate* (IP_3) from phospholipids in the plasma membrane. The IP_3 molecules diffuse through the cytoplasm to the endoplasmic reticulum and bind to the Ca^{++} channels. This opens the channels and allows Ca^{++} to flow from the endoplasmic reticulum into the cytoplasm (figure 7.9*b*).

Ca^{++} initiates some cellular responses by binding to *calmodulin*, a 148-amino acid cytoplasmic protein that contains four binding sites for Ca^{++} (figure 7.10). When four Ca^{++} ions are bound to calmodulin, the calmodulin/Ca^{++} complex binds to other proteins, and activates them.

Cyclic AMP and Ca^{++} often behave as second messengers, intracellular substances that relay messages from receptors to target proteins.

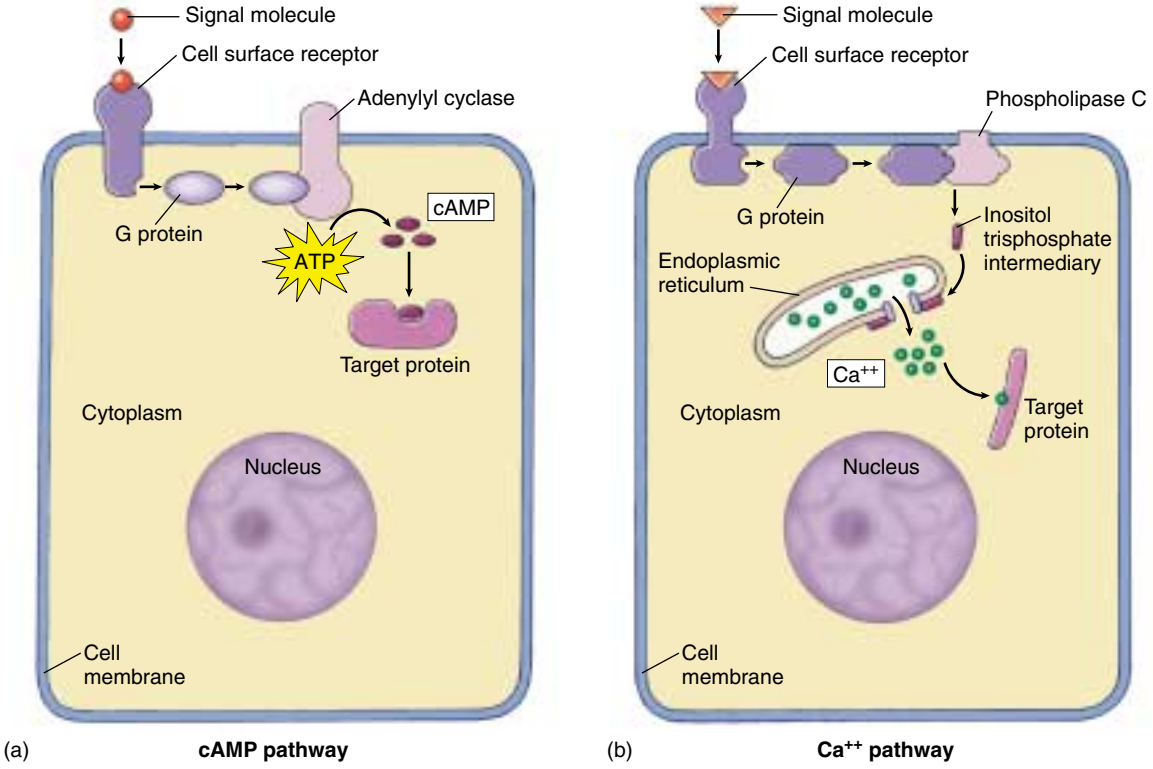


FIGURE 7.9
How second messengers work. (*a*) The cyclic AMP (cAMP) pathway. An extracellular receptor binds to a signal molecule and, through a G protein, activates the membrane-bound enzyme, adenylyl cyclase. This enzyme catalyzes the synthesis of cAMP, which binds to the target protein to initiate the cellular change. (*b*) The calcium (Ca^{++}) pathway. An extracellular receptor binds to another signal molecule and, through another G protein, activates the enzyme phospholipase C. This enzyme stimulates the production of inositol trisphosphate, which binds to and opens calcium channels in the membrane of the endoplasmic reticulum. Ca^{++} is released into the cytoplasm, effecting a change in the cell.

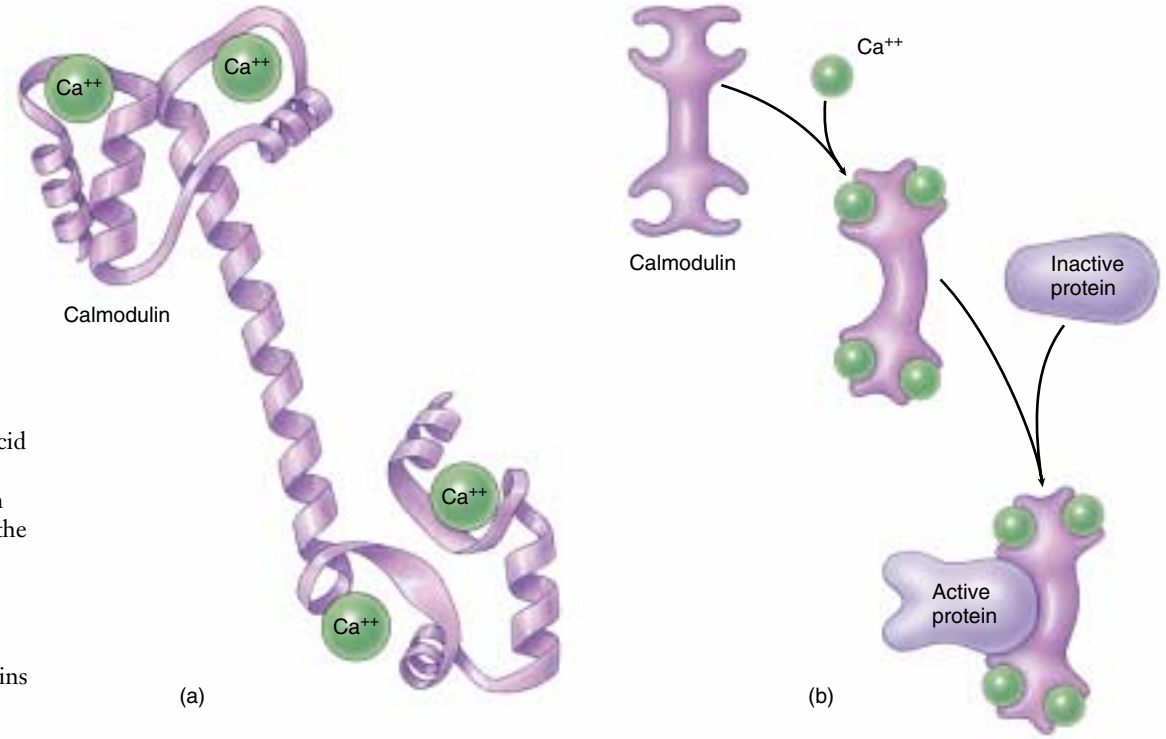


FIGURE 7.10
Calmodulin. (*a*) Calmodulin is a protein containing 148 amino acid residues that mediates Ca^{++} function. (*b*) When four Ca^{++} are bound to the calmodulin molecule, it undergoes a conformational change that allows it to bind to other cytoplasmic proteins and effect cellular responses.

Amplifying the Signal: Protein Kinase Cascades

Both enzyme-linked and G-protein-linked receptors receive signals at the surface of the cell, but as we've seen, the target cell's response rarely takes place there. In most cases the signals are relayed to the cytoplasm or the nucleus by second messengers, which influence the activity of one or more enzymes or genes and so alter the behavior of the cell. But most signaling molecules are found in such low concentrations that their diffusion across the cytoplasm would take a great deal of time unless the signal is amplified. Therefore, most enzyme-linked and G-protein-linked receptors use a chain of other protein messengers to amplify the signal as it is being relayed to the nucleus.

How is the signal amplified? Imagine a relay race where, at the end of each stage, the finishing runner tags five new runners to start the next stage. The number of runners would increase dramatically as the race progresses: 1, then 5, 25, 125, and so on. The same sort of process takes place as a signal is passed from the cell surface to the cytoplasm or nucleus. First the receptor activates a stage-one protein, almost always by phosphorylating it. The receptor either adds a phosphate group directly, or, it activates a G protein that goes on to activate a second protein that does the phosphorylation. Once activated, each of these stage-one proteins in turn activates a large number of stage-two pro-

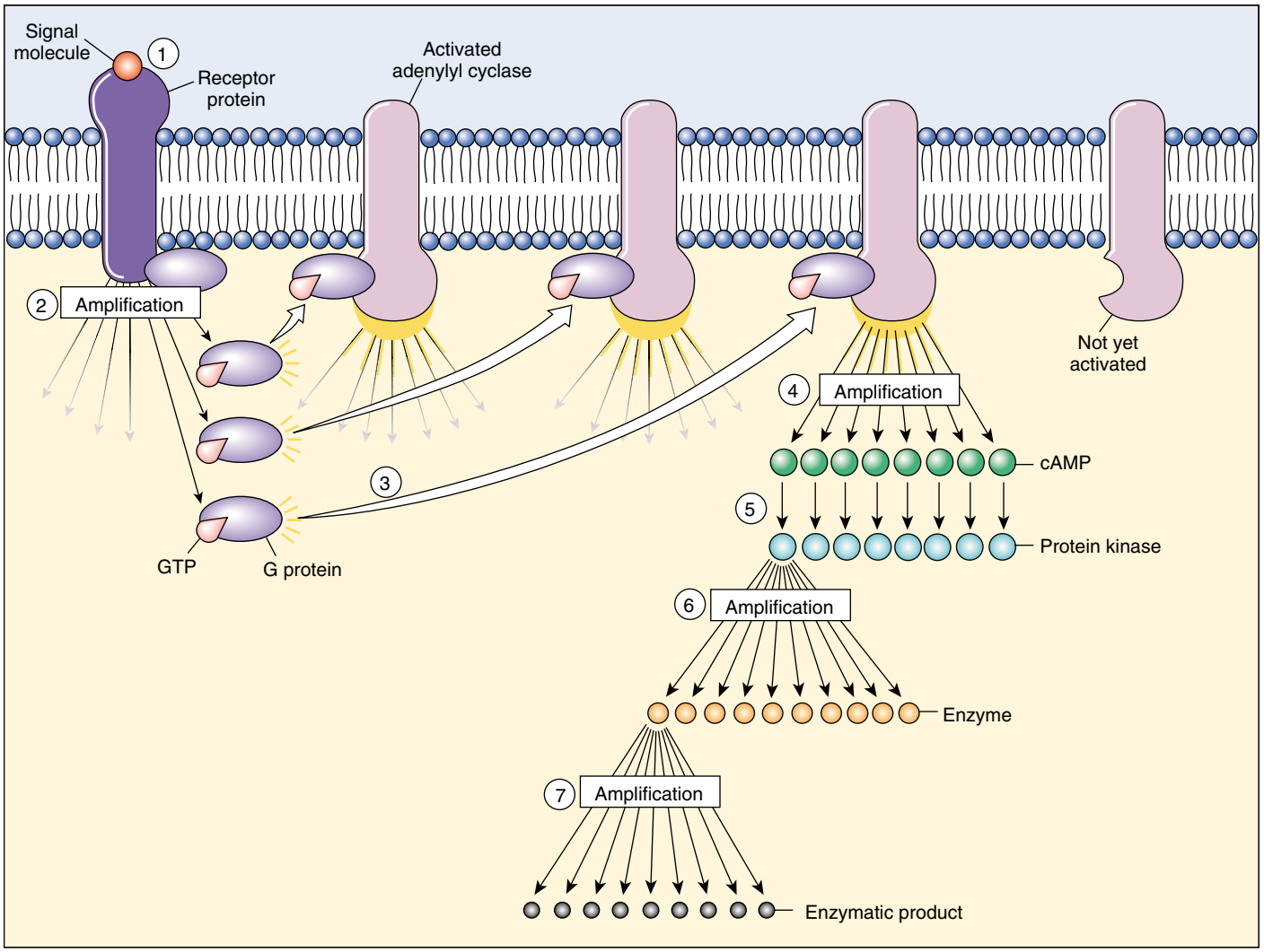
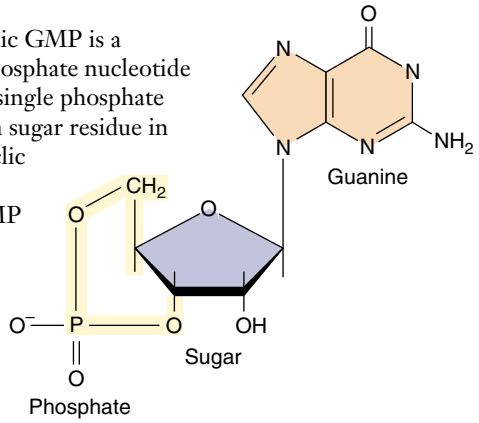


FIGURE 7.11
Signal amplification. Amplification at many steps of the cell-signaling process can ultimately produce a large response by the cell. One cell surface receptor (*1*), for example, may activate many G protein molecules (*2*), each of which activates a molecule of adenylyl cyclase (*3*), yielding an enormous production of cAMP (*4*). Each cAMP molecule in turn will activate a protein kinase (*5*), which can phosphorylate and thereby activate several copies of a specific enzyme (*6*). Each of *those* enzymes can then catalyze many chemical reactions (*7*). Starting with 10^{-10} M of signaling molecule, one cell surface receptor can trigger the production of 10^{-6} M of one of the products, an amplification of four orders of magnitude.

FIGURE 7.12
Cyclic GMP. Cyclic GMP is a guanosine monophosphate nucleotide molecule with the single phosphate group attached to a sugar residue in two places (this cyclic part is shown in yellow). Cyclic GMP is an important second messenger linking G proteins to signal transduction pathways within the cytoplasm.



teins; then each of them activates a large number of stage-three proteins, and so on (figure 7.11). A single cell surface receptor can thus stimulate a cascade of protein kinases to amplify the signal.

The Vision Amplification Cascade

Let's trace a protein amplification cascade to see exactly how one works. In vision, a single light-activated rhodopsin (a G-protein-linked receptor) activates hundreds of molecules of the G protein transducin in the first stage of the relay. In the second stage, each transducin causes an enzyme to modify thousands of molecules of a special inside-the-cell messenger called cyclic GMP (figure 7.12). (We will discuss cyclic GMP in more detail later.) In about 1 second, a single rhodopsin signal passing through this two-step cascade splits more than 10^5 (100,000) cyclic GMP molecules (figure 7.13)! The rod cells of humans are sufficiently sensitive to detect brief flashes of 5 photons.

The Cell Division Amplification Cascade

The amplification of signals traveling from the plasma membrane to the nucleus can be even more complex than the process we've just described. Cell division, for example, is controlled by a receptor that acts as a protein kinase. The receptor responds to growth-promoting signals by phosphorylating an intracellular protein called ras, which then activates a series of interacting phosphorylation cascades, some with five or more stages. If the ras protein becomes hyperactive for any reason, the cell acts as if it is being constantly stimulated to divide. Ras proteins were first discovered in cancer cells. A mutation of the gene that encodes ras had caused it to become hyperactive, resulting in unrestrained cell proliferation. Almost one-third of human cancers have such a mutation in a *ras* gene.

A small number of surface receptors can generate a vast intracellular response, as each stage of the pathway amplifies the next.

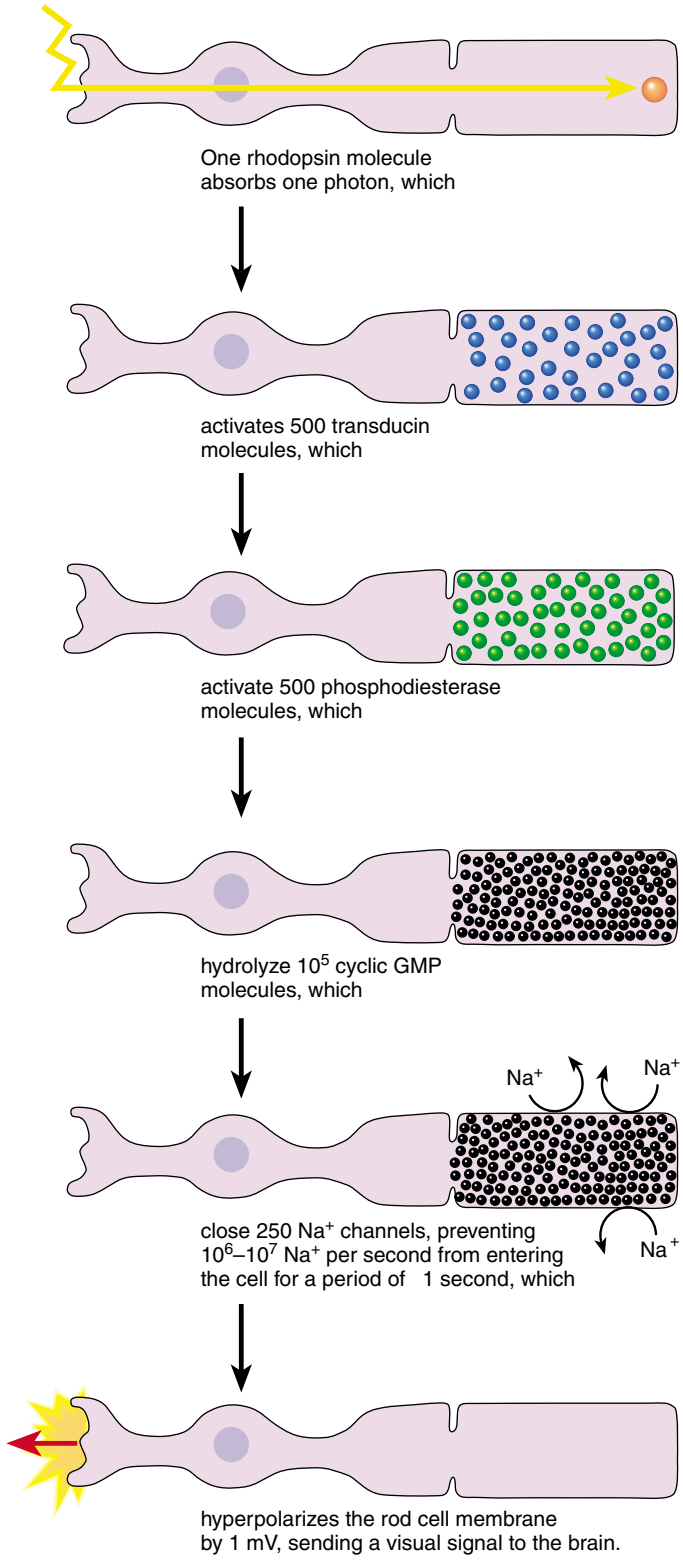


FIGURE 7.13
The role of signal amplification in vision. In this vertebrate rod cell (the cells of the eye responsible for interpreting light and dark), *one* single rhodopsin pigment molecule, when excited by a photon, ultimately yields *100,000* split cGMP molecules, which will then effect a change in the membrane of the rod cell, which will be interpreted by the organism as a visual event.

7.4 Cell surface proteins mediate cell-cell interactions.

The Expression of Cell Identity

With the exception of a few primitive types of organisms, the hallmark of multicellular life is the development of highly specialized groups of cells called **tissues,** such as blood and muscle. Remarkably, each cell within a tissue performs the functions of that tissue and no other, even though all cells of the body are derived from a single fertilized cell and contain the same genetic information. How do cells sense where they are, and how do they "know" which type of tissue they belong to?

Tissue-Specific Identity Markers

As it develops, each animal cell type acquires a unique set of cell surface molecules. These molecules serve as markers proclaiming the cells' tissue-specific identity. Other cells that make direct physical contact with them "read" the markers.

Glycolipids. Most tissue-specific cell surface markers are glycolipids, lipids with carbohydrate heads. The glycolipids on the surface of red blood cells are also responsible for the differences among A, B, and O blood types. As the cells in a tissue divide and differentiate, the population of cell surface glycolipids changes dramatically.

MHC Proteins. The immune system uses other cell surface markers to distinguish between "self" and "nonself" cells. All of the cells of a given individual, for example, have the same "self" markers, called *major histocompatibility complex* (MHC) *proteins.* Because practically every individual makes a different set of MHC proteins, they serve as distinctive identity tags for each individual. The MHC proteins and other self-identifying markers are single-pass proteins anchored in the plasma membrane, and many of them are members of a large superfamily of receptors, the immunoglobulins (figure 7.14). Cells of the immune system continually inspect the other cells they encounter in the body, triggering the destruction of cells that display foreign or "nonself" identity markers.

The immune systems of vertebrates, described in detail in chapter 57, shows an exceptional ability to distinguish self from nonself. However, other vertebrates and even some simple animals like sponges are able to make this distinction to some degree, even though they lack a complex immune system.

Every cell contains a specific array of marker proteins on its surface. These markers identify each type of cell in a very precise way.

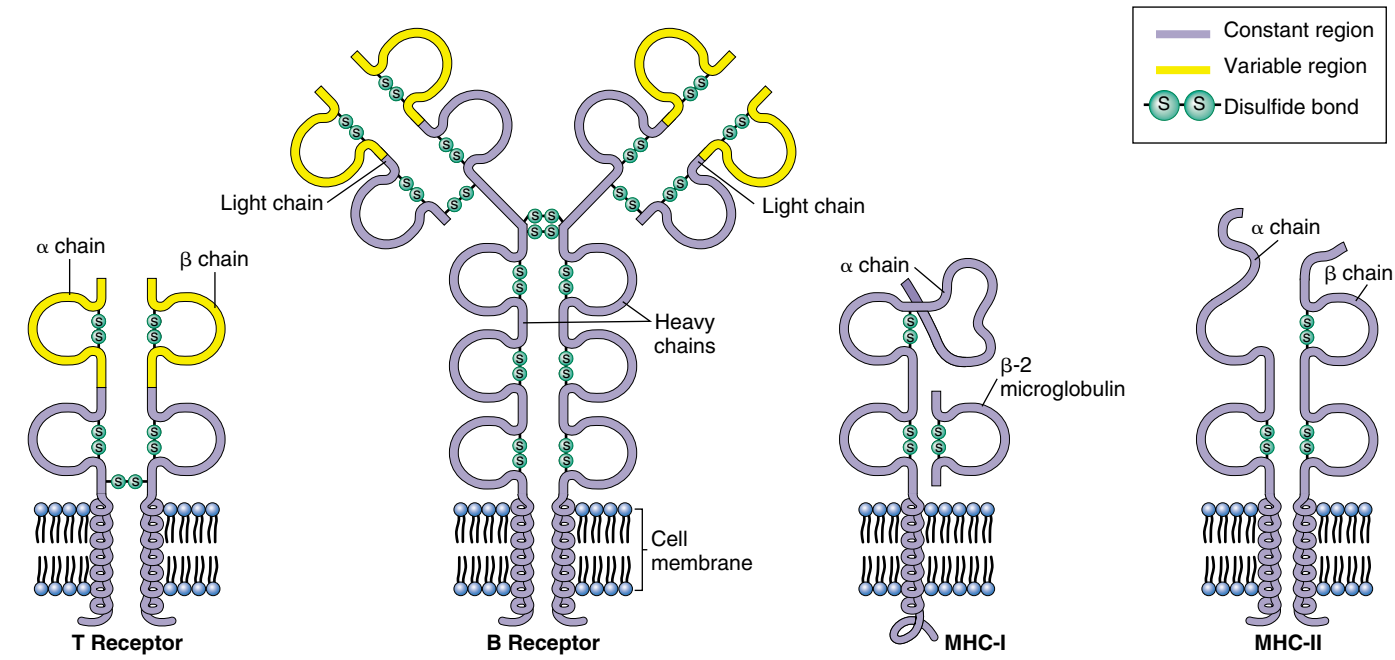


FIGURE 7.14
Structure of the immunoglobulin family of cell surface marker proteins. T and B cell receptors help mediate the immune response in organisms by recognizing and binding to foreign cell markers. MHC antigens label cells as "self," so that the immune system attacks only invading entities, such as bacteria, viruses, and usually even the cells of transplanted organs!

Intercellular Adhesion

Not all physical contacts between cells in a multicellular organism are fleeting touches. In fact, most cells are in physical contact with other cells at all times, usually as members of organized tissues such as those in the lungs, heart, or gut. These cells and the mass of other cells clustered around them form long-lasting or permanent connections with each other called **cell junctions** (figure 7.15). The nature of the physical connections between the cells of a tissue in large measure determines what the tissue is like. Indeed, a tissue's proper functioning often depends critically upon how the individual cells are arranged within it. Just as a house cannot maintain its structure without nails and cement, so a tissue cannot maintain its characteristic architecture without the appropriate cell junctions.

Cells attach themselves to one another with long-lasting bonds called cell junctions.

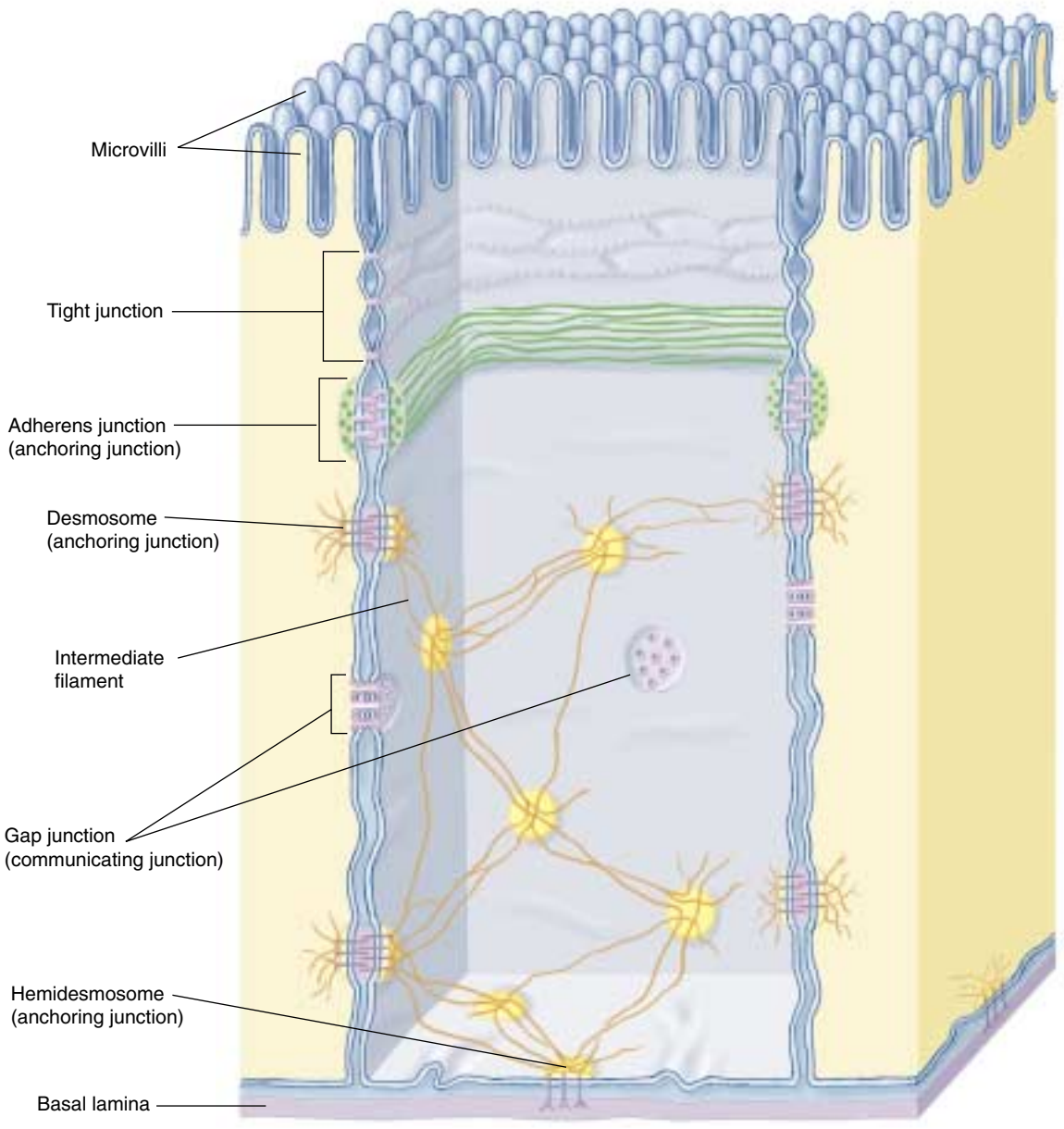


FIGURE 7.15
A summary of cell junction types. Gut epithelial cells are used here to illustrate the comparative structures and locations of common cell junctions.

Tight Junctions

Cell junctions are divided into three categories, based upon the functions they serve (figure 7.16): tight junctions, anchoring junctions, and communicating junctions.

Sometimes called occluding junctions, tight junctions connect the plasma membranes of adjacent cells in a sheet, preventing small molecules from leaking between the cells and through the sheet (figure 7.17). This allows the sheet of cells to act as a wall within the organ, keeping molecules on one side or the other.

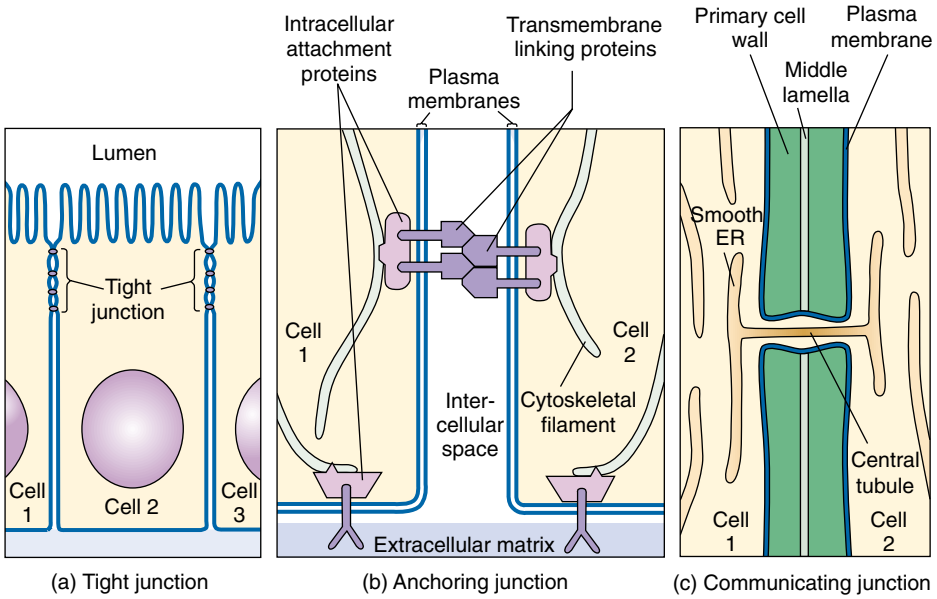


FIGURE 7.16
The three types of cell junctions. These three models represent current thinking on how the structures of the three major types of cell junctions facilitate their function: (*a*) tight junction; (*b*) anchoring junction; (*c*) communicating junction.

Creating Sheets of Cells

The cells that line an animal's digestive tract are organized in a sheet only one cell thick. One surface of the sheet faces the inside of the tract and the other faces the extracellular space where blood vessels are located. Tight junctions encircle each cell in the sheet, like a belt cinched around a pair of pants. The junctions between neighboring cells are so securely attached that there is no space between them for leakage. Hence, nutrients absorbed from the food in the digestive tract must pass directly through the cells in the sheet to enter the blood.

Partitioning the Sheet

The tight junctions between the cells lining the digestive tract also partition the plasma membranes of these cells into separate compartments. Transport proteins in the membrane facing the inside of the tract carry nutrients from that side to the cytoplasm of the cells. Other proteins, located in the membrane on the opposite side of the cells, transport those nutrients from the cytoplasm to the extracellular fluid, where they can enter the blood. For the sheet to absorb nutrients properly, these proteins must remain in the correct locations within the fluid membrane. Tight junctions effectively segregate the proteins on opposite sides of the sheet, preventing them from drifting within the membrane from one side of the sheet to the other. When tight junctions are experimentally disrupted, just this sort of migration occurs.

Tight junctions connect the plasma membranes of adjacent cells into sheets.

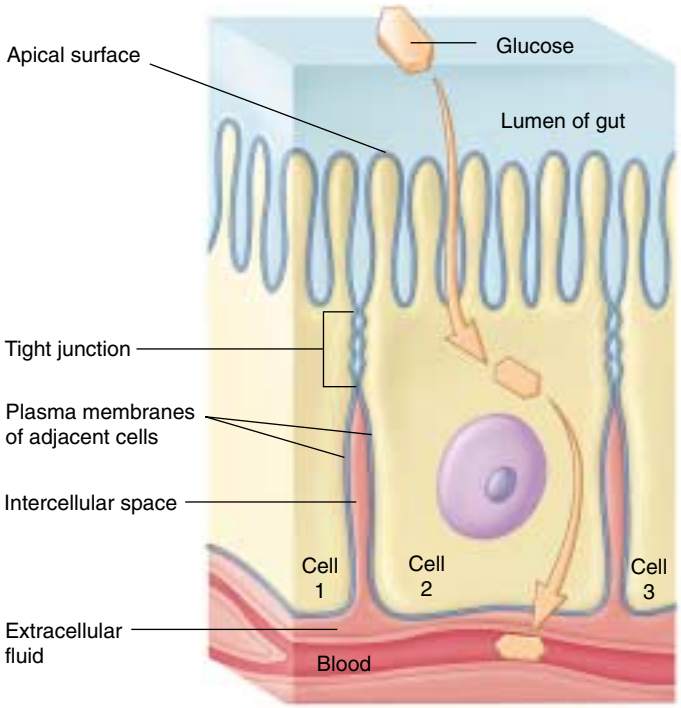


FIGURE 7.17
Tight junctions. Encircling the cell like a tight belt, these intercellular contacts ensure that materials move through the cells rather than between them.

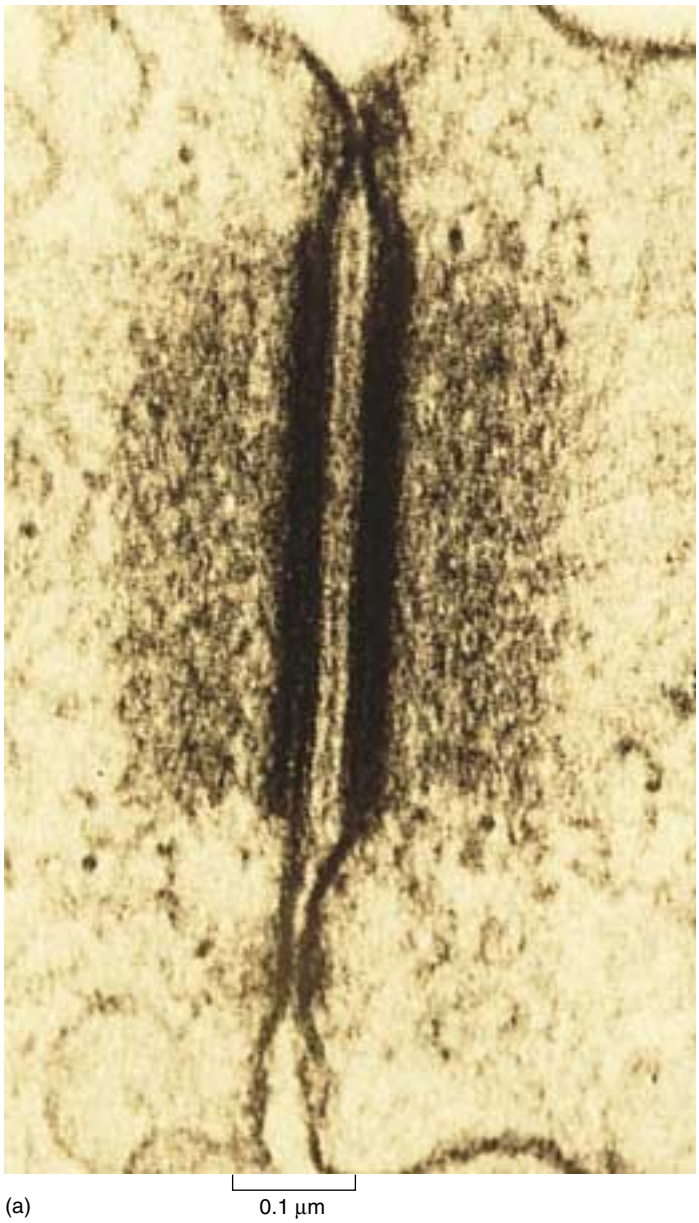
Anchoring Junctions

Anchoring junctions mechanically attach the cytoskeleton of a cell to the cytoskeletons of other cells or to the extracellular matrix. They are commonest in tissues subject to mechanical stress, such as muscle and skin epithelium.

Cadherin and Intermediate Filaments: Desmosomes

Anchoring junctions called **desmosomes** connect the cytoskeletons of adjacent cells (figure 7.18), while hemidesmosomes anchor epithelial cells to a basement membrane. Proteins called cadherins, most of which are single-pass transmembrane glycoproteins, create the critical link. A variety of attachment proteins link the short cytoplasmic end of a cadherin to the intermediate filaments in the cytoskeleton. The other end of the cadherin molecule projects outward from the plasma membrane, joining directly with a cadherin protruding from an adjacent cell in a firm handshake binding the cells together.

Connections between proteins tethered to the intermediate filaments are much more secure than connections between free-floating membrane proteins. Proteins are suspended within the membrane by relatively weak interactions between the nonpolar portions of the protein and the membrane lipids. It would not take much force to pull an untethered protein completely out of the membrane, as if pulling an unanchored raft out of the water.



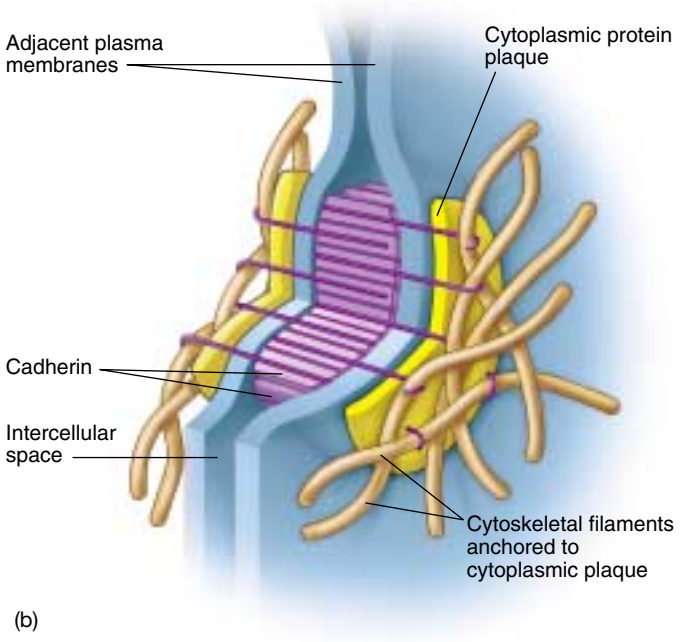


FIGURE 7.18
Desmosomes. (*a*) Desmosomes anchor adjacent cells to each other. (*b*) Cadherin proteins create the adhering link between adjoining cells.

Cadherin and Actin Filaments

Cadherins can also connect the actin frameworks of cells in cadherin-mediated junctions (figure 7.19). When they do, they form less stable links between cells than when they connect intermediate filaments. Many kinds of actin-linking cadherins occur in different tissues, as well as in the same tissue at different times. During vertebrate development, the migration of neurons in the embryo is associated with changes in the type of cadherin expressed on their plasma membranes. This suggests that gene-controlled changes in cadherin expression may provide the migrating cells with a "roadmap" to their destination.

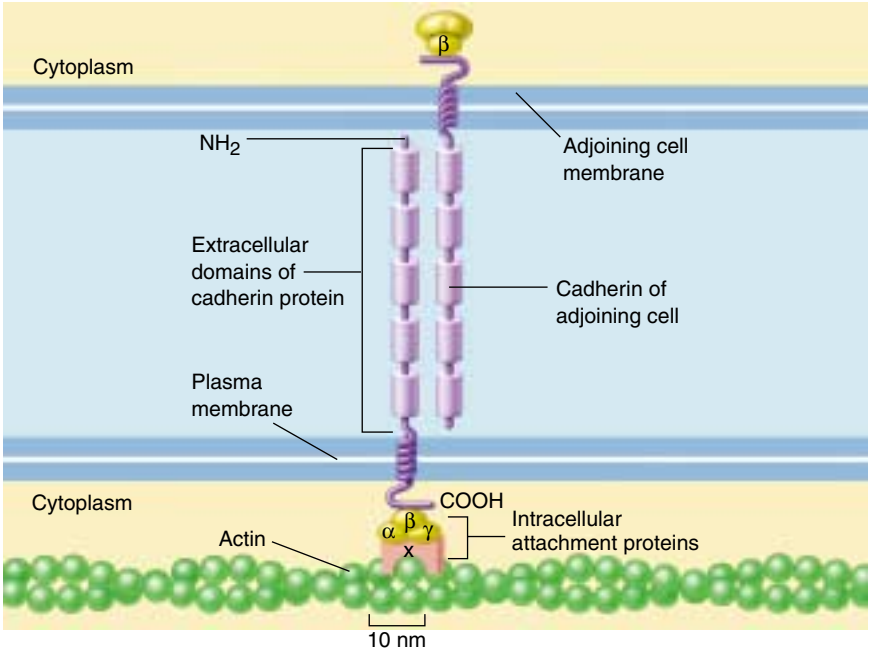


FIGURE 7.19
A cadherin-mediated junction. The cadherin molecule is anchored to actin in the cytoskeleton and passes through the membrane to interact with the cadherin of an adjoining cell.

Integrin-Mediated Links

Anchoring junctions called **adherens junctions** are another type of junction that connects the actin filaments of one cell with those of neighboring cells or with the extracellular matrix (figure 7.20). The linking proteins in these junctions are members of a large superfamily of cell surface receptors called integrins. Each integrin is a transmembrane protein composed of two different glycoprotein subunits that extend outward from the plasma membrane. Together, these subunits bind a protein component of the extracellular matrix, like two hands clasping a pole. There appear to be many different kinds of integrin (cell biologists have identified 20), each with a slightly different shaped "hand." The exact component of the matrix that a given cell binds to depends on which combination of integrins that cell has in its plasma membrane.

Anchoring junctions attach the cytoskeleton of a cell to the matrix surrounding the cell, or to the cytoskeleton of another cell.

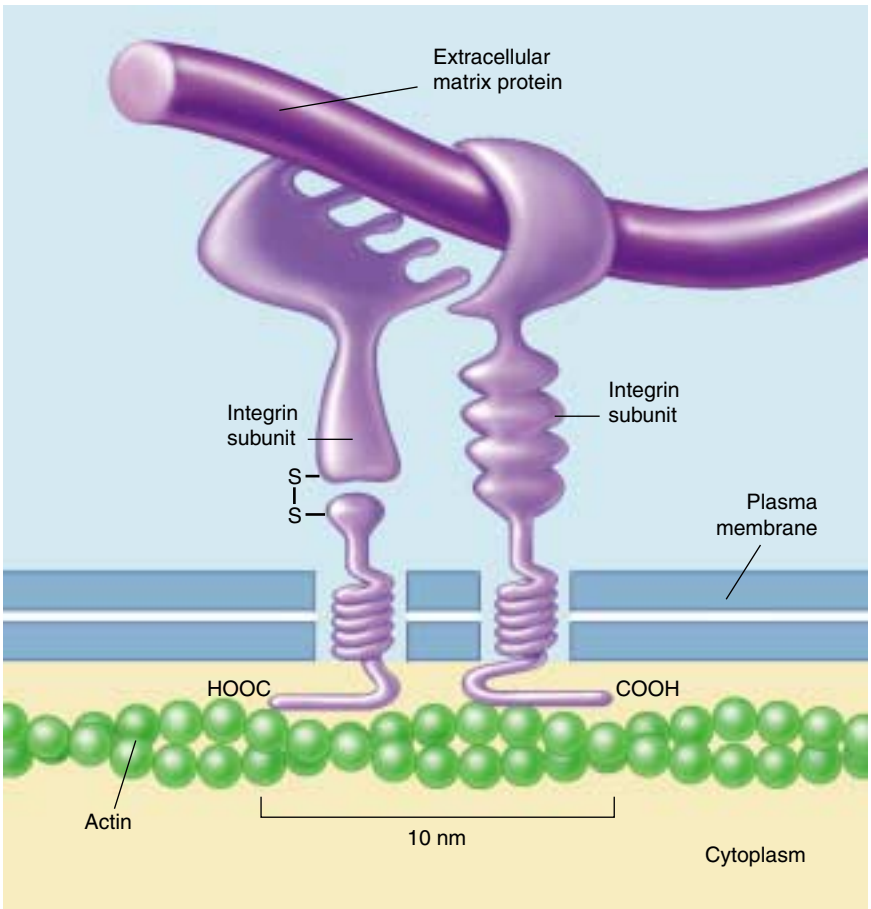


FIGURE 7.20
An integrin-mediated junction. These adherens junctions link the actin filaments inside cells to their neighbors and to the extracellular matrix.

Communicating Junctions

Many cells communicate with adjacent cells through direct connections, called **communicating junctions.** In these junctions, a chemical signal passes directly from one cell to an adjacent one. Communicating junctions establish direct physical connections that link the cytoplasms of two cells together, permitting small molecules or ions to pass from one to the other. In animals, these direct communication channels between cells are called gap junctions. In plants, they are called plasmodesmata.

Gap Junctions in Animals

Communicating junctions called gap junctions are composed of structures called connexons, complexes of six identical transmembrane proteins (figure 7.21). The proteins in a connexon are arranged in a circle to create a channel through the plasma membrane that protrudes several nanometers from the cell surface. A gap junction forms when the connexons of two cells align perfectly, creating an open channel spanning the plasma membranes of both cells. Gap junctions provide passageways large enough to permit small substances, such as simple sugars and amino acids, to pass from the cytoplasm of one cell to that of the next, yet small enough to prevent the passage of larger molecules such as proteins. The connexons hold the plasma membranes of the paired cells about 4 nanometers apart, in marked contrast to the more-or-less direct contact between the lipid bilayers in a tight junction.

Gap junction channels are dynamic structures that can open or close in response to a variety of factors, including Ca^{++} and H^{+} ions. This gating serves at least one important function. When a cell is damaged, its plasma membrane often becomes leaky. Ions in high concentrations outside the cell, such as Ca^{++}, flow into the damaged cell and shut its gap junction channels. This isolates the cell and so prevents the damage from spreading to other cells.

Plasmodesmata in Plants

In plants, cell walls separate every cell from all others. Cell-cell junctions occur only at holes or gaps in the walls, where the plasma membranes of adjacent cells can come into contact with each other. Cytoplasmic connections that form across the touching plasma membranes are called plasmodesmata (figure 7.22). The majority of living cells within a higher plant are connected with their neighbors by these junctions. Plasmodesmata function much like gap junctions in animal cells, although their structure is more complex. Unlike gap junctions, plasmodesmata are lined with plasma membrane and contain a central tubule that connects the endoplasmic reticulum of the two cells.

Communicating junctions permit the controlled passage of small molecules or ions between cells.

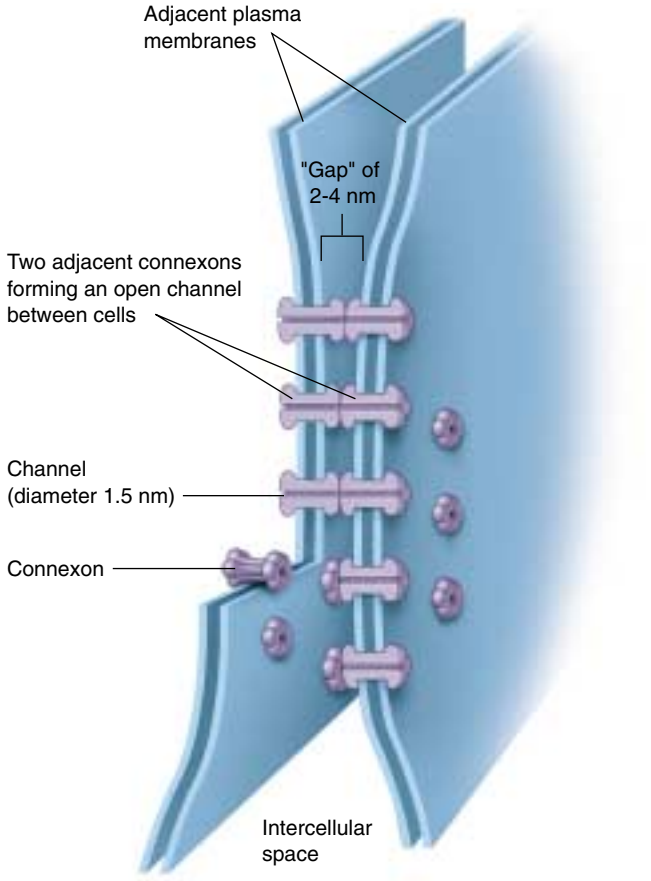


FIGURE 7.21
Gap junctions. Connexons in gap junctions create passageways that connect the cytoplasms of adjoining cells. Gap junctions readily allow the passage of small molecules and ions required for rapid communication (such as in heart tissue), but do not allow the passage of larger molecules like proteins.

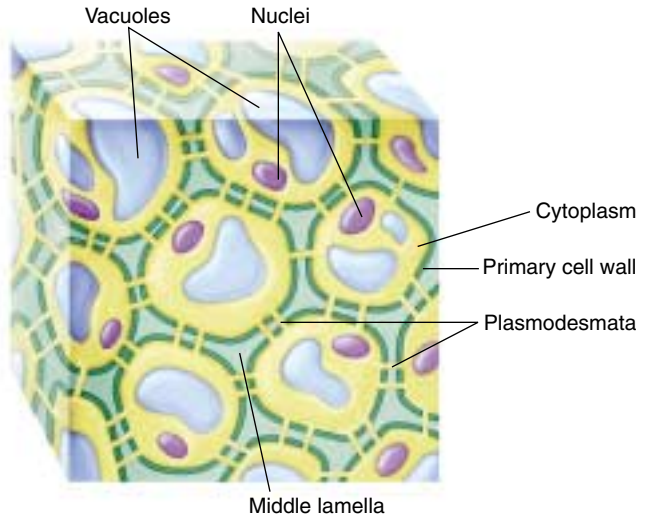


FIGURE 7.22
Plasmodesmata. Plant cells can communicate through specialized openings in their cell walls, called plasmodesmata, where the cytoplasms of adjoining cells are connected.

Summary

Questions

Media Resources

7.1 Cells signal one another with chemicals.

- Cell signaling is accomplished through the recognition of signal molecules by target cells.

1. What determines which signal molecules in the extracellular environment a cell will respond to?

2. How do paracrine, endocrine, and synaptic signaling differ?

- Cell Interactions
- Student Research: Retrograde Messengers between Nerve Cells
- Student Research: Vertebrate Limb formation

7.2 Proteins in the cell and on its surface receive signals from other cells.

- The binding of a signal molecule to an intracellular receptor usually initiates transcription of specific regions of DNA, ultimately resulting in the production of specific proteins.
- Cell surface receptors bind to specific molecules in the extracellular fluid. In some cases, this binding causes the receptor to enzymatically alter other (usually internal) proteins, typically through phosphorylation.
- G proteins behave as intracellular shuttles, moving from an activated receptor to other areas in the cell.

3. Describe two of the ways in which intracellular receptors control cell activities.

4. What structural features are characteristic of chemically gated ion channels, and how are these features related to the function of the channels?

5. What are G proteins? How do they participate in cellular responses mediated by G-protein-linked receptors?

7.3 Follow the journey of information into the cell.

- There are usually several amplifying steps between the binding of a signal molecule to a cell surface receptor and the response of the cell. These steps often involve phosphorylation by protein kinases.

6. How does the binding of a single signal molecule to a cell surface receptor result in an amplified response within the target cell?

- Exploration: Cell-Cell Interactions
- Scientists on Science: G Proteins

7.4 Cell surface proteins mediate cell-cell interactions.

- Tight junctions and desmosomes enable cells to adhere in tight, leakproof sheets, holding the cells together such that materials cannot pass between them.
- Gap junctions (in animals) and plasmodesmata (in plants) permit small substances to pass directly from cell to cell through special passageways.

7. What are the functions of tight junctions? What are the functions of desmosomes and adherens junctions, and what proteins are involved in these junctions?

8. What are the molecular components that make up gap junctions? What sorts of substances can pass through gap junctions?

9. Where are plasmodesmata found? What cellular constituents are found in plasmodesmata?