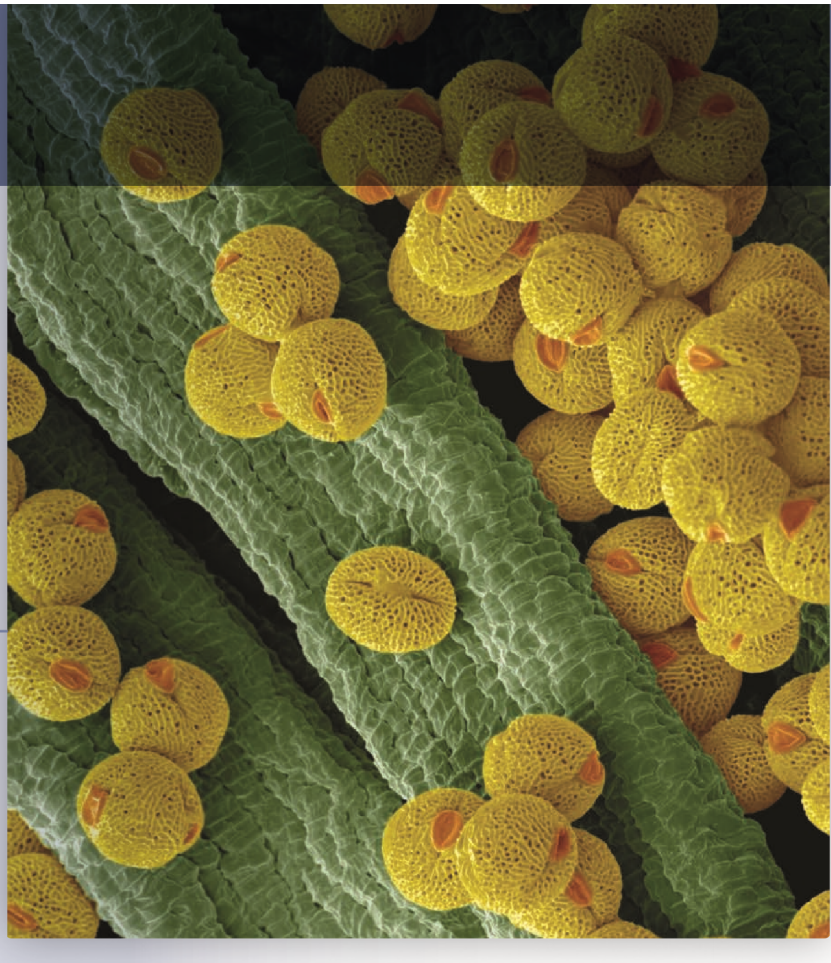
CHAPTER 9

Cell Communication



Chapter Contents

Introduction

Springtime is a time of rebirth and renewal. Trees that have appeared dead produce new leaves and buds, and flowers sprout from the ground. For sufferers of seasonal allergy, this is not quite such a pleasant time. The pollen in the micrograph and other allergens produced stimulate the immune system to produce the molecule histamine and other molecules that form cellular signals. These signals cause inflammation, mucus secretion, vasodilation, and other responses that together cause the runny nose, itching, watery eyes, and other symptoms that make up the allergic reaction. We treat allergy symptoms by using drugs called antihistamines that interfere with this cellular signaling. The popular drug loratadine (better known as Claritin), for example, acts by blocking the receptor for histamine, thus preventing its action.

We will begin this chapter with a general overview of signaling, and the kinds of receptors cells use to respond to signals. Then we will look in more detail at how these different types of receptors can elicit a response from cells, and finally, how cells make connections with one another.

9.1 Overview of Cell Communication

Learning Outcomes

1. *Discriminate between methods of signaling based on distance from source to reception.*
2. *Describe how phosphorylation can affect protein function.*

Communication between cells is common in nature. Cell signaling occurs in all multicellular organisms, providing an indispensable mechanism for cells to influence one another. Effective signaling requires a signaling molecule, called a **ligand,** and a molecule to which the signal binds, called a **receptor protein.** The interaction of these two components initiates the process of *signal transduction,* which converts the information in the signal into a cellular response (figure 9.1).

The cells of multicellular organisms use a variety of molecules as signals, including but not limited to, peptides, large proteins, individual amino acids, nucleotides, and steroids and other lipids. Even dissolved gases such as NO (nitric oxide) are used as signals.

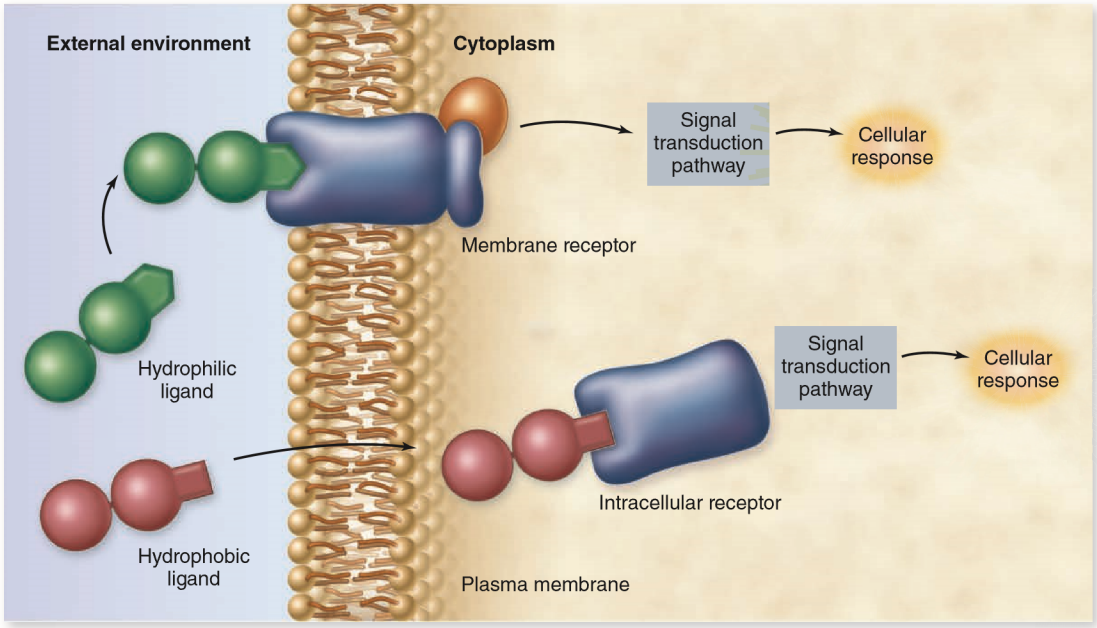


Figure 9.1 Overview of cell signaling. Cell signaling involves a signal molecule called a ligand, a receptor, and a signal transduction pathway that produces a cellular response. The location of the receptor can either be intracellular, for hydrophobic ligands that can cross the membrane, or in the plasma membrane, for hydrophilic ligands that cannot cross the membrane.

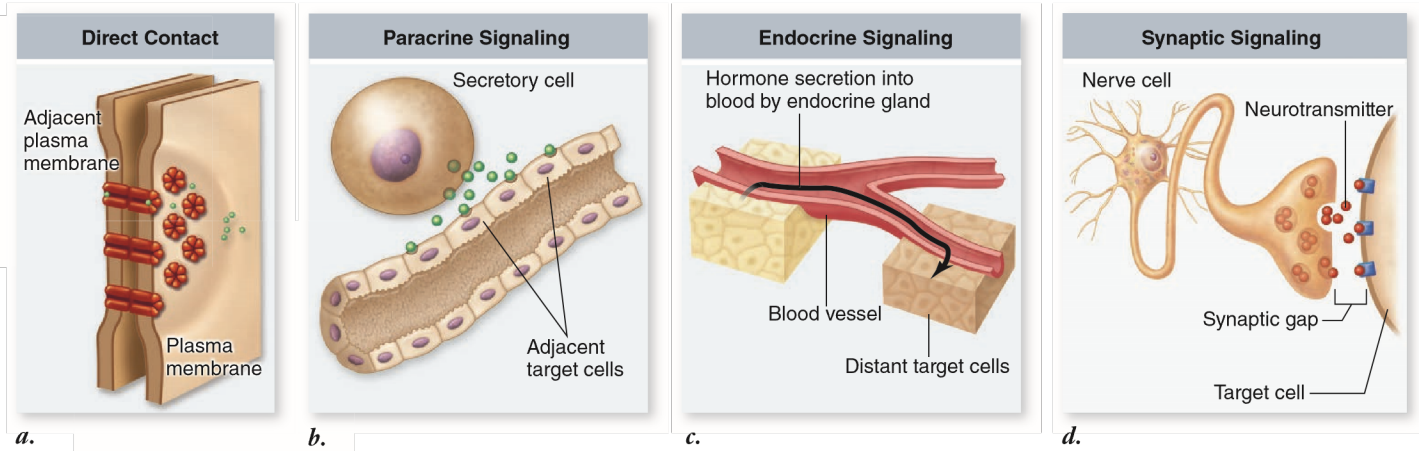
Any cell of a multicellular organism is exposed to a constant stream of signals. At any time, hundreds of different chemical signals may be present in the environment surrounding the cell. Each cell responds only to certain signals, however, and ignores the rest, like a person following the conversation of one or two individuals in a noisy, crowded room.

How does a cell "choose" which signals to respond to? The number and kind of receptor molecules determine this. When a ligand approaches a receptor protein that has a complementary shape, the two can bind, forming a complex. This binding induces a change in the receptor protein's shape, ultimately producing a response in the cell via a signal transduction pathway. In this way, a given cell responds to the signaling molecules that fit the particular set of receptor proteins it possesses and ignores those for which it lacks receptors.

Signaling is defined by the distance from source to receptor

Cells can communicate through any of four basic mechanisms, depending primarily on the distance between the signaling and responding cells (figure 9.2). These mechanisms are (1) direct contact, (2) paracrine signaling, (3) endocrine signaling, and (4) synaptic signaling.

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, and it is an important component of signaling in the immune system (see chapter 51).



a. *b.* *c.* *d.*

Figure 9.2 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 organism's circulatory system, which carries them to the target cells. ***d.*** Chemical synapse signaling involves transmission of signal molecules, called neurotransmitters, from a neuron over a small synaptic gap to the target cell.

Direct contact

As you saw in chapter 5, the surface of a eukaryotic cell is richly populated with 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 plasma membrane of one cell can be recognized by receptors on the plasma membrane of an adjacent cell. Many of the important interactions between cells in early development occur by means of direct contact between cell surfaces. Cells also signal through gap junctions (figure 9.2*a*). We'll examine contact-dependent interactions during development in chapter 19.

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 9.2*b*).

Like direct contact, paracrine signaling plays an important role in early development, coordinating the activities of clusters of neighboring cells. The immune response in vertebrates also involves paracrine signaling between immune cells (see chapter 51).

Endocrine signaling

A released signal molecule that remains in the extracellular fluid 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 9.2*c*). Chapter 45 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 as hormones do. Rather, the long, fiberlike extensions of nerve cells release neurotransmitters from their tips very close to the target cells (figure 9.2*d*). The association of a neuron and its target cell is called a **chemical synapse,** and this type of intercellular communication is called **synaptic signaling.** Whereas paracrine signals move through the fluid between cells, neuro-transmitters cross the synaptic gap and persist only briefly. We will examine synaptic signaling more fully in chapter 43.

Signal transduction pathways lead to cellular responses

The types of signaling just outlined are descriptive and say nothing about how cells respond to signals. The events that occur within the cell on receipt of a signal are called **signal transduction.** These events form discrete pathways that lead to a cellular response to the signal received by receptors. Knowledge of these signal transduction pathways has accumulated over many years of work and indicates a high degree of complexity that explains how in some cases different cell types can have the same response to different signals, and in other cases different cell types can have a different response to the same signal.

For example, a variety of cell types respond to the hormone glucagon by mobilizing glucose as part of the body's mechanism to control blood glucose (see chapter 45). This involves breaking down stored glycogen into glucose and turning on the genes that encode the enzymes necessary to synthesize glucose. In contrast, the hormone epinephrine has diverse effects on different cell types. We have all been startled or frightened by a sudden event. Your heart beats faster, you feel more alert, and you can even feel the hairs on your skin stand up. All of this is due in part to your body releasing the hormone epinephrine (also called adrenaline) into the bloodstream. This leads to the heightened state of alertness and increased heart rate and energy that prepare us to respond to extreme situations.

These differing effects of epinephrine depend on the different cell types with receptors for this hormone. In the liver, cells are stimulated to mobilize glucose, while in the heart muscle cells contract more forcefully to increase blood flow. In addition, blood vessels respond by expanding in some areas and contracting in others to redirect blood flow to the liver, heart, and skeletal muscles. These different reactions depend on the fact that each cell type has a receptor for epinephrine, but different sets of proteins that respond to this signal.

Phosphorylation is key in control of protein function

The function of a signal transduction pathway is to change the behavior or nature of a cell. This action may require changing the composition of proteins that make up a cell or altering the activity of cellular proteins. Many proteins are inactive or nonfunctional as they are initially synthesized and require modification after synthesis for activation. In other cases, a protein may be deactivated by modification. A major source of control for protein function is the addition or removal of phosphate groups, called **phosphorylation** or **dephosphorylation,** respectively.

As you learned in chapters 7 and 8, the end result of the metabolic pathways of cellular respiration and photosynthesis was the phosphorylation of ADP to ATP. The ATP synthesized by these processes can donate phosphate groups to proteins. The phosphorylation of proteins alters their function by either turning their activity on or off. This is one way that the information from extracellular signals can result in changes in cellular activities.

Protein kinases

The class of enzyme that adds phosphate groups from ATP to proteins is called a *protein kinase.* These phosphate groups can be added to the three amino acids that have an OH as part of their R group, namely serine, threonine, and tyrosine. We categorize protein kinases as either serine–threonine or tyrosine kinases based on the amino acids they modify (figure 9.3). Most cytoplasmic protein kinases fall into the serine–threonine kinase class.

Phosphatases

Part of the reason for the versatility of phosphorylation as a form of protein modification is that it is reversible. Another class of enzymes called **phosphatases** removes phosphate groups, reversing the action of kinases (figure 9.3). Thus, a protein activated by a kinase will be deactivated by a phosphatase, and a protein deactivated by a kinase will be activated by a phosphatase.

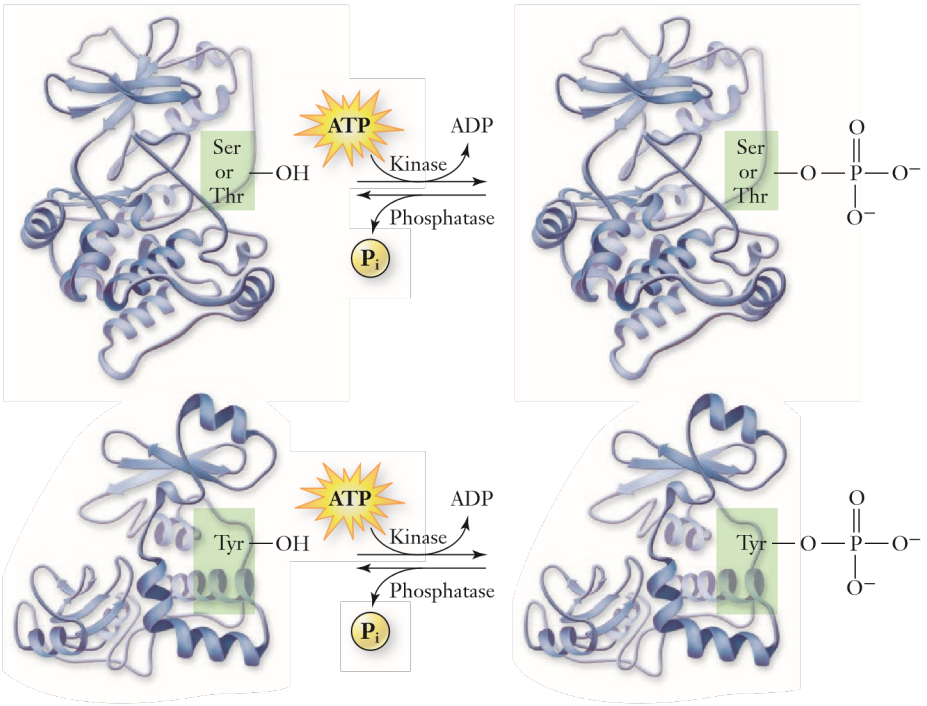


Figure 9.3 Phosphorylation of proteins. Many proteins are controlled by their phosphorylation state—that is, they are activated by phosphorylation and deactivated by dephosphorylation or the reverse. The enzymes that add phosphate groups are called kinases. These form two classes depending on the amino acid the phosphate is added to, either serine–threonine kinases or tyrosine kinases. The action of kinases is reversed by protein phosphatase enzymes.

Learning Outcomes Review 9.1

Cell communication involves chemical signals, or ligands, that bind to cellular receptors. Binding of ligand to receptor initiates signal transduction pathways that lead to a cellular response. Different cells may have the same response to one signal and the same signal can also elicit different responses in different cells. The phosphorylation–dephosphorylation of proteins is a common mechanism of controlling protein function found in signaling pathways.

- *How are receptor ligand interactions similar to enzyme substrate interactions?*

9.2 Receptor Types

Learning Outcome

1. *Contrast the different types of receptors.*

Understanding cell signaling requires first understanding the receptors themselves. For a cell to be able to respond to a specific signaling molecule, it must have a receptor that can bind to the signaling molecule. This specific binding interaction of receptor and ligand is an example of molecular recognition, where one molecule interacts with another based on their complementary shapes. This interaction causes subtle changes in the structure of the receptor, thereby activating it. This is the beginning of any signal transduction pathway.

Receptors are defined by location

Receptors can be differentiated based on their location and the chemical nature of their ligands. Intracellular receptors bind to hydrophobic ligands that can easily cross the plasma membrane to enter the cell. In contrast, cell-surface or membrane receptors bind to hydrophilic ligands outside the cell because these ligands cannot easily cross the membrane (see figure 9.1). Membrane receptors are transmembrane proteins with cytoplasmic and extracellular domains that allow them to interact with other molecules both inside and outside the cell. Table 9.1 summarizes the types of receptors and communication mechanisms discussed in this chapter.

Membrane receptors include three subclasses

When a receptor is a transmembrane protein, the ligand binds to the receptor outside of the cell and never actually crosses the plasma membrane. In this case, the receptor itself, and not the signaling molecule is responsible for information crossing the membrane. Membrane receptors can be categorized based on their structure and function.

Channel-linked receptors

Chemically gated ion channels are receptor proteins that allow the passage of ions (figure 9.4*a*). The receptor proteins that bind many neurotransmitters have the same basic structure. Each is a membrane protein with multiple transmembrane domains, 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 only when a chemical (the neurotransmitter) binds to it. The type of ion that flows across the membrane when a chemically gated ion channel opens depends on the shape and charge structure of the channel. Sodium, potassium, calcium, and chloride ions all have specific ion channels.

TABLE 9.1	Receptors Involved in Cell Signaling		
Receptor Type	**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
Enzymatic receptors	Single-pass transmembrane protein	Binds signal extracellularly; catalyzes response intracellularly	Phosphorylation of protein kinases
G protein–coupled 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

The acetylcholine receptor found in muscle cell membranes functions as an Na^+ channel. When the receptor binds to its ligand, the neurotransmitter acetylcholine, the channel opens allowing Na^+ to flow into the muscle cell. This is a critical step linking the signal from a motor neuron to muscle cell contraction (see chapter 46).

Enzymatic receptors

Many cell-surface receptors either act as enzymes or are directly linked to enzymes (figure 9.4*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

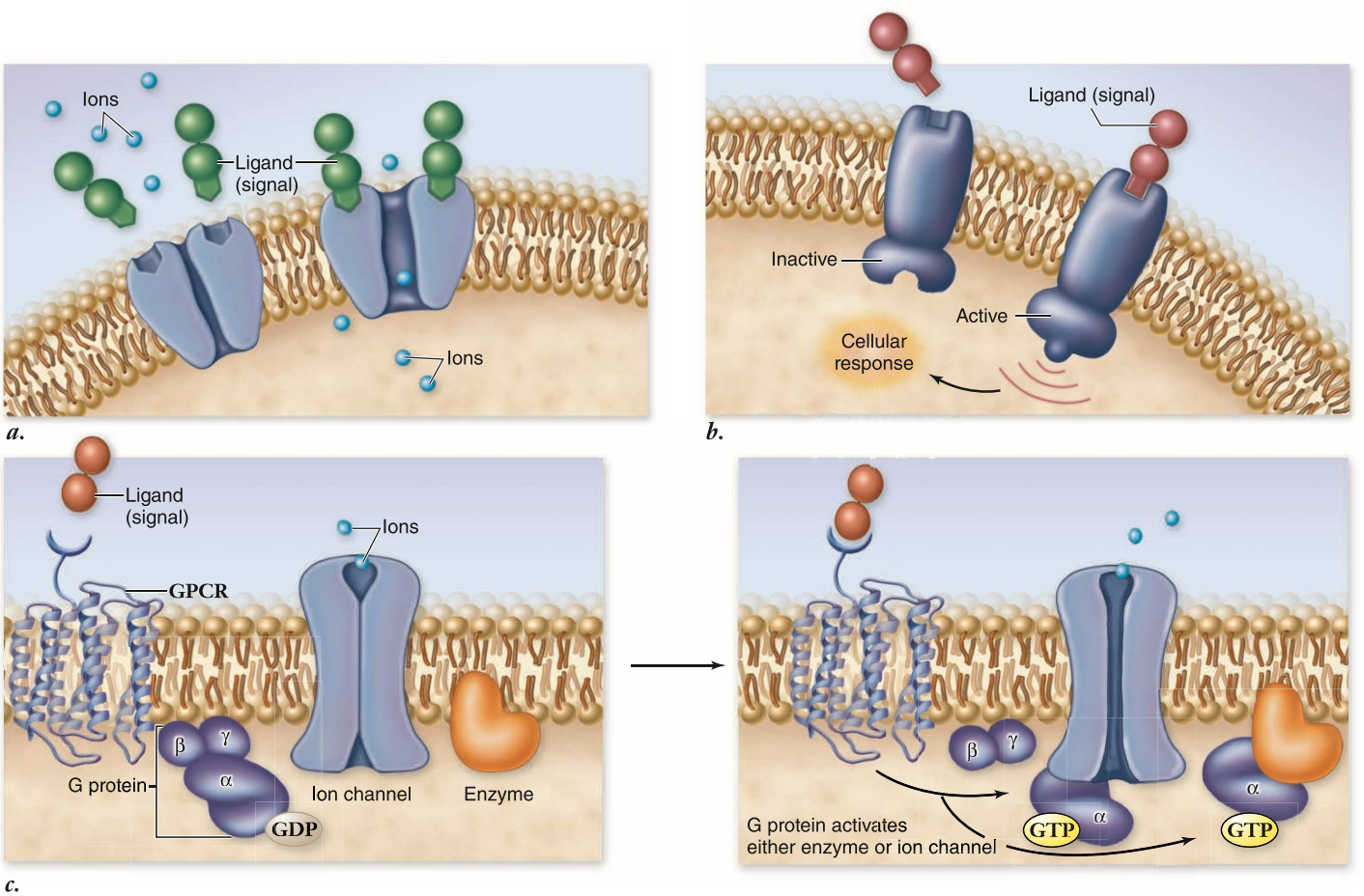


Figure 9.4 Cell-surface receptors. ***a.*** Chemically gated ion channels form a pore in the plasma membrane that can be opened or closed by chemical signals. They are usually selective, allowing the passage of only one type of ion. ***b.*** Enzymatic receptors bind to ligands on the extracellular surface. A catalytic region on their cytoplasmic portion transmits the signal across the membrane by acting as an enzyme in the cytoplasm. ***c.*** G protein–coupled receptors (GPCRs) bind to ligands outside the cell and to G proteins inside the cell. The G protein then activates an enzyme or ion channel, transmitting signals from the cell's surface to its interior.

to proteins. We discuss these receptors in detail in section 9.4 of this chapter.

G Protein–coupled 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 **G protein.** The G protein, which is so named because it binds the nucleotide *guanosine triphosphate* (GTP), can be thought of as being inserted between the receptors and the enzyme (effector). That is, the ligand binds to the receptor, activating it, which activates the G protein, which in turn activates the effector protein (figure 9.4*c*). These receptors are discussed in detail in section 9.5.

Membrane receptors can generate second messengers

Some enzymatic receptors and most G protein–coupled receptors utilize other substances to relay the message within the cytoplasm. These other substances, small molecules or ions called **second messengers,** alter the behavior of cellular proteins by binding to them and changing their shape. (The original signal molecule is considered the "first messenger.") Two common second messengers are **cyclic adenosine monophosphate (cyclic AMP,** or **cAMP)** and calcium ions. The role of these second messengers will be explored in more detail in section 9.5.

Learning Outcome Review 9.2

Receptors may be internal (intracellular receptors) or external (membrane receptors). Membrane receptors include channel-linked receptors, enzymatic receptors, and G protein–coupled receptors. Signal transduction through membrane receptors often involves the production of a second signaling molecule, or second messenger, inside the cell.

- *Would a hydrophobic molecule be expected to have an internal or membrane receptor?*

9.3 Intracellular Receptors

Learning Outcomes

1. *Describe the chemical nature of ligands for intracellular receptors.*
2. *Diagram the pathway of signal transduction through intracellular receptors.*

Many cell signals are lipid-soluble or very small molecules that can readily pass through the plasma membrane of the target cell and into the cell, where they interact with an *intracellular receptor.* Some of these ligands bind to protein receptors located in the cytoplasm, others pass across the nuclear membrane as well and bind to receptors within the nucleus.

Steroid hormone receptors affect gene expression

Of all of the receptor types discussed in this chapter, the action of the steroid hormone receptors is the simplest and most direct.

Steroid hormones form a large class of compounds, including cortisol, estrogen, progesterone, and testosterone, that share a common nonpolar structure. Estrogen, progesterone, and testosterone are involved in sexual development and behavior (see chapter 52). Other steroid hormones, such as cortisol, also have varied effects depending on the target tissue, ranging from the mobilization of glucose to the inhibition of white blood cells to control inflammation. Their anti-inflammatory action is the basis of their use in medicine.

The nonpolar structure allows these hormones to cross the membrane and bind to intracellular receptors. The location of steroid hormone receptors prior to hormone binding is cytoplasmic, but their primary site of action is in the nucleus. Binding of

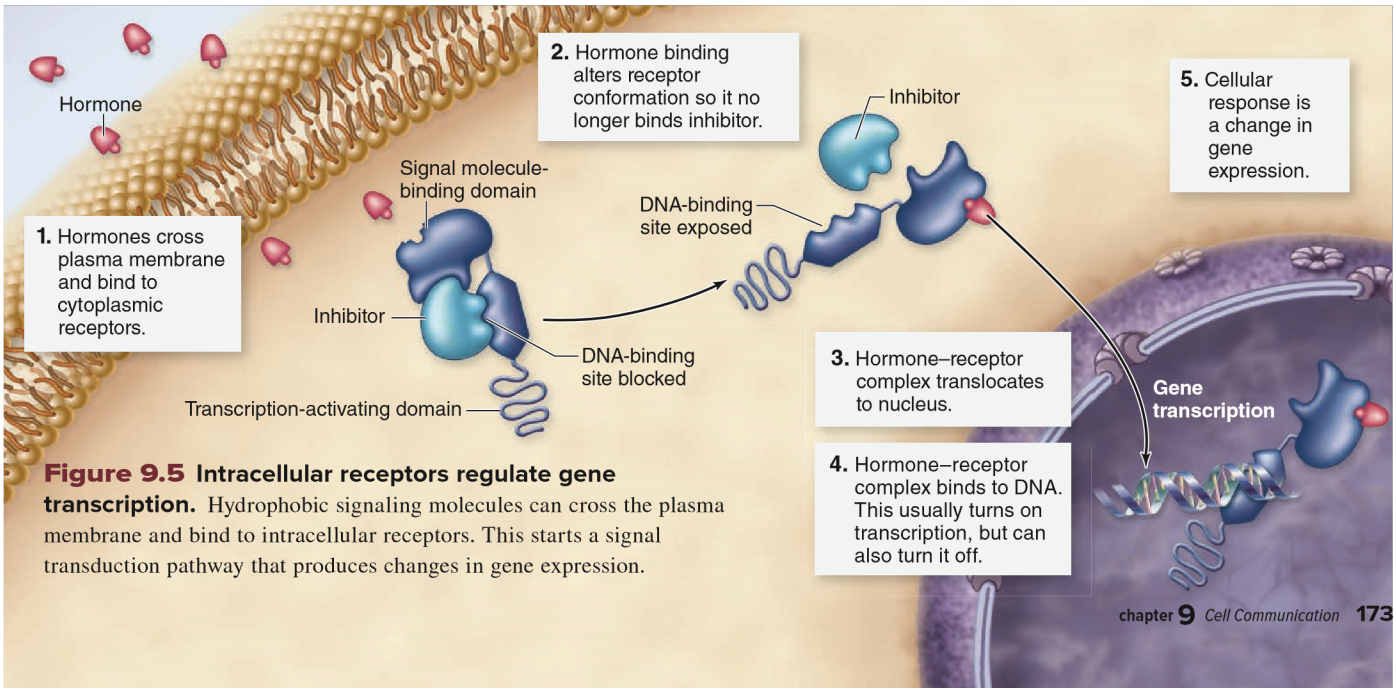


Figure 9.5 Intracellular receptors regulate gene transcription. Hydrophobic signaling molecules can cross the plasma membrane and bind to intracellular receptors. This starts a signal transduction pathway that produces changes in gene expression.