Chapter 11

Cell Communication

Key Concepts

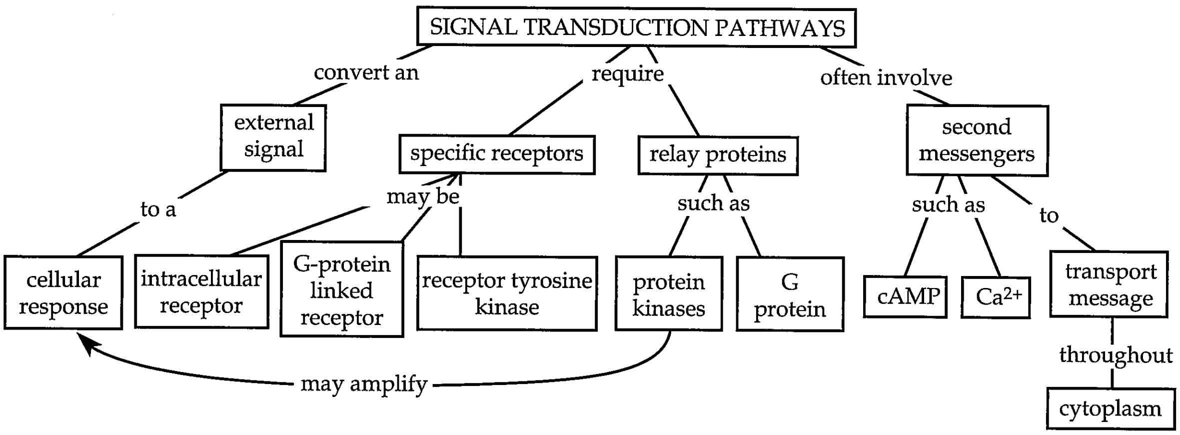
11.1 **External signals are converted into responses within the cell**

11.2 **Reception: A signal molecule binds to a receptor protein, causing it to change shape**

11.3 **Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell**

11.4 **Response: Cell signaling leads to regulation of cytoplasmic activities or transcription**

Framework



Chapter Review

Cell-to-cell communication is critical to the development and functioning of multicellular organisms and also to communication between unicellular organisms. Some universal mechanisms of cellular interaction provide evidence for the evolutionary relatedness of all life.

11.1 External signals are converted into responses within the cell

Evolution of Cell Signaling The two mating types of yeast secrete chemical factors that bind to receptors on the other cell type, initiating fusion (mating) of the cells. The series of steps involved in the conversion of a cell surface signal to a cellular response is called a **signal transduction pathway.** Similarities among these pathways in bacteria, yeast, plants, and animals suggest an early evolution of cell-signaling mechanisms.

Local and Long-Distance Signaling Chemical signals may be communicated between cells through direct cytoplasmic connections (gap junctions or plasmodesmata) or through contact of surface molecules (cell-cell recognition in animal cells).

In *paracrine signaling* in animals, a signaling cell releases messenger molecules into the extracellular fluid, and these **local regulators** influence nearby cells. In another type of local signaling called *synaptic signaling*, a nerve cell releases neurotransmitter molecules into the narrow synapse separating it from its target cell.

Hormones are chemical signals that travel to more distant cells. In hormonal or endocrine signaling in animals, the circulatory system transports hormones throughout the body to reach target cells with appropriate receptors.

Transmission of signals through the nervous system is also a type of long-distance signaling.

■ INTERACTIVE QUESTION 11.1

a. Do plant cells communicate using hormones?

b. If so, how do those hormones travel between secreting cells and target cells?

The Three Stages of Cell Signaling: A Preview E. W. Sutherland's work studying epinephrine's effect on the hydrolysis of glycogen in liver cells established that cell signaling involves three stages: **reception** of a chemical signal by binding to a receptor protein either inside the cell or on its surface; **transduction** of the signal, often by a signal transduction pathway—a sequence of changes in relay molecules; and the final **response** of the cell.

11.2 Reception: A signal molecule binds to a receptor protein, causing it to change shape

A signal molecule acts as a **ligand,** which specifically binds to a receptor protein and usually induces a change in the receptor's conformation.

Intracellular Receptors Hydrophobic chemical messengers may cross a cell's plasma membrane and bind to receptors in the cytoplasm or nucleus of target cells. Steroid hormones activate receptors in target cells that function as *transcription factors* to regulate gene expression.

Receptors in the Plasma Membrane There are three major types of membrane receptors that bind with water-soluble signal molecules and transmit information into the cell.

The various receptors that work with the aid of a G protein, called **G-protein-linked receptors,** are structurally similar, with seven α helices spanning the plasma membrane. Binding of the appropriate extracellular signal to a G-protein-linked receptor activates the receptor, which binds to and activates a specific **G protein** located on the cytoplasmic side of the membrane. This activation occurs when a GTP nucleotide replaces the GDP bound to the G protein. The G protein then activates a membrane-bound enzyme, after which it hydrolyzes its GTP and becomes inactive again. The activated enzyme triggers the next step in the pathway to the cell's response.

G-protein-linked receptor systems are used by many hormones and neurotransmitters and are involved in embryological development and sensory reception. Many bacteria produce toxins that interfere with G-protein systems; up to 60% of all medicines influence G-protein pathways.

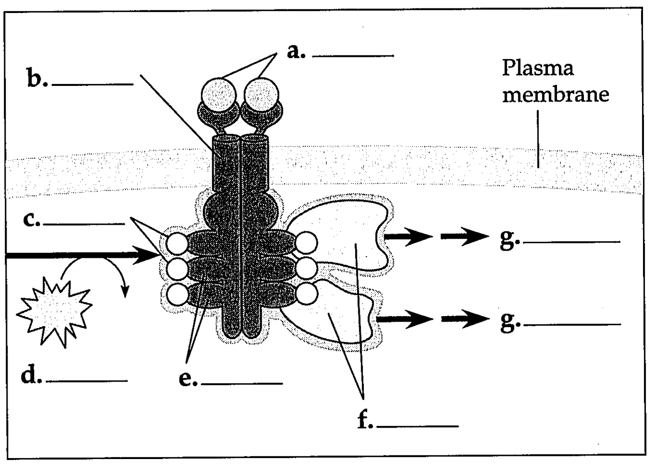
■ INTERACTIVE QUESTION 11.2

Explain why G-protein-regulated pathways shut down rapidly in the absence of a signal molecule.

Receptor tyrosine kinases are receptor proteins with enzymatic activity that can trigger several pathways at once. Part of the receptor protein is tyrosine kinase, an enzyme that transfers phosphate groups from ATP to the amino acid tyrosine on a protein. Many receptor tyrosine receptors exist as single transmembrane polypeptides with a signal binding site, a transmembrane α helix, and a cytoplasmic tail with a series of tyrosine amino acids. Ligand binding causes two receptors to form a dimer, which activates the tyrosine kinase portions of the molecules. These then phosphorylate the tyrosines on each other's cytoplasmic tails. Different relay proteins now bind to specific phosphorylated tyrosines and become activated, triggering many different transduction pathways in response to one type of signal.

■ INTERACTIVE QUESTION 11.3

Label the parts in this diagram of an activated receptor tyrosine kinase dimer.



The binding of a chemical signal to a **ligand-gated ion channel** opens or closes the protein pore, thus allowing or blocking the flow of specific ions through the membrane. The resulting change in ion concentration inside the cell triggers a cellular response. Neurotransmitters often bind to ligand-gated ion channels in the transmission of nervous signals.

■ INTERACTIVE QUESTION 11.4

a. What determines whether a cell is a target cell for a particular signal molecule?

b. What determines whether a signal molecule binds to a membrane-surface receptor or an intracellular receptor?

11.3 Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell

Multistep signal pathways allow a small number of extracellular signal molecules to be amplified to produce a large cellular response.

Signal Transduction Pathways The relay molecules in a signal transduction pathway are usually proteins, which interact as they pass the message from the extracellular signal to the protein that produces the cellular response.

Protein Phosphorylation and Dephosphorylation **Protein kinases** are enzymes that transfer phosphate groups from ATP to proteins, often to the amino acid serine or threonine. Relay molecules in signal transduction pathways are often protein kinases, which are sequentially phosphorylated, producing a conformational change that activates each enzyme. Hundreds of different kinds of protein kinases regulate the activity of a cell's proteins.

Protein phosphatases are enzymes that remove phosphate groups from proteins. They effectively shut down signaling pathways when the extracellular signal is no longer present.

■ INTERACTIVE QUESTION 11.5

a. What does a protein kinase do?

b. What does a protein phosphatase do?

c. What is a phosphorylation cascade?

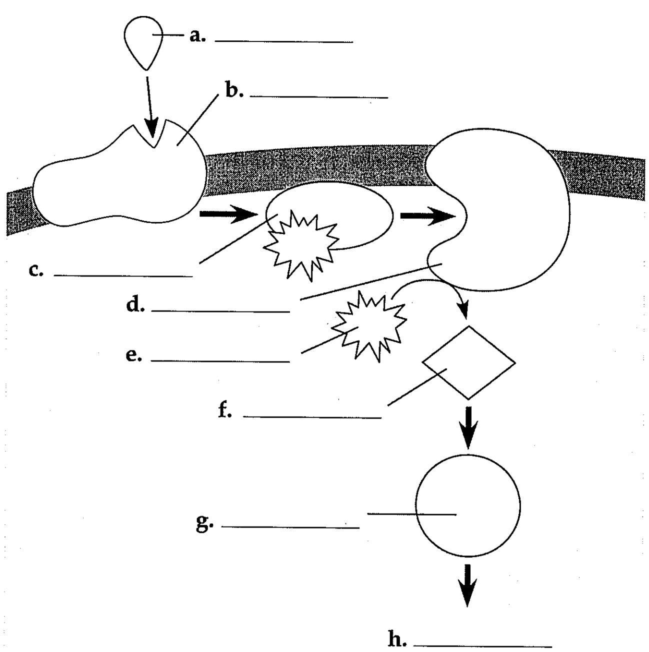
Small Molecules and Ions as Second Messengers Small, water-soluble molecules or ions often function as **second messengers,** which rapidly relay the signal from the membrane-receptor-bound "first messenger" into a cell's interior.

Binding of an extracellular signal to a G-protein-linked receptor activates a G protein that may activate **adenylyl cyclase,** a membrane protein that converts ATP to cyclic adenosine monophosphate (**cyclic AMP** or **cAMP**). The cAMP often activates *protein kinase A,* which phosphorylates other proteins. A cytoplasmic enzyme, phosphodiesterase, converts cAMP to inactive AMP, thus removing the second messenger.

Some signal molecules may activate an inhibitory G protein that inhibits adenylyl cyclase.

■ INTERACTIVE QUESTION 11.6

Label the components in this diagram of the steps in a signal transduction pathway that uses cAMP as a second messenger.



Calcium ions are widely used as a second messenger in many G-protein-linked and receptor tyrosine kinase pathways. Cytosolic concentration of Ca^{2+} is usually kept very low by active transport of calcium out of the cell and into the endoplasmic reticulum. The release of Ca^{2+} from the ER involves another second messenger, **inositol trisphosphate (IP_3).** In response to the reception of a signal, the enzyme phospholipase C cleaves a membrane phospholipid into two second messengers, IP_3 and **diacylglycerol (DAG).** IP_3 binds to and opens ligand-gated calcium channels in the ER. The calcium ions then induce cellular responses.

■ INTERACTIVE QUESTION 11.7

Fill in the blanks to review the steps in a signal transduction pathway involving a G-protein-linked receptor and Ca^{2+} as a second messenger.

A a. __________ binds to a G-protein-linked receptor. An activated b. __________ activates the enzyme phospholipase C, which cleaves a c. __________ into DAG and d. __________, which binds to and opens a ligand-gated channel, releasing e. __________ from the f. __________.

11.4 Response: Cell signaling leads to regulation of cytoplasmic activities or transcription

Cytoplasmic and Nuclear Responses Signal transduction pathways may lead to the activation of cytoplasmic enzymes or other proteins, or may lead to the synthesis of such proteins by affecting gene expression. Growth factors and certain animal and plant hormones may initiate pathways that ultimately activate transcription factors, which regulate the transcription of mRNA from specific genes.

Fine-Tuning of the Response A signal transduction pathway can amplify a signal in an enzyme cascade, as each successive enzyme in the pathway can process multiple molecules that then activate the next step.

As a result of their particular set of receptor proteins, relay proteins, and effector proteins, different cells can respond to different signals or can exhibit different responses to the same molecular signal. Pathways may branch to produce multiple responses, or two pathways may interact ("cross-talk") to mediate a single response.

Scaffolding proteins are large relay proteins to which other relay proteins attach, increasing the efficiency of signal transduction in a pathway.

Inactivation mechanisms that discontinue a cell's response to a signal are essential in keeping a cell responsive to regulation.

■ INTERACTIVE QUESTION 11.8

How do the following mechanisms or molecules maintain a cell's ability to respond to fresh signals?

a. reversible binding of signal molecules

b. GTPase activity of G protein

c. phosphodiesterase

d. protein phosphatases

Word Roots

liga- = bound or tied (*ligand:* a small molecule that specifically binds to a larger one)

trans- = across (*signal transduction pathway:* the process by which a signal on a cell's surface is converted into a specific cellular response inside the cell)

-yl = substance or matter (*adenylyl cyclase:* an enzyme built into the plasma membrane that converts ATP to cAMP)

Structure Your Knowledge

1. Why is cell signaling such an important component of a cell's life?
2. Briefly describe the three stages of cell signaling.
3. Some signal pathways alter a protein's activity; others may result in the production of new proteins. Explain the mechanisms for these two different responses.
4. How does an enzyme cascade produce an amplified response to a signal molecule?

Test Your Knowledge

MULTIPLE CHOICE: *Choose the one best answer.*

1. When epinephrine binds to cardiac (heart) muscle cells, it speeds their contraction. When it binds to muscle cells of the small intestine, it inhibits their contraction. How can the same hormone have different effects on muscle cells?
   a. Cardiac cells have more receptors for epinephrine than do intestinal cells.
   b. Epinephrine circulates to the heart first and thus is in higher concentration around cardiac cells.
   c. The two types of muscle cells have different signal transduction pathways for epinephrine and thus have different cellular responses.
   d. Cardiac muscle is stronger than intestinal muscle and thus has a stronger response to epinephrine.
   e. Epinephrine binds to G-protein-linked receptors in cardiac cells, and these receptors always increase a response to the signal. Epinephrine binds to receptor tyrosine kinases in intestinal cells, and these receptors always inhibit a response to the signal.

2. Which of the following would be used in the type of local signaling called paracrine signaling in animals?
   a. the neurotransmitter acetylcholine
   b. the hormone epinephrine
   c. the neurotransmitter norepinephrine
   d. a local regulator such as a growth factor
   e. Both a and c are correct.

3. A signal molecule that binds to a plasma-membrane protein functions as a
   a. ligand.
   b. second messenger.
   c. protein phosphatase.
   d. protein kinase.
   e. receptor protein.

4. What is a G protein?
   a. a specific type of membrane-receptor protein
   b. a protein on the cytoplasmic side of a membrane that becomes activated by a receptor protein
   c. a membrane-bound enzyme that converts ATP to cAMP
   d. a tyrosine kinase relay protein
   e. a guanine nucleotide that converts between GDP and GTP to activate and inactivate relay proteins

5. How do receptor tyrosine kinases transduce a signal?
   a. They transport the signal molecule into the cell, where it binds to and activates a transcription factor. The transcription factor then alters gene expression.
   b. Signal binding causes a conformational change that activates membrane-bound tyrosine kinase relay proteins that phosphorylate serine and threonine amino acids.
   c. Their activated tyrosine kinases convert ATP to cAMP; cAMP acts as a second messenger to activate other protein kinases.
   d. When activated, they cleave a membrane phospholipid into two second-messenger molecules. One of the molecules opens Ca^{2+} ion channels on the endoplasmic reticulum.
   e. They form a dimer; they phosphorylate each other's tyrosines; specific proteins bind to and are activated by these phosphorylated tyrosines.

6. Which of the following can activate a protein by transferring a phosphate group to it?
   a. cAMP
   b. G protein
   c. phosphodiesterase
   d. protein kinase
   e. protein phosphatase

7. Many signal transduction pathways use second messengers to
   a. transport a signal through the lipid bilayer portion of the plasma membrane.
   b. relay a signal from the outside to the inside of the cell.
   c. relay the message from the inside of the membrane throughout the cytoplasm.
   d. amplify the message by phosphorylating proteins.
   e. dampen the message once the signal molecule has left the receptor.

8. What is a function of the second messenger IP_3?
   a. bind to and activate protein kinase A
   b. activate transcription factors
   c. activate other membrane-bound relay molecules
   d. convert ATP to cAMP
   e. bind to and open ligand-gated calcium channels on the ER

9. Many human diseases, including bacterial infections, and also many medicines used to treat these diseases produce their effects by influencing which of the following?
   a. cAMP concentrations in the cell
   b. Ca^{2+} concentrations in the cell
   c. G-protein pathways
   d. gene expression
   e. receptor tyrosine kinases

10. Signal amplification is most often achieved by
   a. an enzyme cascade involving multiple protein kinases.
   b. the binding of multiple signal molecules.
   c. branching pathways that produce multiple cellular responses.
   d. activating transcription factors that affect gene expression.
   e. the action of adenylyl cyclase in converting ATP to ADP.

11. From studying the effects of epinephrine on liver cells, Sutherland concluded that
   a. there is a one-to-one correlation between the number of epinephrine molecules bound to receptors and the number of glucose molecules released from glycogen.
   b. epinephrine enters liver cells and binds to receptors that function as transcription factors to turn on the gene for glycogen phosphorylase.
   c. there is a "second messenger" that transmits the signal of epinephrine binding on the plasma membrane to the enzymes involved in glycogen breakdown inside the cell.
   d. the signal transduction pathway through which epinephrine signals glycogen breakdown involves receptor tyrosine kinases and the release of calcium ions that activate glycogen phosphorylase.
   e. epinephrine functions as a ligand to open ion channels in the plasma membrane that allow calcium ions to enter and initiate a cellular response.

12. Which of the following is a similarity between G-protein-linked receptors and receptor tyrosine kinases?
   a. signal-binding sites specific for steroid hormones
   b. formation of a dimer following binding of a signal molecule
   c. activation that results from binding of GTP
   d. phosphorylation of specific amino acids in direct response to signal binding
   e. α-helix regions of the receptor that span the plasma membrane

13. Which of the following is *incorrectly* matched with its description?
   a. scaffolding protein—large relay protein that may bind with several other relay proteins to increase the efficiency of a signaling pathway
   b. protein phosphatase—enzyme that transfers a phosphate group from ATP to a protein, causing a conformational change that usually activates that protein
   c. adenylyl cyclase—enzyme attached to plasma membrane that converts ATP to cAMP in response to an extracellular signal
   d. phospholipase C—enzyme that may be activated by a G protein or receptor tyrosine kinase and cleaves a plasma-membrane phospholipid into the second messengers IP_3 and DAG
   e. G protein—relay protein attached to the inside of plasma membrane that, when activated by an activated G-protein-linked receptor, binds GTP and then usually activates another membrane-attached protein

14. Which of the following signal molecules pass through the plasma membrane and bind to intracellular receptors that move into the nucleus and function as transcription factors to regulate gene expression?
   a. epinephrine
   b. growth factors
   c. yeast mating factors α and a
   d. testosterone, a steroid hormone
   e. neurotransmitter released into synapse between nerve cells