Chapter 6

Cell Communication

Review

All cells in a multicellular organism have the same genetic makeup. How then do cells become different, and how are the various cell types able to carry out different cellular processes? Chapter 9, "Gene Expression and Regulation," will review how genes, the units of heredity, are able to produce traits. In short, the information stored in DNA is used to make another nucleic acid, messenger RNA (mRNA). The information in mRNA is then used to make proteins. As enzymes, proteins regulate chemical reactions that generate traits. Other proteins may serve to regulate gene expression. In summary:

genes (DNA) → mRNA → proteins (enzymes) → structure, physiology, behavior

Still, this does not explain how the same set of genes can produce different kinds of structures or promote different cellular processes. Cells become different because gene expression varies among cells; that is, in some cells genes are turned on, while in others, those same genes are turned off. The major factor that influences which genes will be expressed is the environment. Each cell receives chemical and physical signals from its surroundings that trigger metabolic activities that direct or influence the expression of its genes.

Signals from the external environment come from biological sources, such as chemicals from a pathogen or a bee sting, or from physical sources, such as light or heat. Within a multicellular organism, cells also receive signals from other cells. This can happen in several ways, depending upon how far the signal needs to travel:

1. **Direct contact** between animal cells allows proteins, carbohydrates, and lipids of the plasma membranes to transmit information. This kind of communication is common among cells during early development. Information is also transmitted through two kinds of communication junctions:
   - **Gap junctions** in *animal* cells allow for chemical and electrical signaling between cells. Ions and small molecules can pass through gap junctions, but larger molecules, like proteins and nucleic acids, cannot.
   - **Plasmodesmata** in *plant* cells are tunnels of cytoplasm between cells. They provide passageways across plasma membranes and cell walls for the movement of ions, amino acids, sugars, small proteins (including transcription factors), and micoRNA (miRNA). Transcription factors and microRNA regulate gene expression. (Details are in Chapter 9, "Gene Expression and Regulation.")
2. **Synaptic signaling** occurs between junctions of nerve cells or between nerve and muscle cells. **Neurotransmitters,** short-lived chemical signals, cross a very small space between these cells to stimulate or inhibit a nerve impulse or muscle contraction.
3. **Paracrine signaling** is a mechanism for local communication. Cells secrete substances that affect only nearby cells because the substances are either readily absorbed by adjacent cells or rapidly broken down in the extracellular fluid. Growth factors, for example, are paracrine signals secreted during early animal development.
4. **Endocrine signaling** provides a mechanism for distributing signals throughout a multicellular organism. For example, hormones produced in one part of the body target cells in another part of the body.

The remainder of this chapter focuses on how a signal, once recognized by a cell, actually manifests a change in the cell. The mechanism for this process is a signal transduction pathway.

Signal Transduction Pathways

A **signal transduction pathway** is a sequence of molecular interactions that transforms an extracellular signal into a specific cellular response. The process can be summarized like this:

Signal (1st messenger) → Receptor → Proteins or other 2nd messengers → Cellular responses

Signaling molecules, or **ligands,** are first messengers. They are small molecules that bind to larger receptor proteins of specific target cells. When the specific ligand binds to a receptor protein, it induces a change in the three-dimensional shape of the receptor protein. That change initiates some kind of activity in the receptor protein. There are two types of signaling molecules:

- **Hydrophilic ligands** are signaling molecules that cannot cross the phospholipid bilayer of a membrane. They bind to **membrane receptors** at the membrane surface.
- **Hydrophobic ligands** and certain small molecules are signaling molecules that are able to cross the membrane unaided. They bind to **intracellular receptors** in the cytoplasm or nucleus.

Receptor proteins are molecules that have binding sites for signaling molecules. When activated by a specific signaling molecule, they initiate a series of reactions that activates a cellular process. There are two kinds of receptor proteins:

- **Membrane receptors** are transmembrane proteins, extending from the outside to the inside of a membrane. The part of the receptor protein that faces away from the cell presents a binding site for a specific signaling molecule. The other end of the protein, facing the cytoplasm, initiates a chemical reaction.
- **Intracellular receptors** are proteins that occur in the cytoplasm or nucleus.

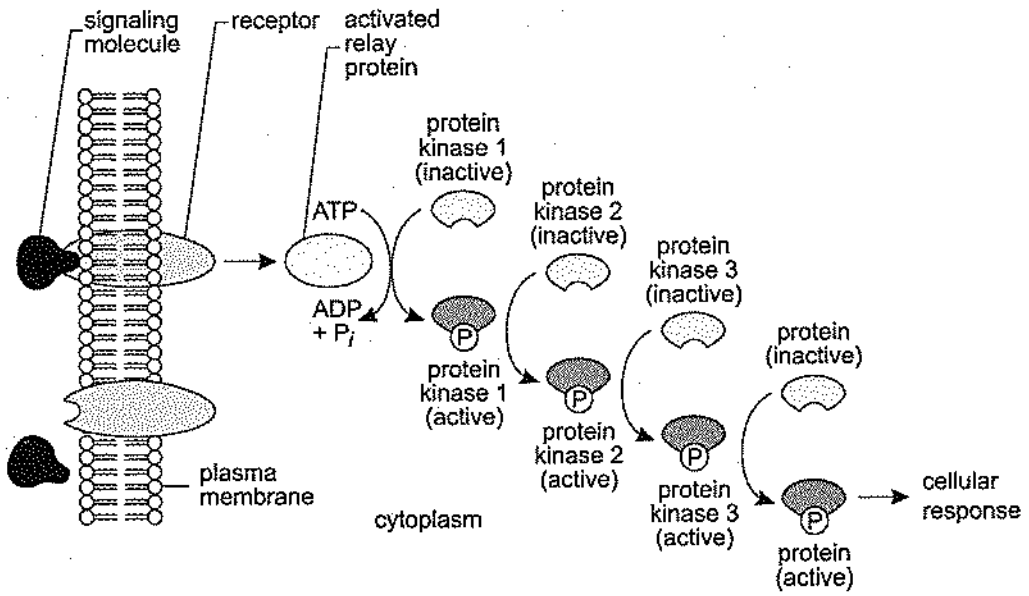
Second messengers are molecules that relay a signal from the inside face of a receptor protein to other molecules that may initiate a cellular response or may act as additional second messengers. They have these characteristics:

- They are small, *nonprotein* molecules.
- They are hydrophilic, hydrophobic, or gaseous molecules.
- Examples include Ca^{2+}, IP_3 (inositol trisphosphate), cAMP (cyclic adenosine monophosphate), and DAG (diacylglycerol).

Various other membrane-bound or cytoplasmic proteins are often additional components of a transduction pathway, carrying the signal response from the receptor protein to other target proteins that may initiate a cellular response. Although these proteins have specific names, they are generally referred to as **relay proteins, response proteins, substrate proteins,** or **effector proteins.**

A **signaling cascade** is a series of enzymatic reactions. The first enzyme in the series activates a second enzyme, the second enzyme activates a third, and so forth. Because each enzyme can be used repeatedly, the products of each reaction magnify as the sequence progresses, like a chain reaction. Ultimately, a signal that may have begun with a single signaling molecule may be amplified to produce a huge number of molecules that elicit a strong cellular response.

- A **kinase cascade,** or **phosphorylation cascade,** is a signaling cascade consisting of a number of different kinase enzymes (Figure 6-1). A kinase is an enzyme that phosphorylates its substrate, that is, adds a phosphate group to it. In a kinase cascade, each kinase phosphorylates and, thus, activates the next kinase in the sequence, ultimately phosphorylating and activating a protein that initiates a cellular response. The kinase cascade amplifies the signaling response.
- **Scaffold proteins** improve the efficiency of a signaling cascade by holding all the participating enzymes in close proximity. The scaffold also serves to keep the members of one signaling cascade isolated from members of another cascade.
- A **protein phosphatase** is an enzyme that dephosphorylates its substrate, that is, removes a phosphate group from it. When these enzymes dephosphorylate the kinases in a kinase cascade, they serve to terminate the signaling response.



A Kinase (or Phosphorylation) Cascade

Figure 6-1

There is both great specificity and great flexibility in transduction pathways. Signaling molecules are specific for the binding sites of receptor proteins. However, the response that a specific signaling molecule initiates varies with cell type and the influence of cytoplasmic substances.

The complexity of many signal transduction pathways has several advantages:

- **Amplification.** It provides a mechanism for amplifying the effect of a signaling molecule.
- **Control.** It gives the cell more control over the accuracy of the signaling pathway. Because all components of the pathway must be functioning properly, there is a smaller chance that the transduction might occur in error.
- **Multiplicity.** A single signaling molecule can activate multiple cytoplasmic proteins, each generating a different biochemical response. As a result, multiple processes can be coordinated to produce a single cellular response.

Table 6-1 summarizes four kinds of receptor proteins—three membrane receptors and one intracellular receptor—and the signal transduction pathways they initiate. You should be prepared to describe at least one of these receptor proteins in detail in a free-response question on the AP exam. In other cases, questions may provide you with a full description of a pathway and ask you to use the descriptions to make conclusions. Familiarity with all four kinds of receptor proteins will work in your favor.

Also note that some of the examples of these pathways are pursued in more detail in subsequent chapters.

Table 6-1: Summary of Receptors and Their Functions

Receptor Type	Receptor Description	Ligand (1st Messengers) Examples	Supporting Mechanisms	Cellular Response Examples
Gated ion receptor	Ligand-gated ion channel	Acetylcholine		Na^+ gate opens; nerve impulse or muscle contraction
	Voltage-gated ion channel	Change in membrane voltage		Na^+, K^+ gates open; nerve transmission

continued

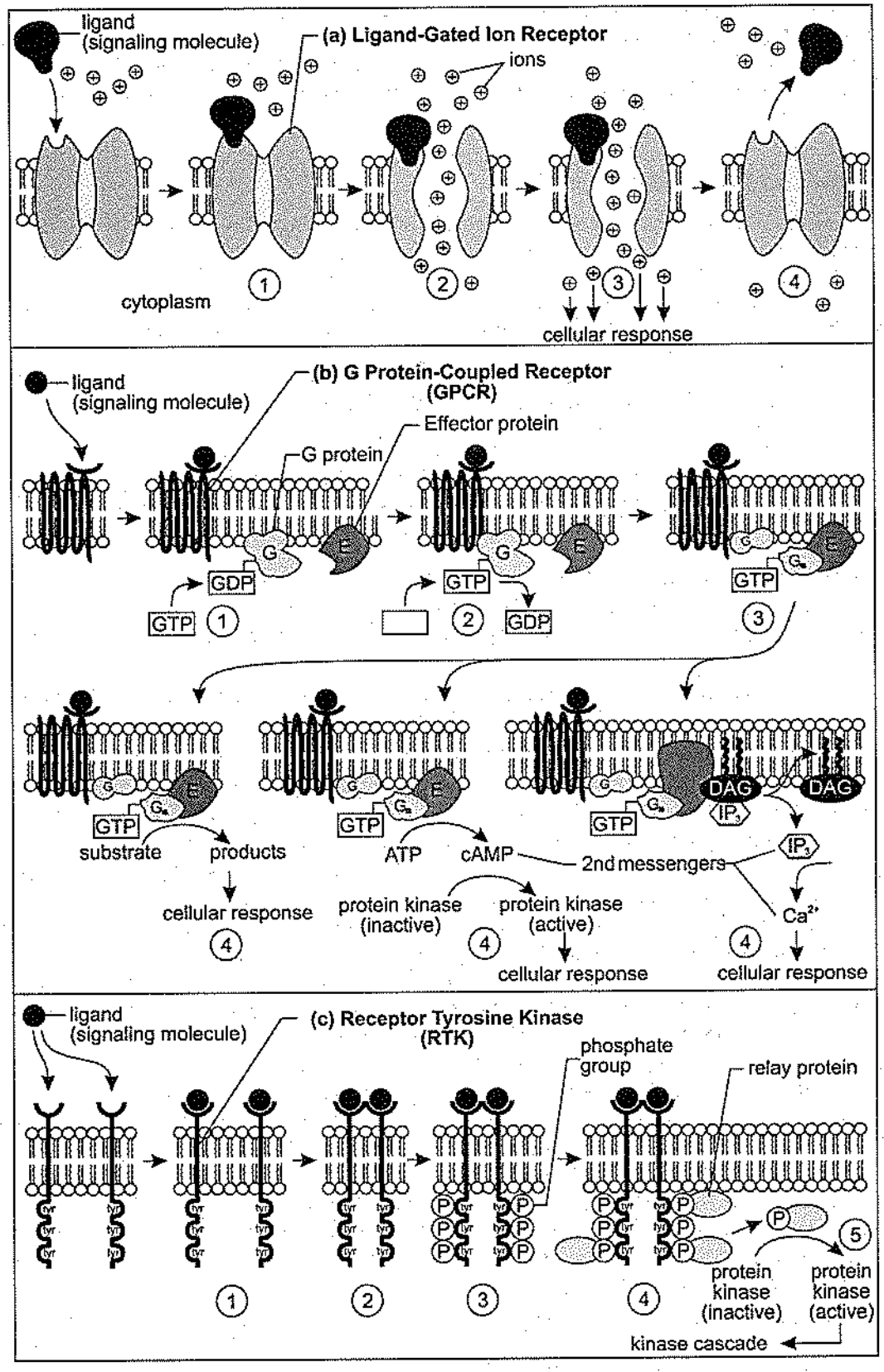
Receptor Type	Receptor Description	Ligand (1st Messengers) Examples	Supporting Mechanisms	Cellular Response Examples
G protein-coupled receptor (GPCR)	GPCR + G protein + effector protein	Various	Enzymatic effector protein	Enzyme activity
			cAMP (2nd messenger)	Glycogen → glucose
			IP_3/DAG (2nd messengers)	IP_3 releases Ca^{2+} as 2nd messenger
			Ca^{2+} (2nd messenger)	Muscle contraction
Protein kinase receptor	Receptor tyrosine kinase (RTK)	Insulin	Multiple kinase cascades	Glucose → glycogen; glucose export
	Receptor serine/ threonine kinase	Mitogens, growth factors	Ras (G protein); mitogen-kinase cascade	Activation of transcription factors that promote growth and cell differentiation
Intracellular receptor	Cytoplasmic or nuclear receptors	Steroid hormones (testosterone, estrogen)		Development of primary and secondary sex characteristics

Gated Ion Receptors

A **gated ion receptor** is a transmembrane protein that contains a gated channel, that is, a channel that opens and closes in response to a specific signal. When open, the channel allows a specific ion to pass through. A **ligand-gated ion receptor** responds to a specific ligand, that is, a *molecular* signal. There are also **voltage-gated-ion receptors** that open or close in response to *voltage* differences across the membrane. A typical ligand-gated ion sequence follows (Figure 6-2a):

1. **Ligand-gated ion receptor receives signal.** A specific messenger ligand binds to the outward-facing surface of the receptor.
2. **Receptor channel opens and ions pass through.** In response to the binding of the ligand, the three-dimensional shape of the receptor changes, opening (or closing) a channel that allows a specific ion to pass through and enter the cytoplasm.
3. **Ions initiate chemical response.** Once in the cytoplasm, the ions initiate a chemical response.
4. **Ligand-gated ion receptor deactivated when ligand detaches from receptor.** The ligand-ion receptor is deactivated when the messenger ligand is broken down by another enzyme, the binding site for the ligand is blocked by an allosteric ligand, or the ion passage is obstructed by a channel blocker.

An important example of **ligand-gated** ion channel involves **acetylcholine,** a neurotransmitter that is the signaling molecule that transmits nerve impulses *between* nerve cells (neurons). A neuron that is transmitting a signal releases acetylcholine into the extracellular space between neurons (the **synaptic cleft,** or **synapse**). When acetylcholine binds to the ligand-gated receptor molecules of the receiving neuron, the receptor molecules open a gated channel that allows sodium ions (Na^+) to enter the cell. As Na^+ enters the cell, the inside of the cell becomes more positive. This change in membrane voltage (called an action potential) initiates a nerve impulse. Neurons stimulate muscle contraction in a similar process.



Membrane Receptor Proteins

Figure 6-2

An example of a **voltage-gated** ion channel is the transmission of a nerve impulse *along* a neuron. When the ligand-gated-ion receptor responds to acetylcholine and Na^+ enters the cytoplasm, the voltage inside the neuron becomes more positive. This voltage change, if strong enough, stimulates a *voltage*-gated Na^+ channel and, subsequently, a *voltage*-gated K^+ channel to open. The opening and closing of these voltage-gated ion channels transmits the nerve impulse along the neuron.

G Protein-Coupled Receptors

A **G protein-coupled receptor (GPCR)** is a transmembrane protein that activates a **G protein.** The G protein, in turn, activates another membrane protein, which, in turn, triggers a cellular response or activates a second messenger. The G protein is so named because it has a GTP (or GDP) attached to it. GTP is functionally and structurally like ATP, except with a guanine instead of an adenine nitrogen base. In its inactive (or "off") state, a GDP is attached to the G protein. It is activated (or turned "on") when the GDP is replaced with a GTP.

GPCRs comprise the largest family of signal receptors. They include receptors for vision, taste, airborne signals (odors and pheromones), hormones, neurotransmitters, and immune system activity. Many pharmaceuticals and opiates are GPCR ligands.

A description of a typical sequence for a GPCR follows (Figure 6-2b). Keep in mind, however, that the GPCR pathway varies based on cell type, the particular GPCR that is activated, and the biochemical makeup of individual cells.

1. **GPCR receives signal.** A specific messenger ligand binds to the outward-facing surface of the receptor.
2. **GPCR activates G protein by exchanging a GTP for a GDP.** As a result of the ligand binding to the GPCR, a conformational change occurs, activating the GPCR. The activated GPCR, in turn, exchanges a GTP for the GDP on a nearby G protein. A GTP is now bound to the G protein.
3. **G protein binds to effector protein.** A subunit of the activated G protein binds to a membrane effector protein (usually an enzyme), activating it.
4. **Effector protein initiates response.** The effector protein, now activated by the bound G protein, elicits a cellular response. Some of the possible responses include the following:
   - *Enzymatic activity.* The effector protein may be an enzyme that catalyzes a specific substrate. More specifically, the enzyme may be a protein kinase and initiate a kinase cascade.
   - *Produce the second messenger **cAMP.*** If the effector protein is the transmembrane enzyme adenylyl cyclase, the enzyme converts an ATP to a cAMP by removing two phosphate groups (ATP → AMP + $2P_i$) and binding the remaining phosphate group so that it is attached to the ribose sugar in two places instead of one (wrapping it around and making it "cyclic"). Many cAMPs are rapidly produced, generating a very strong and rapid response. The cAMP signaling pathway then activates a cytoplasmic response protein, such as an enzyme protein kinase. Depending upon the cell type, the response protein initiates some specific cellular response that may be stimulatory or inhibitory.
   - *Produce the second messengers **IP_3 and DAG.*** If the effector protein is the transmembrane enzyme phospholipase C, the enzyme cleaves a membrane phospholipid, PIP_2, to generate two second messengers—**IP_3** and **DAG.** DAG, the lipid portion of PIP_2, remains embedded in the membrane, while the soluble IP_3 moves into the cytoplasm. As second messengers, IP_3 and DAG initiate a variety of cellular responses, depending upon cell type.
   - *Produce the second messenger **Ca^{2+}**.* In many cells, IP_3 triggers the transport of calcium ions (Ca^{2+}) across membranes. For example, in secretory cells of salivary glands, IP_3 binds and activates receptor proteins in membranes of the smooth ER to release Ca^{2+} into the cytoplasm. Here, Ca^{2+} is a second messenger, triggering the release of saliva.
5. **GPCR signaling is deactivated when GTP is hydrolyzed** (not shown in Figure 6-2). When the GTP that is attached to the effector protein is hydrolyzed (GTP → GDP + P_i), the GPCR pathway is deactivated. The released GDP is free to reassociate with the G protein.

Glycogen breakdown in muscle and liver cells is an example of a cAMP signaling pathway. When a G protein is activated by a signaling molecule (the hormone epinephrine), the G protein exchanges GTP for GDP on the effector protein (adenylyl cyclase), which, in turn, converts ATP to cAMP, a second messenger. The cAMP phosphorylates (thus, activating) a protein kinase (called PKA). Protein kinase activity leads to the activation of an enzyme that removes single units of glucose from glycogen.

Protein Kinase Receptors

A **protein kinase receptor** is a transmembrane-protein enzyme. These enzymes are **kinases,** enzymes that add a phosphate group to a protein. Phosphorylation replaces the hydroxyl (OH^-) group that occurs in an R group of an amino acid with a phosphate (PO_4^{3-}) group. Such hydroxyl groups only occur in three amino acids: tyrosine, serine, and threonine. The best understood of these receptors is the **receptor tyrosine kinase (RTK).**

A typical RTK sequence follows (Figure 6-2c):

1. **RTK receives signal.** At the outer surface of the membrane, the RTK binds to a signaling molecule.
2. **RTK forms dimer.** Two RTKs associate, forming a pair (dimer).
3. **RTK is activated by autophosphorylation.** On the inner surface of the membrane, each of the two RTKs in the dimer phosphorylates the other RTK using phosphate groups from ATPs. This process, called autophosphorylation, activates the protein complex. Multiple phosphate groups can attach, each to a tyrosine amino acid.
4. **Relay protein is phosphorylated.** Relay proteins bind to the tyrosine-phosphate domains of the RTK. The phosphates are then transferred from the tyrosines to the relay proteins. *More than one kind of protein may be phosphorylated by a single RTK dimer and each kind of phosphorylated protein can serve as a relay protein that initiates a different transduction pathway.*
5. **Relay protein initiates transduction pathway.** The relay proteins, now activated by the addition of a phosphate group, are released. A relay protein can activate a cellular response or initiate a protein kinase transduction pathway that leads to a cellular response. Each kind of relay protein participates in a different cellular response.
6. **RTK pathway is deactivated by dephosphorylation or receptor protein isolation** (not shown in Figure 6-2). The RTK pathway is deactivated when dephosphorylating enzymes remove phosphate groups from the kinases or when the membrane folds to encircle and internalize the receptor protein in a vesicle (endocytosis).

There are two fundamental differences between an RTK receptor pathway and the GPCR pathway discussed earlier:

1. The RTK receptor is usually *directly* responsible for initiating a transduction pathway. In contrast, the GPCR *indirectly* activates a transduction pathway via a G protein and an effector molecule.
2. The RTK receptor may trigger multiple transduction pathways, directing a host of coordinated cellular responses. In contrast, a typical GPCR triggers a single transduction pathway, ultimately activating a single final product that leads to a specific cellular response.

Insulin signal transduction is an example of an RTK pathway. Insulin, a protein hormone produced in the pancreas, is secreted into the blood in response to excess glucose in the blood. The hormone regulates the cellular intake and utilization of glucose. Insulin, the signaling molecule, binds to the insulin receptor, an RTK of target cells. Binding stimulates conformational changes that activate the receptor, which then trigger the formation of an RTK dimer and autophosphorylation. Then, the complex binds to and phosphorylates an insulin response protein. This response protein, now activated, initiates several signaling cascades. In muscle cells, one cascade leads to glycogen synthesis (the formation of glycogen from glucose monomers) for short-term energy storage, another to the transport of glucose into the cell. In liver cells, glycogen synthesis is also stimulated, and in addition, glucose synthesis from smaller molecules is inhibited. In fat cells, the pathway leads to triglyceride formation (for long-term energy storage) instead of glycogen formation.

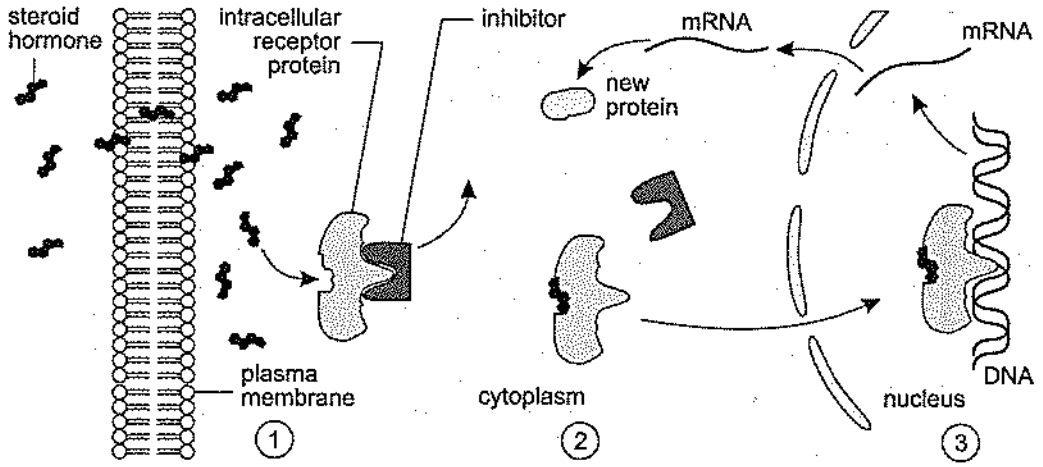
The **mitogen-activated protein (MAP)** kinases are an example of a kinase cascade activated by a G protein. **Mitogens** (mitosis + generating) are substances that stimulate cell division. After a protein kinase receptor is activated by a

signaling molecule, the receptor dimerizes, autophosphorylates, and activates **Ras,** a G protein, by exchanging a GTP for a GDP. The Ras protein then activates a mitogen-kinase (MK) cascade, where one mitogen kinase catalyzes the phosphorylation of the next mitogen kinase in the sequence. In this fashion, mitogen kinase kinase kinase (MKKK) activates MKK, which activates MK. This final MK activates nuclear regulatory proteins, called **transcription factors,** which turn genes on or off. These genes manage cell division and cell differentiation. Note that the Ras protein associated with the RTK receptor and the G protein associated with a GPCR are both G proteins because they are activated when a GTP replaces a GDP, but the series of steps that define the pathways of these two receptors is very different. Ras is the first *cytoplasmic* enzyme in a kinase cascade, whereas the G protein associated with a GPCR is *membrane bound* and activates another *membrane-bound* effector protein.

Intracellular Receptors

In contrast to the membrane-bound receptor proteins discussed earlier, **intracellular receptors** are positioned in the cytoplasm or nucleus. The ligands for these intracellular receptor proteins are small molecules or lipid-soluble, nonpolar molecules that can passively diffuse across the plasma membrane. Ligands also include second messengers, like IP_3, that are products of a signal transduction pathway generated by a membrane-bound receptor protein. Like other kinds of transduction pathways, the cellular response elicited by a particular receptor protein varies among cell types. Also, various molecules specific to individual cells may act as coactivators to direct the target of the transduction pathway. The target of receptor protein activity may be in the cytoplasm or the nucleus. When the target is in the nucleus (typically, the DNA), the receptor is often called a **nuclear receptor.** A description of a typical intracellular receptor pathway follows (Figure 6-3):

1. **A signaling molecule enters the cytoplasm.** The signaling molecule can be a first messenger lipid-soluble molecule or small molecule that diffuses across the plasma membrane or a second messenger molecule that is introduced into the cytoplasm as a product of an intracellular transduction pathway.
2. **The signaling molecule binds to the intracellular receptor, activating it.** The receptor may be in the cytoplasm or in the nucleus. In some cases, activation of the receptor triggers the release of an inhibitor that prevented the receptor from functioning.
3. **The receptor-signaling molecule complex acts as a transcription factor.** The receptor-signal complex binds to the DNA, promoting (or suppressing) the transcription of genes.
4. **Deactivation of the pathway can occur when signaling molecules or receptor proteins are enzymatically degraded.** In some cases, phosphorylation of the receptor protein results in deactivation. In addition, the release of hormones into the blood is typically shut down by negative feedback mechanisms.



Intracellular Receptor Protein

Figure 6-3

Steroid hormones, such as **testosterone** or **estrogen,** are examples of ligands that bind to intracellular receptors. These signaling molecules diffuse across the plasma membrane and bind to a specific receptor protein in the cytoplasm. The now activated complex (hormone + receptor protein) moves to the nucleus, where it binds to DNA and promotes transcription of genes that direct cellular activities. Gene expression varies depending on cell type and gender. In males, for example, testosterone activates genes in the testes that direct the development of sperm cells, but in muscle cells, it stimulates the production of muscle fibers. In females, estrogen activates genes that direct cells in the uterus to prepare for pregnancy, but in mammary cells, estrogen inactivates those same genes.

Disease and Cancer

Although genes contain the information for what a cell will become and how that cell will function, external signals strongly influence how those genes actually express that information. For various reasons, signals are sometimes inaccurately acted upon because the signal transduction pathway is distorted and does not operate properly. Here are two examples.

Cholera is a waterborne disease caused by bacteria. When contaminated water is ingested, the bacteria secrete a toxin that disrupts the normal activity of GPCRs of intestinal cells. In particular, the GTP attached to the G protein cannot be converted back to a GDP, so the protein cannot be deactivated. In these cells, this G protein regulates the concentration of Cl^- and, when locked in its active state, continuously generates cAMP. In response, Cl^- is continuously transported out of the cell. Water follows the Cl^- by osmosis into the lumen of the intestines. If not treated, the resulting diarrhea can lead to dehydration and death, and the severe diarrhea assists the bacteria in returning to the water supply.

Cancer is the result of uncontrolled cell division. Normally, cell division is highly regulated, with multiple checkpoints during a cell cycle to ensure that the process is progressing correctly. Some cells initiate cell division in response to **growth factors,** proteins released by cells to stimulate other cells to divide. Growth factors activate a protein kinase receptor, which, in turn, activates the Ras protein. The Ras protein then initiates a MAK cascade, which ultimately activates a transcription factor. One such transcription factor binds to DNA at the gene called *p53*. The product of *p53*, protein 53, checks for DNA damage. If the DNA is damaged, p53 directs enzymes to repair the DNA. Once repaired, p53 permits cell division to proceed. If repair is unsuccessful, it directs other enzymes to kill the cell, thus preventing the proliferation of damaged cells. Such programed cell death is called **apoptosis.** If a member protein in the MAP signal transduction pathway is damaged or if the DNA contains a mutated version of *p53,* the p53 protein product may be critically altered or nonexistent. As a result, DNA surveillance does not occur and cell division progresses even if the DNA is damaged. Continued uncontrolled cell division leads to a proliferation of cancer cells. Although mutations in *p53* and other genes can be inherited, they are also caused by the ultraviolet radiation in sunlight and by chemicals in tobacco smoke.

Review Questions

Multiple-Choice Questions

The questions that follow provide a review of the material presented in this chapter. Use them to evaluate how well you understand the terms, concepts, and processes presented. Actual AP multiple-choice questions are often more general, covering a broad range of concepts, and often more lengthy. For multiple-choice questions typical of the exam, take the two practice exams in this book.

Directions: Each of the following questions or statements is followed by four possible answers or sentence completions. Choose the one best answer or sentence completion.

1. Insulin is a signaling molecule that

A. is a ligand for a membrane receptor protein
B. is a ligand for an intracellular receptor protein
C. enters the nucleus and acts as a transcription factor
D. is a second messenger that activates cAMP

2. Cortisol is a steroid signaling molecule that communicates its signal by

- **A.** binding to a membrane receptor protein
- **B.** binding to an intracellular receptor protein
- **C.** binding to DNA
- **D.** binding to mRNA

3. All of the following are second messengers EXCEPT:

- **A.** cAMP
- **B.** Ca^{2+}
- **C.** IP_3
- **D.** FOXP2, a transcription factor

4. Gap junctions and plasmodesmata allow signaling

- **A.** by direct contact
- **B.** across synapses that span the synaptic cleft between nerve cells
- **C.** among nearby cells during early animal development
- **D.** between different organs of a multicellular organism

5. Receptor protein activation occurs when

- **A.** ADP is phosphorylated to ATP
- **B.** ATP is converted to cAMP
- **C.** there is a conformation change in the receptor protein
- **D.** the receptor protein binds to a second messenger

6. A consequence of a signaling cascade is that it

- **A.** supplies energy to the cell
- **B.** accelerates mRNA activity
- **C.** is less susceptible to the impact of mutations
- **D.** amplifies the signaling response

Questions 7–12 refer to the following. Each answer in the key may be used once, more than once, or not at all.

- **A.** a protein kinase receptor
- **B.** a G protein-coupled receptor (GPCR)
- **C.** an intracellular receptor
- **D.** a ligand-gated ion receptor

7. Nonpolar ligands bind to

8. An exchange of a GTP for a GDP in a membrane-bound protein is characteristic of

9. Dimerization and autophosphorylation are characteristic of

10. A second membrane-bound protein is activated by

11. Passageways allowing movement of substances across the membrane are characteristic of

12. Second messengers are generated by the action of

Free-Response Questions

The AP exam has long and short free-response questions. The long questions have considerable descriptive information that may include tables, graphs, or figures. The short questions are brief but may also include figures. Both kinds of questions have four parts and generally require that you bring together concepts from multiple areas of biology.

The questions that follow are designed to further your understanding of the concepts presented in this chapter. Unlike the free-response questions on the exam, they are narrowly focused on the material in this chapter. For free-response questions typical of the exam, take the two practice exams in this book.

Directions: The best way to prepare for the AP exam is to write out your answers as if you were taking the exam. Use complete sentences for all your answers and do *not* use outline form or bullets. You may use diagrams to supplement your answers, but be sure to describe the importance or relevance of your diagrams.

1. Although there are significant differences among the four receptor protein mechanisms, two aspects of their activity are the same. Describe the two aspects of their mechanisms that are the same.
2. Although both a protein kinase receptor and a G protein-coupled receptor (GPCR) can phosphorylate a cytoplasmic protein kinase, they do it in very different ways. Contrast how these two signaling mechanisms phosphorylate a protein kinase.
3. There are four major kinds of signal transduction pathways, each employing a different kind of receptor protein:
   - ligand-gated ion receptor
   - G protein-coupled receptor (GPCR)
   - receptor tyrosine kinase (RTK) receptor
   - intracellular receptor

   For each of these pathways, answer each of the following questions:

   a. Describe how the receptor protein is activated.
   b. Describe the signal transduction pathway.
   c. Describe how the signal transduction pathway is deactivated.
   d. Provide an example of the pathway.

Answers and Explanations

Multiple-Choice Questions

1. **A.** Because insulin is a protein, it is both a large and a charged molecule. As a result, it is unable to cross the plasma membrane. Therefore, it must bind to a membrane receptor protein, never actually entering the cell.
2. **B.** Steroids are nonpolar molecules able to traverse the plasma membrane unaided. After crossing the membrane, cortisol binds to an intracellular receptor protein. Note that signaling molecules do not themselves bind to DNA or mRNA, but rather activate receptor proteins that initiate the appropriate chemical responses.
3. **D.** Second messengers are small nonprotein molecules. Transcription factors are proteins.
4. **A.** Gap junctions in animals and plasmodesmata in plants provide a passageway between adjacent cells for signaling molecules to pass. Synaptic signaling occurs across synapses, the small gaps between nerve cells. Paracrine signaling occurs among nearby cells, and endocrine signaling occurs for cells separated by relatively large distances.

5. **C.** A receptor protein becomes activated when it undergoes a three-dimensional conformational change. The new arrangement of atoms in the protein opens passageways or exposes active sites for binding.
6. **D.** At each step of the signaling cascade, a kinase enzyme can catalyze multiple reactions. Each of those reactions is then the beginning of the next step of the cascade, now multiplied many times over. Each step, then, has a multiplier effect, amplifying the signal. Also, because there are multiple participants, the signaling cascade is more susceptible to the influence of mutations, as a mutation in any member of the cascade can have a deleterious effect on the ultimate product of the signal.
7. **C.** Nonpolar ligands can cross the plasma membrane without assistance. They enter the cytoplasm and bind to intracellular receptor proteins.
8. **B.** An activated GPCR exchanges a GTP for a GDP on a nearby membrane-bound G protein. The exchange activates the G protein. A GTP exchange for GDP can also occur for an RTK receptor pathway (like the one involving Ras), but that exchange occurs on a cytoplasmic protein, not a membrane-bound protein.
9. **A.** When a ligand binds to a protein kinase receptor (such as receptor tyrosine kinase, RTK), it causes it to form a dimer with a second protein kinase receptor. Once the dimer forms, it attaches phosphate groups to itself (autophosphorylates).
10. **B.** An activated GPCR exchanges a GTP for a GDP on the G protein. The G protein is a nearby membrane-bound protein.
11. **D.** A ligand-gated ion receptor opens a gate, providing a passageway for ions to enter or exit the cell.
12. **B.** Second messengers are activated by the protein that is activated by the G protein of a GPCR.

Free-Response Questions

1. Each of the receptor proteins requires activation by the binding of a ligand. Also, the binding of the ligand to the receptor protein causes a conformational change in its three-dimensional structure.
2. Once activated, a protein kinase receptor, like RTK, *directly* phosphorylates and, thus, activates a cytoplasmic protein kinase. In contrast, a GPCR is *indirectly* responsible for the phosphorylation event. For a GPCR, phosphorylation of a protein kinase begins when the GPCR activates a membrane-bound G protein, which, in turn, activates a second membrane-bound enzyme, which then can phosphorylate a protein kinase.
3. a. The binding of a specific ligand (signaling molecule) to the receptor protein triggers a conformational change in the receptor of each of these signal transduction pathways, putting it in its activated state.
   b. *Step-by-step descriptions for each of these four signal transduction pathways are provided in the text.*
   c. *Deactivation is the last step in the step-by-step descriptions of the pathways in the text.*
   d. *Examples are provided in the text.*