Communication, Integration, and Homeostasis

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Future progress in medicine will require a quantitative understanding of the many interconnected networks of molecules that comprise our cells and tissues, their interactions, and their regulation.
—Overview of the NIH Roadmap, 2003

Background Basics
- Homeostasis
- Nucleotides
- Cell junctions
- Extracellular matrix
- Endocrine glands
- Membrane structure
- Membrane proteins
- Diffusion
- Exocytosis
In 2003 the United States National Institutes of Health embarked on an ambitious project to promote translation of basic research into new medical treatments and strategies for disease prevention. Contributors to the NIH Common Fund Programs (http://commonfund.nih.gov) are compiling information on biological pathways in an effort to understand how cells communicate with one another and maintain the body in a healthy state. In this chapter, we examine the basic patterns of cell-to-cell communication and see how the coordination of function resides in chemical and electrical signals. Each cell in the body can communicate with most other cells. To maintain homeostasis, the body uses a combination of simple diffusion across small distances; widespread distribution of molecules through the circulatory system; and rapid, specific delivery of messages by the nervous system.

**Cell-to-Cell Communication**

In recent years the amount of information available about cell-to-cell communication has mushroomed as a result of advances in research technology. Signal pathways that once seemed fairly simple and direct are now known to be incredibly complex networks and webs of information transfer. In the sections that follow, we distill what is known about cell-to-cell communication into some basic patterns that you can recognize when you encounter them again in your study of physiology.

By most estimates the human body is composed of about 75 trillion cells. Those cells face a daunting task—to communicate with one another in a manner that is rapid and yet conveys a tremendous amount of information. Surprisingly, there are only two basic types of physiological signals: electrical and chemical. **Electrical signals** are changes in a cell's membrane potential. **Chemical signals** are molecules secreted by cells into the extracellular fluid. Chemical signals are responsible for most communication within the body. The cells that respond to electrical or chemical signals are called **target cells**, or **targets** for short.

Our bodies use four basic methods of cell-to-cell communication (Fig. 6.1). **Local communication** includes (1) **gap junctions**, which allow direct cytoplasmic transfer of electrical and chemical signals between adjacent cells; (2) **contact-dependent signals**, which occur when surface molecules on one cell membrane bind to surface molecules on another cell's membrane; and (3) **chemicals** that diffuse through the extracellular fluid to act on cells close by. **Long-distance communication** (4) uses a combination of chemical and electrical signals carried by nerve cells and chemical signals transported in the blood.

A given molecule can function as a signal by more than one method. For example, a molecule can act close to the cell that released it (local communication) as well as in distant parts of the body (long-distance communication).

**Gap Junctions Create Cytoplasmic Bridges**

The simplest form of cell-to-cell communication is the direct transfer of electrical and chemical signals through **gap junctions**, protein channels that create cytoplasmic bridges between adjacent cells (Fig. 6.1a). A gap junction forms from the union of membrane-spanning proteins, called **connexins**, on two adjacent cells. The united connexins create a protein channel, or **connexon**, that can open and close. When the channel is open, the connected cells function like a single cell that contains multiple nuclei (a **syncytium**).

When gap junctions are open, ions and small molecules such as amino acids, ATP, and cyclic AMP diffuse directly from the cytoplasm of one cell to the cytoplasm of the next. Larger molecules cannot pass through gap junctions. In addition, gap junctions are the only means by which electrical signals can pass **directly** from cell to cell. Movement of molecules and electrical signals through gap junctions can be modulated or shut off completely.

Gap junctions are not all alike. Scientists have discovered more than 20 different isoforms of connexins that may mix or match to form gap junctions. The variety of connexin isoforms allows gap junction selectivity to vary from tissue to tissue. In mammals, gap junctions are found in almost every cell type, including heart muscle, some types of smooth muscle, lung, liver, and neurons of the brain.

**Contact-Dependent Signals Require Cell-to-Cell Contact**

Some cell-to-cell communication requires that surface molecules on one cell membrane bind to a membrane protein of another cell (Fig. 6.1b). Such **contact-dependent signaling** occurs in the immune system and during growth and development, such as when nerve cells send out long extensions that must grow from the central axis of the body to the **distal** (distant) ends of...
Communication in the Body

Cell-to-cell communication uses chemical and electrical signaling to coordinate function and maintain homeostasis.

**LOCAL COMMUNICATION**

(a) Gap junctions form direct cytoplasmic connections between adjacent cells.

(b) Contact-dependent signals require interaction between membrane molecules on two cells.

(c) Autocrine signals act on the same cell that secreted them. Paracrine signals are secreted by one cell and diffuse to adjacent cells.

**LONG-DISTANCE COMMUNICATION**

Long-distance signaling may be electrical signals passing along neurons or chemical signals that travel through the circulatory system.

**Endocrine System**

(d) Hormones are secreted by endocrine glands or cells into the blood. Only target cells with receptors for the hormone respond to the signal.

**Nervous System**

(e) Neurotransmitters are chemicals secreted by neurons that diffuse across a small gap to the target cell.

(f) Neurohormones are chemicals released by neurons into the blood for action at distant targets.
the developing limbs. **Cell adhesion molecules (CAMs)** first known for their role in cell-to-cell adhesion, have now been shown to act as receptors in cell-to-cell signaling. CAMs are linked to the cytoskeleton and to intracellular enzymes. Through these linkages, CAMs transfer signals in both directions across cell membranes.

### Paracrine and Autocrine Signals Carry Out Local Communication

Local communication takes place through paracrine and autocrine signaling. A **paracrine signal** (para−, beside + krinen, to secrete) is a chemical that acts on cells in the immediate vicinity of the cell that secreted the signal. A chemical signal that acts on the cell that secreted it is called an **autocrine signal** (auto−, self). In some cases a molecule may act as both an autocrine signal and a paracrine signal.

Paracrine and autocrine signal molecules reach their target cells by diffusing through the interstitial fluid (Fig. 6.1c). Because distance is a limiting factor for diffusion, the effective range of paracrine signals is restricted to adjacent cells. A good example of a paracrine molecule is **histamine**, a chemical released from damaged cells. When you scratch yourself with a pin, the red, raised **wheat** that results is due in part to the local release of histamine from the injured tissue. The histamine acts as a paracrine signal, diffusing to capillaries in the immediate area of the injury and making them more permeable to white blood cells and antibodies in the plasma. Fluid also leaves the blood vessels and collects in the interstitial space, causing swelling around the area of injury.

Several important classes of molecules act as local signals. **Cytokines** are regulatory peptides, and **eicosanoids** are lipid-derived paracrine and autocrine signal molecules. We discuss cytokines and eicosanoids in more detail below.

### Long-Distance Communication May Be Electrical or Chemical

All cells in the body can release paracrine signals, but most long-distance communication between cells takes place through the nervous and endocrine systems. The endocrine system communicates by using **hormones** (hormon, to excite), chemical signals that are secreted into the blood and distributed all over the body by the circulation. Hormones come in contact with most cells of the body, but only those cells with receptors for the hormone are target cells (Fig. 6.1d).

The nervous system uses a combination of chemical signals and electrical signals to communicate over long distances. An electrical signal travels along a nerve cell (neuron) until it reaches the very end of the cell, where it is translated into a chemical signal secreted by the neuron. Such a chemical signal is called a **neurotransmitter**.

If a neurocrine molecule diffuses from the neuron across a narrow extracellular space to a target cell and has a rapid effect, it is called a **neurotransmitter** (Fig. 6.1f). If a neurocrine acts more slowly as an autocrine or paracrine signal, it is called a **neuromodulator**. If a neurocrine released by a neuron diffuses into the blood for distribution, it is called a **neurohormone** (Fig. 6.1e). The similarities between neurohormones and classic hormones secreted by the endocrine system blur the distinction between the nervous and endocrine systems, making them a functional continuum rather than two distinct systems.

### Cytokines May Act as Both Local and Long-Distance Signals

Cytokines are among the most recently identified communication molecules. Initially the term **cytokine** referred only to proteins that modulate immune responses, but in recent years the definition has been broadened to include a variety of regulatory peptides. All nucleated cells synthesize and secrete cytokines in response to stimuli. Cytokines control cell development, cell differentiation, and the immune response. In development and differentiation, cytokines usually function as autocrine or paracrine signals. In stress and inflammation, some cytokines may act on relatively distant targets and may be transported through the circulation just as hormones are.

How do cytokines differ from hormones? In general, cytokines act on a broader spectrum of target cells. In addition, cytokines are not produced by specialized cells the way hormones are, and they are made on demand. In contrast, most protein or peptide hormones are made in advance and stored in the endocrine cell until needed. Also, the signal pathways for cytokines are usually different from those for hormones. However, the distinction between cytokines and hormones is sometimes blurry. For example, erythropoietin, the molecule that controls synthesis of red blood cells, is by tradition considered a hormone but functionally fits the definition of a cytokine.
Communication, Integration, and Homeostasis

Signal Pathways

Chemical signals in the form of paracrine and autocrine molecules and hormones are released from cells into the extracellular compartment. This is not a very specific way for these signals to find their targets because substances that travel through the blood reach nearly every cell in the body. Yet cells do not respond to every signal that reaches them.

Why do some cells respond to a chemical signal while other cells ignore it? The answer lies in the target-cell receptor proteins to which chemical signals bind. A cell can respond to a chemical signal only if the cell has the appropriate receptor proteins for that signal (Fig. 6.1).

If a target cell has a receptor for a signal molecule, binding of the signal to the receptor protein initiates a response. All signal pathways share the following features (Fig. 6.2):

1. The signal molecule is a ligand that binds to a protein receptor. The ligand is also known as a first messenger because it brings information to the target cell.
2. Ligand-receptor binding activates the receptor.
3. The receptor in turn activates one or more intracellular signal molecules.
4. The last signal molecule in the pathway initiates synthesis of target proteins or modifies existing target proteins to create a response.

In the following sections, we describe some basic signal pathways. They may seem complex at first, but they follow patterns that you will encounter over and over as you study the systems of the body. Most physiological processes, from the beating of your heart to learning and memory, use some variation of these pathways. One of the wonders of physiology is the fundamental importance of these signal pathways and the way they have been conserved in animals ranging from worms to humans.

Receptor Proteins Are Located Inside the Cell or on the Cell Membrane

Protein receptors for signal molecules play an important role in physiology and medicine. About half of all drugs currently in use act on receptor proteins. Target-cell receptor proteins may be found in the nucleus, in the cytosol, or on the cell membrane as integral proteins. Where a chemical signal binds to its receptor largely depends on whether that signal molecule is lipophilic or lipophobic (Fig. 6.3).

Lipophilic signal molecules can diffuse through the phospholipid bilayer of the cell membrane and bind to cytosolic receptors or nuclear receptors (Fig. 6.3a). In these cases, receptor activation often turns on a gene and directs the nucleus to make new mRNA (transcription). The mRNA then provides a template for synthesis of new proteins (translation). This process is relatively slow and the cell's response may not be noticeable for an hour or longer. In some instances the activated receptor can also turn off, or repress, gene activity. Many lipophilic signal molecules that follow this pattern are hormones.

RUNNING PROBLEM

Later that day in the physician’s office, the nurse practitioner explains diabetes to Marvin. Diabetes mellitus is a family of metabolic disorders caused by defects in the homeostatic pathways that regulate glucose metabolism. Several forms of diabetes exist, and some can be inherited. One form, called type 1 diabetes mellitus, occurs when endocrine cells of the pancreas are destroyed and stop making insulin, a protein hormone involved in blood glucose homeostasis. In another form, type 2 diabetes mellitus, insulin may be present in normal or above-normal levels, but the insulin-sensitive cells of the body do not respond normally to the hormone.

Q1: In which type of diabetes is the target cell signal pathway for insulin more likely to be defective?

Q2: Insulin is a protein hormone. Would you expect to find its receptor on the cell surface or in the cytoplasm of the target cells?
Communication, Integration, and Homeostasis

Lipophilic signal molecules are unable to diffuse through the phospholipid bilayer of the cell membrane. Instead, these signal molecules remain in the extracellular fluid and bind to receptor proteins on the cell membrane (Fig. 6.3b). (Some lipophilic signal molecules also bind to cell membrane receptors in addition to their intracellular receptors.) In general, the response time for pathways linked to membrane receptor proteins is very rapid: responses can be seen within milliseconds to minutes.

We can group membrane receptors into four major categories, illustrated in Figure 6.3c. The simplest receptors are chemically gated (ligand-gated) ion channels called receptor-channels. Ligand binding opens or closes the channel and alters ion flow across the membrane.

Three other receptor types are shown in Figure 6.3c: receptor-enzymes, G protein–coupled receptors, and integrin receptors. For all three, information from the signal molecule must be passed across the membrane to initiate an intracellular

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**Fig. 6.3** Target cell receptors may be located on the cell surface or inside the cell
response. This transmission of information from one side of a membrane to the other using membrane proteins is known as signal transduction. We will take a closer look at signal transduction before returning to the four receptor types that participate in it.

**Concept Check**

4. List four components of signal pathways.
5. Name three cellular locations of receptors.

**Membrane Proteins Facilitate Signal Transduction**

Signal transduction is the process by which an extracellular signal molecule activates a membrane receptor that in turn alters intracellular molecules to create a response. The extracellular signal molecule is the first messenger, and the intracellular molecules form a second messenger system. The term signal transduction comes from the verb to transduce, meaning “to lead across” (trans, across + ducere, to lead).

A transducer is a device that converts a signal from one form into a different form. For example, the transducer in a radio converts radio waves into sound waves (Fig. 6.4).

In biological systems, membrane proteins act as transducers. They convert the message of extracellular signals into intracellular messenger molecules that trigger a response.

The basic pattern of a biological signal transduction pathway is shown in Figure 6.5a and can be broken down into the following events.

1. An extracellular signal molecule (the first messenger) binds to and activates a membrane receptor.
2. The activated membrane receptor turns on its associated proteins and starts an intracellular cascade of second messengers.
3. The last second messenger in the cascade acts on intracellular targets to create a response.

A more detailed version of the basic signal transduction pathway is shown in Figure 6.5b.

1. Membrane receptors and their associated proteins usually either
   (a) activate protein kinases, which are enzymes that transfer a phosphate group from ATP to a protein. Phosphorylation is an important biochemical method of regulating cellular processes.
   (b) activate amplifier enzymes that create intracellular second messengers.
2. Second messenger molecules in turn
   (a) alter the gating of ion channels. Opening or closing ion channels creates electrical signals by altering the cell’s membrane potential.
   (b) increase intracellular calcium. Calcium binding to proteins changes their function, creating a cellular response.
   (c) change enzyme activity, especially of protein kinases or protein phosphatases, enzymes that remove a phosphate group. The phosphorylation or dephosphorylation of a protein can change its configuration and create a response. Examples of changes that occur with phosphorylation include increased or decreased enzyme activity and opening or closing of gated ion channels.
3. The proteins modified by calcium binding and phosphorylation control one or more of the following:
   (a) metabolic enzymes
   (b) motor proteins for muscle contraction and cytoskeletal movement
   (c) proteins that regulate gene activity and protein synthesis
   (d) membrane transport and receptor proteins

If you think this list includes almost everything a cell does, you’re right!

Figure 6.6a shows how the steps of a signal transduction pathway form a cascade. A signaling cascade starts when
a stimulus (the signal molecule) converts inactive molecule A (the receptor) to an active form. Active A then converts inactive molecule B into active B, active molecule B in turn converts inactive molecule C into active C, and so on, until at the final step a substrate is converted into a product. Many intracellular signal pathways are cascades. Blood clotting is an important example of an extracellular cascade.

In signal transduction pathways, the original signal is not only transformed but also amplified (amplificare, to make larger). In a radio, the radio wave signal is also amplified. In cells, signal amplification turns one signal molecule into multiple second messenger molecules (Fig. 6.6b). The process begins when the first messenger ligand combines with its receptor. The receptor-ligand complex turns on an amplifier enzyme. The amplifier enzyme activates several molecules, which in turn each activate several more molecules as the cascade proceeds. By the end of the process, the effects of the ligand have been amplified much more than if there were a 1:1 ratio between each step. Amplification gives the body “more bang for the buck” by enabling a small amount of ligand to create a large effect. The most common amplifier enzymes and second messengers are listed in the table in Figure 6.6c.

In the sections that follow, we will examine in more detail the four major types of membrane receptors (see Fig. 6.3c). Keep in mind that these receptors may be responding to any of the different kinds of signal molecules—hormones, neurotransmitters, cytokines, paracrines, or autocrines.

### Concept Check

6. What are the four steps of signal transduction?
7. What happens during amplification?
8. Why do steroid hormones not require signal transduction and second messengers to exert their action? (Hint: Are steroids lipophobic or lipophilic?)

### Receptor-Enzymes Have Protein Kinase or Guanylyl Cyclase Activity

Receptor-enzymes have two regions: a receptor region on the extracellular side of the cell membrane, and an enzyme region on the cytoplasmic side (see Fig. 6.3c). In some instances,
### Signal Transduction

#### (a) Signal transduction pathways form a cascade.

![Signal transduction pathway](image)

- **Signal**
  - Inactive A
  - Active A
  - Inactive B
  - Active B
  - Inactive C
  - Active C

- **Substrate**
- **Product**

- Conversion of substrate to product is the final step of the cascade.

#### (b) Signal amplification allows a small amount of signal to have a large effect.

![Signal amplification diagram](image)

- **Receptor-ligand complex activates an amplifier enzyme (AE).**

- **Extracellular Fluid**
- **Cell membrane**
- **Intracellular Fluid**

- **One ligand is amplified into many intracellular molecules.**

#### (c) Second messenger pathways

<table>
<thead>
<tr>
<th>SECOND MESSENGER</th>
<th>MADE FROM</th>
<th>AMPLIFIER ENZYME</th>
<th>LINKED TO</th>
<th>ACTION</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleotides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cAMP</td>
<td>ATP</td>
<td>Adenylyl cyclase (membrane)</td>
<td>GPCR*</td>
<td>Activates protein kinases, especially PKA. Binds to ion channels.</td>
<td>Phosphorylates proteins. Alters channel opening.</td>
</tr>
<tr>
<td>cGMP</td>
<td>GTP</td>
<td>Guanylyl cyclase (membrane)</td>
<td>Receptor-enzyme</td>
<td>Activates protein kinases, especially PKG.</td>
<td>Phosphorylates proteins.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guanylyl cyclase (cytosol)</td>
<td>Nitric oxide (NO)</td>
<td>Binds to ion channels.</td>
<td>Alters channel opening.</td>
</tr>
<tr>
<td><strong>Lipid-derived</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP₃</td>
<td>Membrane phospholipids</td>
<td>Phospholipase C (membrane)</td>
<td>GPCR</td>
<td>Releases Ca²⁺ from intracellular stores.</td>
<td>See Ca²⁺ effects below.</td>
</tr>
<tr>
<td>DAG</td>
<td></td>
<td></td>
<td></td>
<td>Activates protein kinase C.</td>
<td>Phosphorylates proteins.</td>
</tr>
<tr>
<td><strong>Ions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca²⁺</td>
<td></td>
<td></td>
<td></td>
<td>Binds to calmodulin. Binds to other proteins.</td>
<td>Alters enzyme activity. Exocytosis, muscle contraction, cytoskeleton movement, channel opening.</td>
</tr>
</tbody>
</table>

*GPCR = G protein–coupled receptor. IP₃ = Inositol trisphosphate. DAG = diacylglycerol
the amplifier enzyme that converts a membrane phospholipid to guanosine diphosphate (GDP). Exchanging the GDP for guanosine triphosphate (GTP) activates the G protein. When G proteins are activated, they either (1) open an ion channel in the membrane or (2) alter enzyme activity on the cytoplasmic side of the membrane.

G proteins linked to amplifier enzymes make up the bulk of all known signal transduction mechanisms. The two most common amplifier enzymes for G protein–coupled receptors are adenyl cyclase and phospholipase C. The pathways for these amplifier enzymes are described next.

**Many Lipophobic Hormones Use GPCR-cAMP Pathways**

The G protein–coupled adenyl cyclase-cAMP system was the first identified signal transduction pathway (Fig. 6.8a). It was discovered in the 1950s by Earl Sutherland when he was studying the effects of hormones on carbohydrate metabolism. This discovery proved so significant to our understanding of signal transduction that in 1971 Sutherland was awarded a Nobel prize for his work.

The G protein–coupled adenyl cyclase-cAMP system is the signal transduction system for many protein hormones. In this system, adenyl cyclase is the amplifier enzyme that converts ATP to the second messenger molecule cyclic AMP (cAMP). Cyclic AMP then activates protein kinase A (PKA), which in turn phosphorylates other intracellular proteins as part of the signal cascade.

**G Protein–Coupled Receptors Also Use Lipid-Derived Second Messengers**

Some G protein–coupled receptors are linked to a different amplifier enzyme: phospholipase C (Fig. 6.8b). When a signal molecule activates this G protein–coupled pathway, phospholipase C (PLC) converts a membrane phospholipid (phosphatidylinositol bisphosphate) into two lipid-derived second messenger molecules: diacylglycerol and inositol trisphosphate.

Diacylglycerol (DAG) is a nonpolar diglyceride that remains in the lipid portion of the membrane and interacts with protein kinase C (PKC), a Ca^{2+}-activated enzyme associated with the cytoplasmic face of the cell membrane. PKC phosphorylates cytosolic proteins that continue the signal cascade.

Inositol trisphosphate (IP$_3$) is a water-soluble messenger molecule that leaves the membrane and enters the cytoplasm. There it binds to a calcium channel on the endoplasmic reticulum (ER). IP$_3$ binding opens the Ca^{2+} channel, allowing Ca^{2+} to diffuse out of the ER and into the cytosol. Calcium is itself an important signal molecule, as discussed below.
Communication, Integration, and Homeostasis

One signal molecule binds to a G protein–coupled receptor (GPCR), which activates the G protein.

G protein turns on adenyl cyclase, an amplifier enzyme.

Adenyl cyclase converts ATP to cyclic AMP.

cAMP activates protein kinase A.

Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.

**FIGURE QUESTION**
Using the pattern shown in Fig. 6.6a, create a cascade that includes ATP, cAMP, adenyl cyclase, a phosphorylated protein, and protein kinase A.

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**G Protein–Coupled Signal Transduction**

(a) GPCR-adenyl Cyclase Signal Transduction and Amplification

1. Signal molecule binds to G protein–coupled receptor (GPCR), which activates the G protein.

2. G protein turns on adenyl cyclase, an amplifier enzyme.

3. Adenyl cyclase converts ATP to cyclic AMP.

4. cAMP activates protein kinase A.

5. Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.

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(b) GPCR-phospholipase C Signal Transduction


2. G protein activates phospholipase C (PLC), an amplifier enzyme.

3. PLC converts membrane phospholipids into diacylglycerol (DAG), which remains in the membrane, and IP$_3$, which diffuses into the cytoplasm.

4. DAG activates protein kinase C (PKC), which phosphorylates proteins.

5. IP$_3$ causes release of Ca$^{2+}$ from organelles, creating a Ca$^{2+}$ signal.
The membrane-spanning proteins called integrins mediate blood clotting, wound repair, cell adhesion and recognition in the immune response, and cell movement during development. On the extracellular side of the membrane, integrin receptors bind either to proteins of the extracellular matrix or to ligands such as antibodies and molecules involved in blood clotting. Inside the cell, integrins attach to the cytoskeleton via anchor proteins (Fig. 6.3c). Ligand binding to the receptor causes integrins to activate intracellular enzymes or alter the organization of the cytoskeleton.

The importance of integrin receptors is illustrated by inherited conditions in which the receptor is absent. In one condition, platelets—cell fragments that play a key role in blood clotting—lack an integrin receptor. As a result, blood clotting is defective in these individuals.

The simplest receptors are ligand-gated ion channels, and most of them are neurotransmitter receptors found in nerve and muscle. The activation of receptor-channels initiates the most rapid intracellular responses of all receptors. When an extracellular ligand binds to the receptor-channel protein, a channel gate opens or closes, altering the cell’s permeability to an ion. Increasing or decreasing ion permeability rapidly changes the cell’s membrane potential, creating an electrical signal that alters voltage-sensitive proteins (Fig. 6.9).

One example of a receptor-channel is the acetylcholine-gated monovalent (“one-charge”) cation channel of skeletal muscle. The neurotransmitter acetylcholine released from an adjacent neuron binds to the acetylcholine receptor and opens the channel. Both Na⁺ and K⁺ flow through the open channel, K⁺ leaving the cell and Na⁺ entering the cell along...
their electrochemical gradients. The sodium gradient is stronger, however, so net entry of positively charged Na$^+$ depolarizes the cell. In skeletal muscle, this cascade of intracellular events results in muscle contraction.

Not all ion channel signal transduction is mediated by receptor-channels. Some ligand-gated ion channels are controlled by intracellular second messengers, such as cAMP or ATP. The ATP-gated K$^+$ channels of the pancreatic beta cell are an example. Other ion channels open or close in response to extracellular signals, but the signal ligand does not bind to the channel protein. Instead it binds to a G protein–coupled receptor that is linked to the ion channel.

Figure 6.10 is a summary map of basic signal transduction, showing the general relationships among first messengers, membrane receptors, second messengers, and cell responses.
Novel Signal Molecules

The following sections introduce you to some unusual signal molecules that are important in physiology and medicine. They include an ion (Ca$^{2+}$), three gases, and a family of lipid-derived messengers. The processes controlled by these signal molecules have been known for years, but the control signals themselves were discovered only relatively recently.

Calcium Is an Important Intracellular Signal

Calcium ions are the most versatile ionic messengers (Fig. 6.11). Calcium enters the cell either through voltage-gated Ca$^{2+}$ channels or through ligand-gated or mechanically gated channels. Calcium can also be released from intracellular compartments by second messengers, such as IP$_3$. Most intracellular Ca$^{2+}$ is stored in the endoplasmic reticulum, where it is concentrated by active transport.

Release of Ca$^{2+}$ into the cytosol (from any of the sources just mentioned) creates a Ca$^{2+}$ signal, or Ca$^{2+}$ “spark,” that can be recorded using special Ca$^{2+}$-imaging techniques (see Biotechnology box on calcium signals). The calcium ions combine with cytoplasmic calcium-binding proteins to exert various effects. Several types of calcium-dependent events occur in the cell:

1. Ca$^{2+}$ binds to the protein calmodulin, found in all cells. Calcium binding alters enzyme or transporter activity or the gating of ion channels.
2. Ca$^{2+}$ binds to other regulatory proteins and alters movement of contractile or cytoskeletal proteins such as microtubules. For example, Ca$^{2+}$ binding to the regulatory protein troponin initiates muscle contraction in a skeletal muscle cell.

3. Ca$^{2+}$ binds to regulatory proteins to trigger exocytosis of secretory vesicles. For example, the release of insulin from pancreatic beta cells occurs in response to a calcium signal.
4. Ca$^{2+}$ binds directly to ion channels to alter their gating state. An example of this target is a Ca$^{2+}$-activated K$^+$ channel found in nerve cells.
5. Ca$^{2+}$ entry into a fertilized egg initiates development of the embryo.

Gases Are Ephemerol Signal Molecules

Soluble gases are short-acting paracrine/autocrine signal molecules that act close to where they are produced. The best-known gaseous signal molecule is nitric oxide (NO), but carbon...
monoxide and hydrogen sulfide, two gases better known for their noxious effects, can also act as local signals.

For years researchers knew of a short-lived signal molecule produced by the endothelial cells lining blood vessels. They initially named it endothelial-derived relaxing factor (EDRF). This molecule diffuses from the endothelium into adjacent smooth muscle cells, causing the muscle to relax and dilate the blood vessel. Scientists took years to identify EDRF as nitric oxide because it is rapidly broken down, with a half-life of only 2 to 30 seconds. (Half-life is the time required for the signal to lose half of its activity.) As a result of this difficult work on NO in the cardiovascular system, Robert Furchgott, Louis Ignarro, and Ferid Murad received the 1998 Nobel prize for physiology and medicine.

In tissues, NO is synthesized by the action of the enzyme nitric oxide synthase (NOS) on the amino acid arginine:

\[
\text{Arginine} + \text{O}_2 \xrightarrow{\text{nitric oxide synthase}} \text{NO} + \text{citrulline} \text{ (an amino acid)}
\]

The NO produced in this reaction diffuses into target cells, where it binds to a receptor that activates the cytosolic form of guanyl cyclase and causes formation of the second messenger cGMP. In addition to relaxing blood vessels, NO in the brain acts as a neurotransmitter and a neuromodulator.

Carbon monoxide (CO), a gas known mostly for its toxic effects, is also a signal molecule produced in minute amounts by certain cells. Like NO, CO activates guanyl cyclase and cGMP, but it may also work independently to exert its effects. Carbon monoxide targets smooth muscle and neural tissue.

The newest gaseous signal molecule to be described is hydrogen sulfide (H₂S). Hydrogen sulfide also acts in the cardiovascular system to relax blood vessels. Garlic is a major dietary source of the sulfur-containing precursors, which may explain studies suggesting that eating garlic has protective effects on the heart.

Some Lipids Are Important Paracrine Signals
One of the interesting developments from sequencing the human genome and using genes to find proteins has been the identification of orphan receptors, receptors that have no known ligand.

**Calcium Signals Glow in the Dark**

If you’ve ever run your hand through a tropical ocean at night and seen the glow of bioluminescent jellyfish, you’ve seen a calcium signal. Aequorin, a protein complex isolated from jellyfish, is one of the molecules that scientists use to monitor the presence of calcium ions during a cellular response. When aequorin combines with calcium, it releases light that can be measured by electronic detection systems. Since the first use of aequorin in 1967, researchers have been designing increasingly sophisticated indicators that allow them to follow calcium signals in cells. With the help of molecules called fura, Oregon green, BAPTA, and chameleons, we can now watch calcium ions diffuse through gap junctions and flow out of intracellular organelles.

**From Dynamite to Medicine**

Who would have thought that a component of smog and a derivative of dynamite would turn out to be a biological messenger? Certainly not the peer reviewers who initially rejected Louis Ignarro’s attempts to publish his research findings on the elusive gas. However, the ability of nitrate-containing compounds to relax blood vessels has been known for more than 100 years, ever since workers in Alfred Nobel’s dynamite factory complained of headaches caused by nitrate-induced vasodilation. Since the 1860s, physicians have used nitroglycerin to relieve angina, heart pain that results from constricted blood vessels. Even today heart patients carry little nitroglycerin tablets to slide under their tongues when angina strikes. Still, it took years of work to isolate nitric oxide (NO), the short-lived gas that is the biologically active molecule derived from nitroglycerin. Despite all our twenty-first-century technology, direct research on NO is still difficult. Many studies look at its influence indirectly by studying the location and activity of nitric oxide synthase (NOS), the enzyme that produces NO.

**BIOTECHNOLOGY**

**Calcium Signals Glow in the Dark**

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The sea nettle *Chrysaora fuscescens.*

**CLINICAL FOCUS**

**From Dynamite to Medicine**

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**Some Lipids Are Important Paracrine Signals**

One of the interesting developments from sequencing the human genome and using genes to find proteins has been the identification of orphan receptors, receptors that have no known ligand.
Scientists are trying to work backward through signal pathways to find the ligands that bind to these orphan receptors. It was from this type of research that investigators recognized the importance and universality of eicosanoids, lipid-derived paracrine signals that play important roles in many physiological processes.

All eicosanoid signal molecules are derived from arachidonic acid, a 20-carbon fatty acid. The synthesis process is a network called the arachidonic acid cascade (Fig. 6.12). For simplicity, we will break the cascade into steps.

Arachidonic acid is produced from membrane phospholipids by the action of an enzyme, phospholipase A2 (PLA2). The activity of PLA2 is controlled by hormones and other signals. Arachidonic acid itself may act directly as a second messenger, altering ion channel activity and intracellular enzymes. It may also be converted into one of several classes of eicosanoid paracines. These lipid-soluble molecules can diffuse out of the cell and combine with receptors on neighboring cells to exert their action.

There are two major groups of arachidonic acid-derived paracines to be aware of:

1. **Leukotrienes** are molecules produced by the action of the enzyme lipoxigenase on arachidonic acid (leuko-+, white + triene, a molecule with three double bonds between carbon atoms). Leukotrienes are secreted by certain types of white blood cells. They play a significant role in asthma, a lung condition in which the smooth muscle of the airways constricts, making it difficult to breathe, and in the severe allergic reaction known as anaphylaxis. For this reason, pharmaceutical companies have been actively developing drugs to block leukotriene synthesis or action.

2. **Prostanoids** are molecules produced when the enzyme cyclooxygenase (COX) acts on arachidonic acid. Prostanoids include prostaglandins and thromboxanes. These eicosanoids act on many tissues of the body, including smooth muscle in various organs, platelets, kidney, and bone. In addition, prostaglandins are involved in sleep, inflammation, pain, and fever.

The nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, help prevent inflammation by inhibiting COX enzymes and decreasing prostaglandin synthesis. However, NSAIDs are not specific and may have serious unwanted side effects, such as bleeding in the stomach. The discovery of two COX isozymes, COX1 and COX2, enabled the design of drugs that target a specific COX isozyme. By inhibiting only COX2, the enzyme that produces inflammatory prostaglandins, physicians hoped to treat inflammation with fewer side effects. However, studies have shown that some patients who take COX2 inhibitors and other NSAIDs have increased risk of heart attacks and strokes, so these drugs are not recommended for long-term use.

Eicosanoids are not the only known lipid signal molecules. Lipids called sphingolipids also act as extracellular signals to help regulate inflammation, cell adhesion and migration, and cell growth and death. Like the eicosanoids, sphingolipids combine with G protein–coupled receptors in the membranes of their target cells.

**Concept Check**

14. One drug blocks leukotriene action in its target cells. A different drug blocks leukotriene synthesis. Use what you have learned about leukotrienes, signal molecules, and signal transduction to predict what these drugs are doing to have those effects.

**Modulation of Signal Pathways**

As you have just learned, signal pathways in the cell can be very complex. To complicate matters, different cells may respond differently to one kind of signal molecule. How can one chemical trigger response A in tissue 1 and response B in tissue 2? For most signal molecules, the target cell response depends on its receptor or its associated intracellular pathways, not on the ligand.

**One Ligand May Have Multiple Receptors**

For many years physiologists were unable to explain the observation that a single signal molecule could have different effects in different tissues. For example, the neurohormone epinephrine dilates blood vessels in skeletal muscle but constricts blood vessels in the intestine. How can one chemical have opposite effects? The answer became clear when scientists discovered that receptors, like other proteins, may come as families of related isoforms.
Communication, Integration, and Homeostasis

norepinephrine and its cousin the neurohormone epinephrine (also called adrenaline). Both molecules bind to a class of receptors called adrenergic receptors. (Adrenergic is the adjective relating to adrenaline.) The ability of adrenergic receptors to bind these neurocrines, but not others, demonstrates the specificity of the receptors.

Epinephrine and norepinephrine also compete for a single receptor type. Both neurocrines bind to subtypes of adrenergic receptors designated alpha (α) and beta (β). However, α-receptors have a higher binding affinity for norepinephrine, and the β₂-receptor subtype has a higher affinity for epinephrine.

Agonists and Antagonists When a ligand combines with a receptor, one of two events follows. Either the ligand activates the receptor and elicits a response, or the ligand occupies the binding site and prevents the receptor from responding (Fig. 6.14). Ligands that turn receptors on are known as agonists. Ligands that block receptor activity are called antagonists.

Pharmacologists use the principle of competing agonists to design drugs that are longer-acting and more resistant to enzymatic degradation than the endogenous ligand produced by the body (end-, within + -genous, developing). One example is the family of modified estrogens (female sex hormones) in birth control pills. These drugs are agonists of naturally occurring estrogens but have chemical groups added to protect them from breakdown and extend their active life.

Receptors Exhibit Saturation, Specificity, and Competition

Because receptors are proteins, receptor-ligand binding exhibits the general protein-binding characteristics of specificity, competition, and saturation. Similar protein-binding reactions occur in enzymes and transporters.

Specificity and Competition: Multiple Ligands for One Receptor Receptors have binding sites for their ligands, just as enzymes and transporters do. As a result, different ligand molecules with similar structures may be able to bind to the same receptor. A classic example of this principle involves two neurocrines responsible for the fight-or-flight response: the neurotransmitter norepinephrine and its cousin the neurohormone epinephrine (also called adrenaline). Both molecules bind to a class of receptors called adrenergic receptors. (Adrenergic is the adjective relating to adrenaline.) The ability of adrenergic receptors to bind these neurocrines, but not others, demonstrates the specificity of the receptors.

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Target response depends on the target receptor.

In this example, blood vessels dilate or constrict depending on their receptor type.

Epinephrine can bind to different isoforms of the adrenergic receptor.

α-Receptor Response

β₂-Receptor Response

Intestinal blood vessel

Epinephrine + α-Receptor

Epinephrine + β₂-Receptor

Vessel constricts.

Vessel dilates.

Fig. 6.13

The cellular response that follows binding of a signal molecule to a receptor depends on which isoform of the receptor is involved. For example, the α- and β₂-adrenergic receptors for epinephrine are isoforms of each other. When epinephrine binds to α-receptors on smooth muscle in intestinal blood vessels, signal pathways begin that cause the vessels to constrict (Fig. 6.13). When epinephrine binds to β₂-receptors on certain skeletal muscle blood vessels, the associated signal transduction pathways cause the vessels to dilate. In other words, the response of the blood vessel to epinephrine depends on the receptor isoform and its signal transduction pathway, not on the ligand that activates the receptor. Many drugs now are designed to be specific for only one receptor isoform.

Concept Check

15. What do receptors, enzymes, and transporters have in common that explains why they all exhibit saturation, specificity, and competition?

16. Insulin increases the number of glucose transporters on a skeletal muscle cell but not on the membrane of a liver cell. List two possible mechanisms that could explain how this one hormone can have these two different effects.
Up- and Down-Regulation Enable Cells to Modulate Responses

Saturation of proteins refers to the fact that protein activity reaches a maximum rate because cells contain limited numbers of protein molecules. Saturation can be observed with enzymes, transporters, and receptors. A cell's ability to respond to a chemical signal therefore can be limited by the number of receptors for that signal.

A single cell contains between 500 and 100,000 receptors on the surface of its cell membrane, with additional receptors in the cytosol and nucleus. In any given cell, the number of receptors changes over time. Old receptors are withdrawn from the membrane by endocytosis and are broken down in lysosomes. New receptors are inserted into the membrane by exocytosis. Intracellular receptors are also made and broken down. This flexibility permits a cell to vary its responses to chemical signals depending on the extracellular conditions and the internal needs of the cell.

What happens when a signal molecule is present in the body in abnormally high concentrations for a sustained period of time? Initially the increased signal level creates an enhanced response. As this enhanced response continues, the target cells may attempt to bring their response back to normal by either down-regulation or desensitization of the receptors for the signal.

Down-regulation is a decrease in receptor number. The cell can physically remove receptors from the membrane through endocytosis. A quicker and more easily reversible way to decrease cell response is desensitization, which can be achieved by binding a chemical modulator to the receptor protein. For example, the β-adrenergic receptors described in the previous section can be desensitized by phosphorylation of the receptor. The result of decreased receptor number or desensitization is a diminished response of the target cell even though the concentration of the signal molecule remains high. Down-regulation and desensitization are one explanation for the development of drug tolerance, a condition in which the response to a given dose decreases despite continuous exposure to the drug.

In the opposite situation, when the concentration of a ligand decreases, the target cell may use up-regulation in an attempt to keep its response at a normal level. In up-regulation, the target cell increases the number of receptors. More receptors make the target cell more responsive to whatever neurotransmitters are present. Up-regulation is also programmed during development as a mechanism that allows cells to vary their responsiveness to growth factors and other signal molecules.

Concept Check

17. To decrease a receptor's binding affinity, a cell might (select all that apply):
   (a) synthesize a new isoform of the receptor
   (b) withdraw receptors from the membrane
   (c) insert new receptors into the membrane
   (d) use a covalent modulator

Cells Must Be Able to Terminate Signal Pathways

In the body, signals turn on and off, so cells must be able to tell when a signal is over. This requires that signaling processes have built-in termination mechanisms. For example, to stop the response to a calcium signal, a cell removes Ca²⁺ from the cytosol by pumping it either back into the endoplasmic reticulum or out into the extracellular fluid.

Receptor activity can be stopped in a variety of ways. The extracellular ligand can be degraded by enzymes in the extracellular space. An example is the breakdown of the neurotransmitter acetylcholine. Other chemical messengers, particularly neurotransmitters, can be removed from the extracellular fluid through transport into neighboring cells. A widely used class of antidepressant drugs called selective serotonin reuptake inhibitors, or SSRIs, extends the active life of the neurotransmitter serotonin by slowing its removal from the extracellular fluid.

Once a ligand is bound to its receptor, activity can also be terminated by endocytosis of the receptor-ligand complex. After the vesicle is in the cell, the ligand is removed, and the receptors can be returned to the membrane by exocytosis.

Many Diseases and Drugs Target the Proteins of Signal Transduction

As researchers learn more about cell signaling, they are realizing how many diseases are linked to problems with signal pathways. Diseases can be caused by alterations in receptors or by problems with G proteins or second messenger pathways.
change occurs in a cell or tissue, and the chemical paracrine or autocrine signals released there are the entire pathway. But in more complicated reflex control pathways, information must be transmitted throughout the body using chemical signals or a combination of electrical and chemical signaling. In the last section of this chapter we look at some of the patterns of reflex control pathways you will encounter as you study the various organ systems of the body.

### Cannon’s Postulates Describe Regulated Variables and Control Systems

Walter Cannon, the father of American physiology, described a number of properties of homeostatic control systems in the 1920s based on his observations of the body in health and disease states.*

Cannon’s four postulates are:

1. **The nervous system has a role in preserving the “fitness” of the internal environment.** *Fitness* in this instance means conditions that are compatible with normal function. The nervous system coordinates and integrates blood volume, blood osmolarity, blood pressure, and body temperature, among other regulated variables. (In physiology, a regulated variable is also known as a parameter [para-, beside + meter, measure]).

2. **Some systems of the body are under tonic control (tonos, tone).** To quote Cannon, “An agent may exist which has a moderate activity which can be varied up and down.” Tonic control is like the volume control on a radio. The radio is always on, but by turning a single knob, you can make the sound level louder or softer.

   A physiological example of a tonically controlled system is the neural regulation of diameter in certain blood vessels, in which increased input from the nervous system decreases diameter, and decreased input from the nervous system increases diameter (Fig. 6.15a). **Tonic control** is one of the more difficult concepts in physiology because we have a tendency to think of responses stopping and starting when a controller turns off or on rather than as a response that is always on but can increase or decrease.

3. **Some systems of the body are under antagonistic control.** Cannon wrote, “When a factor is known which can shift a homeostatic state in one direction, it is reasonable to look for a factor or factors having an opposing effect.” Systems that are not under tonic control are usually under antagonistic control, either by hormones or the nervous system.

   In pathways controlled by the nervous system, the sympathetic and parasympathetic divisions often have opposing effects. For example, chemical signals from a

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### Homeostatic Reflex Pathways

The cellular signal mechanisms just described are often just one small component of the body’s signaling systems that maintain homeostasis. For local control mechanisms, a relatively isolated...
Fig. 6.15 Tonic and antagonist control of regulated variables

(a) Tonic control regulates physiological parameters in an up-down fashion. The signal is always present but changes in intensity.

Electrical signals from neuron

Moderate signal rate results in a blood vessel of intermediate diameter.

(b) Antagonistic control uses different signals to send a parameter in opposite directions. In this example, antagonistic neurons control heart rate: some speed it up, while others slow it down.

Sympathetic neuron

Parasympathetic neuron

Stimulation by sympathetic nerves increases heart rate.

Stimulation by parasympathetic nerves decreases heart rate.

What heart rates (in beats/min) are shown on the two ECG tracings?

FIGURE QUESTION

Fig. 6.15 Tonic and antagonist control of regulated variables
**Long-Distance Pathways Maintain Homeostasis**

Long-distance reflex pathways are traditionally considered to involve two control systems: the nervous system and the endocrine system. However, cytokines are now known to be involved in some long-distance pathways. During stress and systemic inflammatory responses, cytokines work together with the nervous and endocrine systems to integrate information from all over the body into coordinated responses.

All reflex pathway **response loops** have three primary components: an input signal, integration of the signal, and an output signal. These three components can be broken down into the following sequence of seven steps to form a pattern that is found with slight variations in all reflex control pathways (Fig. 6.16):

1. **Stimulus** → sensor or receptor → input signal → integrating center → output signal → target → response

**RUNNING PROBLEM**

“Why is an elevated blood glucose concentration bad?” Marvin asks. “The elevated blood glucose itself is not bad,” says the nurse practitioner, “but when it is high after an overnight fast, it suggests that there is something wrong with the way your body is regulating its glucose metabolism.” When a normal person absorbs a meal containing carbohydrates, blood glucose levels increase and stimulate insulin release. When cells have taken up the glucose from the meal and blood glucose levels fall, secretion of another pancreatic hormone, glucagon, increases. Glucagon raises blood glucose and helps keep the level within the homeostatic range.

Q4: The homeostatic regulation of blood glucose levels by the hormones insulin and glucagon is an example of which of Cannon’s postulates?

sympathetic neuron increase heart rate, but chemical signals from a parasympathetic neuron decrease it (Fig. 6.15b).

When chemical signals have opposing effects, they are said to be antagonistic to each other. For example, insulin and glucagon are antagonistic hormones. Insulin decreases the glucose concentration in the blood and glucagon increases it.

4. **One chemical signal can have different effects in different tissues.** Cannon observed correctly that “homeostatic agents antagonistic in one region of the body may be cooperative in another region.” However, it was not until scientists learned about cell receptors that the basis for the seemingly contradictory actions of some hormones or nerves became clear. As you learned in the first part of this chapter, a single chemical signal can have different effects depending on the receptor and signal pathway of the target cell. For example, epinephrine constricts or dilates blood vessels, depending on whether the vessel has $\alpha$- or $\beta_2$-adrenergic receptors (Fig. 6.13).

The remarkable accuracy of Cannon’s postulates, now confirmed with cellular and molecular data, is a tribute to the observational skills of scientists in the nineteenth and early twentieth centuries.

**Concept Check**

18. What is the difference between tonic control and antagonistic control?

19. How can one chemical signal have opposite effects in two different tissues?
A **stimulus** is the disturbance or change that sets the pathway in motion. The stimulus may be a change in temperature, oxygen content, blood pressure, or any one of a myriad of other regulated variables.

A **sensor** or sensory receptor continuously monitors its environment for a particular variable. When activated by a change, the sensor sends an **input (afferent) signal** to the integrating center for the reflex. The **integrating center** compares the input signal with the **setpoint**, or desired value of the variable.

If the variable has moved out of the acceptable range, the integrating center initiates an output signal. The **output (efferent) signal** is an electrical and/or chemical signal that travels to the target.

The **target**, or **effector** (effectus, the carrying out of a task) is the cell or tissue that carries out the appropriate **response** to bring the variable back within normal limits.

Let’s look in more detail at these components of a reflex.

**Sensors** In the first step in a physiological response loop, a stimulus activates a sensor or receptor. Notice that this is a new and different application of the word **receptor**. Like many other terms in physiology, receptor can have different meanings (Fig. 6.17). The sensory receptors of a neural reflex are not protein receptors that bind to signal molecules, like those involved in signal transduction. Rather, neural receptors are specialized cells, parts of cells, or complex multicellular receptors (such as the eye) that respond to changes in their environment.

There are many sensory receptors in the body, each located in the best position to monitor the variable it detects. The eyes, ears, and nose are receptors that sense light, sound and motion, and odors, respectively. Your skin is covered with less complex receptors that sense touch, temperature, vibration, and pain. Other sensors are internal: receptors in the joints of the skeleton that send information to the brain about body position, or blood pressure and oxygen receptors in blood vessels that monitor conditions in the circulatory system. The sensory receptors involved in neural reflexes are divided into central receptors and peripheral receptors. **Central receptors** are located in the brain or are closely linked to the brain. An example is the brain’s chemoreceptor for carbon dioxide. **Peripheral receptors** reside elsewhere in the body and include the skin receptors and internal receptors just described.

![Fig. 6.17 Multiple meanings of the word receptor](image_url)

The word receptor may mean a protein that binds to a ligand. Receptor can also mean a specialized cell or structure for transduction of stimuli into electrical signals (a sensory receptor or sensor). Sensory receptors are classified as central or peripheral, depending on whether they are found in the brain or outside the brain.
All sensors have a **threshold**, the minimum stimulus needed to set the reflex response in motion. If a stimulus is below the threshold, no response loop is initiated.

You can demonstrate threshold in a sensory receptor easily by touching the back of your hand with a sharp, pointed object, such as a pin. If you touch the point to your skin lightly enough, you can see the contact between the point and your skin even though you do not feel anything. In this case, the stimulus (pressure from the point of the pin) is below threshold, and the pressure receptors of the skin are not responding. As you press harder, the stimulus reaches threshold, and the receptors respond by sending a signal to the brain, causing you to feel the pin.

Endocrine reflexes that are not associated with the nervous system do not use sensory receptors to initiate their pathways. Instead, endocrine cells act both as sensor and integrating center for the reflex. For example, a pancreatic beta cell sensing and responding directly to changes in blood glucose concentrations is an endocrine cell that is both sensor and integrating center.

**Input Signal** The input signal in a reflex varies depending on the type of reflex. In a neural pathway, such as the pin touch above, the input signal is electrical and chemical information transmitted by a sensory neuron. In an endocrine reflex, there is no input pathway because the stimulus acts directly on the endocrine cell, which serves as both sensor and integrating center.

**Integrating Center** The integrating center in a reflex pathway is the cell that receives information about the regulated variable and can initiate an appropriate response. In endocrine reflexes, the integrating center is the endocrine cell. In neural reflexes, the integrating center usually lies within the central nervous system (CNS), which is composed of the brain and the spinal cord.

If information is coming from a single stimulus, it is a relatively simple task for an integrating center to compare that information with the setpoint and initiate a response if appropriate. Integrating centers really “earn their pay,” however, when two or more conflicting signals come in from different sources. The center must evaluate each signal on the basis of its strength and importance and must come up with an appropriate response that integrates information from all contributing receptors. This is similar to the kind of decision-making you must do when on one evening your parents want to take you to dinner, your friends are having a party, there is a television program you want to watch, and you have a major physiology test in three days. It is up to you to rank those items in order of importance and decide what you will do.

**Output Signals** Output signal pathways are relatively simple. In the nervous system, the output signal is always the electrical and chemical signals transmitted by an efferent neuron. Because all electrical signals traveling through the nervous system are identical, the distinguishing characteristic of the signal is the anatomical pathway of the neuron—the route through which the neuron delivers its signal. For example, the vagus nerve carries neural signals to the heart, and the phrenic nerve carries neural signals to the diaphragm. Output pathways in the nervous system are given the anatomical name of the nerve that carries the signal. For example, we speak of the vagal control of heart rate (vagal is the adjective for vagus).

In the endocrine system, the anatomical routing of the output signal is always the same—all hormones travel in the blood to their target. Hormonal output pathways are distinguished by the chemical nature of the signal and are therefore named for the hormone that carries the message. For example, the output signal for a reflex integrated through the endocrine pancreas will be either the hormone insulin or the hormone glucagon, depending on the stimulus and the appropriate response.

**Targets** The targets of reflex control pathways are the cells or tissues that carry out the response. The targets of neural pathways may be any type of muscle, endocrine or exocrine glands, or adipose tissue. Targets of an endocrine pathway are the cells that have the proper receptor for the hormone.

**Responses** There are two levels of response for any reflex control pathway. One is the very specific ***cellular response*** that takes place in the target cell. The more general ***systemic response*** describes what those specific cellular events mean to the organism as a whole. For example, when the hormone epinephrine combines with β-adrenergic receptors on the walls of certain blood vessels, the cellular response is relaxation of the smooth muscle. The systemic response to relaxation of the blood vessel wall is increased blood flow through the vessel.
Control Systems Vary in Their Speed and Specificity

Physiological reflex control pathways are mediated by the nervous system, the endocrine system, or a combination of the two (Fig. 6.18). A reflex mediated solely by the nervous system or solely by the endocrine system is relatively simple, but combination reflex pathways can be quite complex. In the most complex pathways, signals pass through three different integrating centers before finally reaching the target tissue. With so much overlap between pathways controlled by the nervous and endocrine systems, it makes sense to consider these systems as parts of a continuum rather than as two discrete systems.

Why does the body need different types of control systems? To answer that question, let us compare endocrine control with neural control to see what the differences are. Five major differences are summarized in Table 6.2 and discussed next.

Specificity Neural control is very specific because each neuron has a specific target cell or cells to which it sends its message. Anatomically, we can isolate a neuron and trace it from its origin to where it terminates on its target.

Endocrine control is more general because the chemical messenger is released into the blood and can reach virtually every cell in the body. As you learned in the first half of this chapter, the body’s response to a specific hormone depends on which cells have receptors for that hormone and which receptor type they have. Multiple tissues in the body can respond to a hormone simultaneously.

Nature of the Signal The nervous system uses both electrical and chemical signals to send information throughout the body. Electrical signals travel long distances through neurons, releasing chemical signals (neurotransmitters) that diffuse across the small gap between the neuron and its target. In a limited number of instances, electrical signals pass directly from cell to cell through gap junctions.

The endocrine system uses only chemical signals: hormones secreted into the blood by endocrine glands or cells. Neurohormone pathways represent a hybrid of the neural and endocrine reflexes. In a neurohormone pathway, a neuron creates an electrical signal, but the chemical released by the neuron is a neurohormone that goes into the blood for general distribution.

Speed Neural reflexes are much faster than endocrine reflexes. The electrical signals of the nervous system cover great distances very rapidly, with speeds of up to 120 m/sec. Neurotransmitters also create very rapid responses, on the order of milliseconds.

Hormones are much slower than neural reflexes. Their distribution through the circulatory system and diffusion from capillary to receptors take considerably longer than signals through neurons. In addition, hormones have a slower onset of action. In target tissues, the response may take minutes to hours before it can be measured.

Why do we need the speedy reflexes of the nervous system? Consider this example. A mouse ventures out of his hole and sees a cat ready to pounce on him and eat him. A signal must go from the mouse’s eyes and brain down to his feet, telling him to run back into the hole. If his brain and feet
were only 5 micrometers (5 μm = 1/200 millimeter) apart, it would take a chemical signal 20 milliseconds (msec) to diffuse across the space and the mouse could escape. If the brain and feet were 50 μm (1/20 millimeter) apart, diffusion would take 2 seconds and the mouse might get caught. But because the head and tail of a mouse are centimeters apart, it would take a chemical signal three weeks to diffuse from the mouse’s head to his feet. Poor mouse!

Even if the distribution of the chemical signal were accelerated by help from the circulatory system, the chemical message would still take 10 seconds to get to the feet, and the mouse would become cat food. The moral of this tale is that reflexes requiring a speedy response are mediated by the nervous system because they are so much more rapid.

**Duration of Action**  Neural control is of shorter duration than endocrine control. The neurotransmitter released by a neuron combines with a receptor on the target cell and initiates a response. The response is usually very brief, however, because the neurotransmitter is rapidly removed from the vicinity of the receptor by various mechanisms. To get a sustained response, multiple repeating signals must be sent through the neuron.

Endocrine reflexes are slower to start, but they last longer. Most of the ongoing, long-term functions of the body, such as metabolism and reproduction, fall under the control of the endocrine system.

**Coding for Stimulus Intensity**  As a stimulus increases in intensity, control systems must have a mechanism for conveying this information to the integrating center. The signal strength from any one neuron is constant in magnitude and therefore cannot reflect stimulus intensity. Instead, the frequency of signaling through the afferent neuron increases. In the endocrine system, stimulus intensity is reflected by the amount of hormone released: the stronger the stimulus, the more hormone is released.

**Complex Reflex Control Pathways Have Several Integrating Centers**  
- Figure 6.19 summarizes variations in the neural, neuroendocrine, and endocrine reflex control pathways.
## Simple and Complex Reflex Pathways

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<thead>
<tr>
<th>Simple Neural Reflex</th>
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<th>Complex Neuroendocrine Reflexes</th>
<th>Simple Endocrine Reflex</th>
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<td>Sensor</td>
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<td>Sensory neuron</td>
<td>CNS</td>
<td>Neurotransmitter</td>
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<td>Efferent neuron</td>
<td>CNS</td>
<td>Neurohormone</td>
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<tr>
<td>Neurotransmitter</td>
<td>CNS</td>
<td>Neurohormone</td>
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<td>Target cell</td>
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<td>Hormone</td>
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<td>Response</td>
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<td>Hormone</td>
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<td>Endocrine cells</td>
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<td>Hormone</td>
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<td>Hormone #2</td>
<td>CNS</td>
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<td></td>
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<td>Response</td>
<td>CNS</td>
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<tr>
<td>Example: The knee jerk reflex</td>
<td>Example: Release of breast milk in response to suckling</td>
<td>Example: Insulin secretion in response to a signal from the brain</td>
<td>Example: Insulin release when blood glucose increases</td>
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<td>Response</td>
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<td>Response</td>
<td>CNS</td>
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</tbody>
</table>

**KEY**
- **S** Stimulus
- **R** Sensor
- Sensory neuron (input pathway)
- CNS integrating center
- Endocrine integrating center

**Output Pathways**
- Efferent neuron
- Neurotransmitter
- Neurohormone
- Classic hormone
- Target cell (effector)

**Example:**
- This pattern occurs with hormones released by the anterior pituitary.
In a simple endocrine reflex pathway (Fig. 6.19), the endocrine cell monitors the regulated variable and acts as both sensor and integrating center; there is no input pathway. The output pathway is the hormone, and the target is any cell having the appropriate receptor protein.

An example of a simple endocrine reflex is secretion of the hormone insulin in response to changes in blood glucose level. The endocrine cells that secrete insulin monitor blood glucose concentrations by using ATP production in the cell as an indicator. When blood glucose increases, intracellular ATP production exceeds the threshold level, and the endocrine cells respond by secreting insulin into the blood. Any target cell in the body that has insulin receptors responds to the hormone and initiates processes that take glucose out of the blood. The removal of the stimulus acts in a negative feedback manner, and the response loop shuts off when blood glucose levels fall below a certain concentration.

In a simple neural reflex, all the steps of the pathway are present, from receptor to target (Fig. 6.19). The neural reflex is represented in its simplest form by the knee jerk (or patellar tendon) reflex. A blow to the knee (the stimulus) activates a stretch receptor. An electrical and chemical signal travels through an afferent neuron to the spinal cord (the integrating center). If the blow is strong enough (exceeds threshold), a signal travels from the spinal cord through an efferent neuron to the muscles of the thigh (the target or effector). In response, the muscles contract, causing the lower leg to kick outward (the knee jerk).

The neurohormone reflex, shown in Figure 6.19, is identical to the neural reflex except that the neurohormone released by the neuron travels in the blood to its target, just like a hormone. A simple neurohormone reflex is the release of breast milk in response to a baby’s suckling. The baby’s mouth on the nipple stimulates sensory signals that travel through sensory neurons to the brain (integrating center). An electrical signal in the efferent neuron triggers the release of the neurohormone oxytocin from the brain into the circulation. Oxytocin is carried to the breast, where it causes contraction of smooth muscles in the breast (the target), resulting in the ejection of milk.

In complex pathways, there may be more than one integrating center. Figure 6.19 shows three examples of complex neuroendocrine pathways. The simplest of these, Figure 6.19, combines a neural reflex with a classic endocrine reflex. An example of this pattern can be found in the control of insulin release. The pancreatic beta cells monitor blood glucose concentrations directly (Fig. 6.19), but they are also controlled by the nervous system. During a meal, the presence of food in the stomach stretches the wall of the digestive tract and sends input signals to the brain. The brain in turn sends excitatory output signals to the beta cells, telling them to release insulin. These signals take place even before the food has been absorbed and blood glucose levels have gone up (a feedforward reflex). This pathway therefore has two integrating centers (the brain and the beta cells).

Another complex reflex (Fig. 6.19) uses a neurohormone to control the release of a classic hormone. The secretion of growth hormone is an example of this pathway. The most complex neuroendocrine pathways, shown as Figure 6.19, include a neurohormone and two classic hormones. This pattern is typical of some hormones released by the anterior pituitary, an endocrine gland located just below the brain.

In describing complex neuroendocrine reflex pathways, we identify only one receptor and input pathway, as indicated in Figure 6.19. In the three complex pathways shown, the brain is the first integrating center and the neurohormone is the first output pathway. In Figure 6.19, the endocrine target (E₂) of the neurohormone is the second integrating center, and its hormone is the second output pathway. The second endocrine gland in the pathway (E₃) is the third integrating center, and its hormone is the third output pathway. The target of the last signal in the sequence is the effector.

Table 6.3 compares the various steps in neural, neuroendocrine, and endocrine reflexes.
**Comparison of Neural, Neuroendocrine, and Endocrine Reflexes**

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Neural</th>
<th>Neuroendocrine</th>
<th>Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input signal</td>
<td>Sensory neuron</td>
<td>Sensory neuron</td>
<td>None</td>
</tr>
<tr>
<td>Integrating center</td>
<td>Brain or spinal cord</td>
<td>Brain or spinal cord</td>
<td>Endocrine cell</td>
</tr>
<tr>
<td>Output signal</td>
<td>Efferent neuron (electrical signal and neurotransmitter)</td>
<td>Efferent neuron (electrical signal and neurohormone)</td>
<td>Hormone</td>
</tr>
<tr>
<td>Target(s)</td>
<td>Muscles and glands, some adipose tissue</td>
<td>Most cells of the body</td>
<td>Most cells of the body</td>
</tr>
<tr>
<td>Response</td>
<td>Contraction and secretion primarily; may have some metabolic effects</td>
<td>Change in enzymatic reactions, membrane transport, or cell proteins</td>
<td>Change in enzymatic reactions, membrane transport, or cell proteins</td>
</tr>
</tbody>
</table>

**RUNNING PROBLEM CONCLUSION**

**Diabetes Mellitus**

Marvin underwent further tests and was diagnosed with early type 2 diabetes. With careful attention to his diet and with a regular exercise program, he has managed to keep his blood glucose levels under control. Diabetes is a growing epidemic in the United States, with more than 25 million diabetics in the United States in 2011 (about 8% of the population). Even scarier is the estimate that another 79 million people are considered “prediabetic”—at significant risk of becoming diabetic. You will learn more about diabetes as you work through the chapters in this course. To learn more about diabetes now, see the American Diabetes Association web site (www.diabetes.org) or the Centers for Disease Control and Prevention (www.cdc.gov/diabetes).

In this running problem, you learned about glucose homeostasis and how it is maintained by insulin and glucagon. The disease diabetes mellitus is an indication that glucose homeostasis has been disrupted. Check your understanding of this running problem by comparing your answers to the information in the summary table.

<table>
<thead>
<tr>
<th>Question</th>
<th>Facts</th>
<th>Integration and Analysis</th>
</tr>
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<tbody>
<tr>
<td>1. In which type of diabetes is the signal pathway for insulin more likely to be defective?</td>
<td>Insulin is a peptide hormone that uses membrane receptors linked to second messengers to transmit its signal to cells. People with type 1 diabetes lack insulin; people with type 2 diabetes have normal-to-elevated insulin levels.</td>
<td>Normal or high insulin levels suggest that the problem is not with amount of insulin but with the action of the insulin at the cell. The problem in type 2 diabetes could be a defective signal transduction mechanism.</td>
</tr>
<tr>
<td>2. Insulin is a protein hormone. Would you expect to find its receptor on the cell surface or in the cytoplasm of the target cells?</td>
<td>Lipophilic signal molecules have intracellular receptors. Lipophobic molecules have cell membrane receptors.</td>
<td>Proteins are lipophobic so protein hormones have cell surface receptors.</td>
</tr>
</tbody>
</table>
3. In which form of diabetes are the insulin receptors more likely to be up-regulated?

**Facts:** Up-regulation of receptors usually occurs if a signal molecule is present in unusually low concentrations. In type 1 diabetes, insulin is not secreted by the pancreas.

**Integration and Analysis:** In type 1 diabetes, insulin levels are low. Therefore, type 1 is more likely to cause up-regulation of the insulin receptors.

4. The homeostatic regulation of blood glucose levels by the hormones insulin and glucagon is an example of which of Cannon’s postulates?

**Facts:** Cannon’s postulates describe the role of the nervous system in maintaining homeostasis, and the concepts of tonic activity, antagonistic control, and different effects of signals in different tissues.

**Integration and Analysis:** Insulin decreases blood glucose levels, and glucagon increases them. Therefore, the two hormones are an example of an antagonistic control.

5. In the insulin pathway that regulates blood glucose levels, what are the stimulus, the sensor, the integrating center, the output signal, the target(s), and the response(s)?

**Facts:** See the steps of reflex pathways.

**Integration and Analysis:** The stimulus for insulin release is an increase in blood glucose levels. In negative feedback, the response offsets the stimulus. In positive feedback, the response enhances the stimulus.

6. Why can’t glucose always diffuse into cells when the blood glucose concentration is higher than the intracellular glucose concentration?

**Facts:** Glucose is lipophobic. Simple diffusion goes across the phospholipid bilayer. Facilitated diffusion uses protein carriers.

**Integration and Analysis:** Because glucose is lipophobic, it cannot cross the membrane by simple diffusion. It must go by facilitated diffusion. If a cell lacks the necessary carriers, facilitated diffusion cannot take place.

7. What do you think happens to the rate of insulin secretion when blood glucose levels fall? What kind of feedback loop is operating?

**Facts:** The stimulus for insulin release is an increase in blood glucose levels. In negative feedback, the response offsets the stimulus. In positive feedback, the response enhances the stimulus.

**Integration and Analysis:** An increase in blood glucose concentration stimulates insulin release; therefore, a decrease in blood glucose should decrease insulin release. In this example, the response (lower blood glucose) offsets the stimulus (increased blood glucose), so a negative feedback loop is operating.

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**Chapter Summary**

Two of the major themes in physiology stand out in this chapter: the control of homeostasis and communication. The sensors, integrating centers, and targets of physiological control systems are described in the context of reflex control pathways, which vary from simple to complex. Functional control systems require efficient communication that uses various combinations of chemical and electrical signals. Those signals that cannot cross cell membranes must use membrane receptor proteins and signal transduction to transfer their information into the cell. The interaction of signal molecules with protein receptors illustrates another fundamental theme of physiology, molecular interactions.
Cell-to-Cell Communication

1. There are two basic types of physiological signals: chemical and electrical. Chemical signals are the basis for most communication within the body.
2. There are four methods of cell-to-cell communication: (1) direct cytoplasmic transfer through gap junctions, (2) contact-dependent signaling, (3) local chemical communication, and (4) long-distance communication. (Fig. 6.1)
3. Gap junctions are protein channels that connect two adjacent cells. When they are open, chemical and electrical signals pass directly from one cell to the next.
4. Contact-dependent signals require direct contact between surface molecules of two cells.
5. Local communication uses paracrine signals, chemicals that act on cells close to the cell that secreted the paracrine. A chemical that acts on the cell that secreted it is called an autocrine signal. The activity of paracrine and autocrine signal molecules is limited by diffusion distance.
6. Long-distance communication uses neurocrine molecules and electrical signals in the nervous system, and hormones in the endocrine system. Only cells that possess receptors for a hormone will be target cells.
7. Cytokines are regulatory peptides that control cell development, differentiation, and the immune response. They serve as both local and long-distance signals.

Signal Pathways

8. Chemical signals bind to receptors and change intracellular signal molecules that direct the response.
9. Lipophilic signal molecules enter the cell and combine with cytoplasmic or nuclear receptors. Lipophilic signal molecules and some lipophilic molecules combine with membrane receptors. (Fig. 6.3)
10. Signal transduction pathways use membrane receptor proteins and intracellular second messenger molecules to translate signal information into an intracellular response. (Fig. 6.4)
11. Some signal transduction pathways activate protein kinases. Others activate amplifier enzymes that create second messenger molecules. (Fig. 6.5)
12. Signal pathways create intracellular cascades that amplify the original signal. (Fig. 6.6)
13. Receptor-enzymes activate protein kinases, such as tyrosine kinase (Fig. 6.7), or the amplifier enzyme guanylyl cyclase, which produces the second messenger cGMP.
14. G proteins linked to amplifier enzymes are the most prevalent signal transduction system. G protein–coupled receptors also alter ion channels. (Fig. 6.8)
15. The G protein–coupled adenylyl cyclase-cAMP-protein kinase A pathway is the most common pathway for protein and peptide hormones. (Fig. 6.8a)
16. In the G protein–coupled phospholipase C pathway, the amplifier enzyme phospholipase C creates two second messengers: IP$_3$ and diacylglycerol (DAG). IP$_3$ causes Ca$^{2+}$ release from intracellular stores. Diacylglycerol activates protein kinase C. (Fig. 6.8b)
17. Integrin receptors link the extracellular matrix to the cytoskeleton. (Fig. 6.3c)
18. Ligand-gated ion channels open or close to create electrical signals. (Fig. 6.9)

Novel Signal Molecules

19. Calcium is an important signal molecule that binds to calmodulin to alter enzyme activity. It also binds to other cell proteins to alter movement and initiate exocytosis. (Fig. 6.11)
20. Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H$_2$S) are short-lived gaseous signal molecules. NO activates guanylyl cyclase directly.
21. The arachidonic acid cascade creates lipid signal molecules, such as leukotrienes, prostaglandins, and thromboxanes. (Fig. 6.12)

Modulation of Signal Pathways

22. The response of a cell to a signal molecule is determined by the cell’s receptor for the signal.
23. Receptors come in related forms called isoforms. One ligand may have different effects when binding to different isoforms. (Fig. 6.13)
24. A receptor may have multiple ligands. Agonists mimic the action of a signal molecule. Antagonists block the signal pathway. (Fig. 6.14)
25. Receptor proteins exhibit specificity, competition, and saturation.
26. Cells exposed to abnormally high concentrations of a signal for a sustained period of time attempt to bring their response back to normal through down-regulation or by desensitization. In down-regulation, the cell decreases the number of receptors. In desensitization, the cell decreases the binding affinity of the receptors. Up-regulation is the opposite of down-regulation and involves increasing the number of receptors for a signal.
27. Cells have mechanisms for terminating signal pathways, such as removing the signal molecule or breaking down the receptor–ligand complex.
28. Many diseases have been linked to defects in various aspects of signal pathways, such as missing or defective receptors. (Tbl. 6.1)

Homeostatic Reflex Pathways

29. Walter Cannon first stated four basic postulates of homeostasis: (1) The nervous system plays an important role in maintaining homeostasis. (2) Some parameters are under tonic control, which allows the parameter to be increased or decreased by a single signal (Fig. 6.14a). (3) Other parameters are under antagonistic control, in which one hormone or neuron increases the parameter while another decreases it (Fig. 6.14b). (4) Chemical signals can have different effects in different tissues of the body, depending on the type of receptor present at the target cell. (Fig. 6.15)
30. In reflex control pathways, the decision to respond to a change is made by an integrating center. A chemical or electrical signal to the target cell or tissue then initiates the response. Long-distance reflex pathways involve the nervous and endocrine systems and cytokines.
31. Neural control is faster and more specific than endocrine control but is usually of shorter duration. Endocrine control is less specific and slower to start but is longer lasting and is usually amplified. (Tbl. 6.2)
32. Many reflex pathways are complex combinations of neural and endocrine control mechanisms. (Fig. 6.19)
Questions

Level One  Reviewing Facts and Terms
1. What are the two routes for long-distance signal delivery in the body?
2. Which two body systems maintain homeostasis by monitoring and responding to changes in the environment?
3. What are the two main classes of physiological signals that the body uses to send messages? Of these two types, which is available to all cells?
4. In a signal pathway, the signal ligand, also called the first messenger, binds to a(n)__________, which activates and changes intracellular__________.
5. The three main amplifier enzymes are (a)__________, which forms cAMP; (b)__________, which forms cGMP; and (c)__________, which converts a phospholipid from the cell's membrane into two different second messenger molecules.
6. An enzyme known as protein kinase adds the functional group _________ to its substrate, by transferring it from a(n)__________molecule.
7. Distinguish between central and peripheral receptors.
8. Receptors for signal pathways may be found in the__________, ________, or ________ of the cell.
9. Down-regulation results in a(n)__________ (increased or decreased?) number of receptors in response to a prolonged signal.
10. List two ways a cell may decrease its response to a signal.
11. In a negative feedback loop, the response moves the system in the__________ (same/opposite) direction as the stimulus moves it.

Level Two  Reviewing Concepts
12. Explain the relationships of the terms in each of the following sets. Give a physiological example or location if applicable.
   (a) gap junctions, connexins, connexon
   (b) autocrine, paracrine, cytokine, neurocrine, hormone
   (c) agonist, antagonist
   (d) transduction, amplification, cascade
13. List and compare the four classes of membrane receptors for signal pathways. Give an example of each.
14. Who was Walter Cannon? Restate his four postulates in your own words.
15. Briefly define the following terms and give an anatomical example when applicable: input signal, integrating center, output signal, response, sensor, stimulus, target.
16. Compare and contrast the advantages and disadvantages of neural versus endocrine control mechanisms.

17. Would the following reflexes have positive or negative feedback?
   (a) glucagon secretion in response to declining blood glucose
   (b) increasing milk release and secretion in response to baby's suckling
   (c) urgency in emptying one's urinary bladder
   (d) sweating in response to rising body temperature
18. Identify the target tissue or organ for each example in question 17.
19. Now identify the integrating center for examples (a), (c), and (d) in question 17.

Level Three  Problem Solving
20. In each of the following situations, identify the components of the reflex.
   (a) You are sitting quietly at your desk, studying, when you become aware of the bitterly cold winds blowing outside at 30 mph, and you begin to feel a little chilly. You start to turn up the thermostat, remember last month's heating bill, and reach for an afghan to pull around you instead. Pretty soon you are toasty warm again.
   (b) While you are strolling through the shopping district, the aroma of cinnamon sticky buns reaches you. You inhale appreciatively, but remind yourself that you're not hungry, because you had lunch just an hour ago. You go about your business, but 20 minutes later you're back at the bakery, sticky bun in hand, ravenously devouring its sweetness, saliva moistening your mouth.
21. A researcher is studying the smooth muscle of the respiratory system airways. When she exposes the airways to the neurotransmitter acetylcholine, the smooth muscle contracts. When she exposes the airways to the neurohormone epinephrine, the airways relax.
   (a) The phenomenon just described is an example of ________ control.
   (b) What distinguishes a neurotransmitter from a neurohormone?
   (c) Which chemical messenger is secreted in higher concentrations: acetylcholine or epinephrine? Defend your answer.

Level Four  Quantitative Problems
22. In a signal cascade for rhodopsin, a photoreceptor molecule, one rhodopsin activates 1000 molecules of transducin, the next molecule in the signal cascade. Each transducin activates one phosphodiesterase, and each phosphodiesterase converts 4000 cGMP to GMP.
   (a) What is the name of the phenomenon described in this paragraph?
   (b) Activation of one rhodopsin will result in the production of how many GMP molecules?
Communication, Integration, and Homeostasis

Answers

Answers to Concept Check Questions

1. All methods listed are chemical signals except for (c) gap junctions, which transfer both chemical and electrical signals. Neurohormones (e) and neurotransmitters (f) are associated with electrical signaling in neurons but are themselves chemicals.

2. Cytokines, hormones, and neurohormones travel through the blood. Cytokines, neurohormones, and neurotransmitters are released by neurons.

3. The signal to pounce could not have been a paracrine signal because the eyes are too far away from the legs and because the response was too rapid for it to have taken place by diffusion.

4. The components of signal pathways are signal molecule, receptor, intracellular signal molecule(s), and target proteins.

5. The cellular locations of receptors are cell membrane, cytosol, and nucleus.

6. The steps of signal transduction are (1) signal molecule binds to receptor that (2) activates a protein that (3) creates second messengers that (4) create a response.

7. Amplification turns one signal molecule (first messenger) into multiple second messenger molecules.

8. Steroids are lipophilic, so they can enter cells and bind to intracellular receptors.

9. Receptors are either ligand-gated ion channels, receptor-enzymes, G protein-coupled receptors, or integrins.

10. First messengers are extracellular; second messengers are intracellular.

11. (a) ligand, receptor, second messenger, cell response; (b) amplifier, enzyme, second messenger, protein kinase, phosphorylated protein, cell response

12. (a) Cl\(^-\) channel opens: cell hyperpolarizes; (b) K\(^+\) channel opens: cell hyperpolarizes; (c) Na\(^+\) channel opens: cell depolarizes.

13. The cell must use active transport to move Ca\(^{2+}\) against its concentration gradient.

14. A drug that blocks leukotriene action could act at the target cell receptor or at any step downstream. A drug that blocks leukotriene synthesis might inhibit lipoxynase.

15. Receptors, enzymes, and transporters are all proteins.

16. Insulin could be using one receptor isoform with different second messenger systems in different cells or could be binding to different receptor isoforms.

17. Choices (a) and (d) could decrease binding affinity. Changing receptor number would not affect binding affinity.

18. Tonic control usually involves one control system, but antagonistic control uses two.

19. A signal can have opposite effects by using different receptors or different signal pathways.

20. In local control, the stimulus, integration of the signal, and response all take place in or very close to the target cell. With reflex control, integration of the input signal and initiation of a response may take place far from the location where the change occurred. In addition, the reflex response is often systemic and not localized.

21. Stimulus, sensor or sensory receptor, input signal (afferent pathway), integrating center, output signal (efferent pathway), target or effector, response (tissue and systemic)

22. (a) The “neural system integrating center” is the brain and spinal cord. (b) “Receptor” represents the sense organs. (c) The dashed line indicating negative feedback runs from “Response” back to “Internal or external change.”

23. blow to knee = internal or external change; leg muscles = targets; neuron to leg muscles = efferent neuron; sensory neuron = input signal; brain and spinal cord = CNS integrating center; stretch receptor = sensor or receptor; muscle contraction = response.

24. food in stomach = stimulus; brain and spinal cord = CNS integrating center; endocrine cells of pancreas = E (integrating center); stretch receptors = receptor; efferent neuron to pancreas = efferent neuron; insulin = classic hormone; adipose cell = target cell; sensory neuron = afferent neuron. Blood is the anatomical route that hormones use to reach their target but is not part of the reflex pathway.

Answers to Figure Questions

Figure 6.8: A (inactive and active) = adenyl cyclase; inactive B = ATP; active B = cAMP; C (inactive and active) = protein kinase A; product = phosphorylated protein.

Figure 6.15: 180 beats/min for the top ECG and 60 beats/min for the bottom ECG.
Answers to Review Questions

Level One  Reviewing Facts and Terms
1. Neurons and blood
2. Nervous and endocrine systems
3. Chemical (available to all cells) and electrical
4. receptor, targets (effectors) or proteins
5. (a) adenyly cyclase, (b) guanylyl cyclase, (c) phospholipase C
6. phosphate, ATP
7. Central: located within the central nervous system. Peripheral: found outside the CNS
8. nucleus, cytosol, cell membrane
9. decreased
10. It may down-regulate receptor number or decrease receptor affinity for the substrate.
11. opposite

Level Two  Reviewing Concepts
12. (a) Gap junctions connect two cells using protein channels called connexons, made from connexin subunits. (b) All are chemicals secreted into the ECF. Paracrines act on nearby cells; autocrines act on the cell that secretes them. Cytokines are peptide autocrine and paracrine signals or hormones. Neurocrines are chemicals secreted by neurons. (c) Agonists have the same action as another molecule; antagonists act to oppose the action of another molecule. (d) Transduction: a signal molecule transfers information from ECF to the cytoplasm. Cascade: a series of steps. Amplification: one signal molecule creates a larger signal.
13. Ligand-gated channels (ATP-gated channel); integrin receptors (platelet receptors); receptor enzymes (tyrosine kinase receptor); G-protein–coupled receptors (adenyl cyclase/cAMP-linked receptors).
14. The father of American physiology. (1) The nervous system keeps body functions within normal limits. (2) Some functions have tonic control rather than on-off control. (3) Some signals act in opposition to each other. (4) Cell response depends on the cell’s receptor for a signal.
15. Input signal: information transmission from stimulus to integrating center (sensory nerve). Integrating center: cell or cells that receive information, decide whether and how it should be acted upon, and send a signal to initiate a response (the brain). Output signal: electrical or chemical signals that take information from integrating center to target (nerve or hormone). Response: what target cell does to react to the stimulus (pull hand away from hot stove). Sensor: cell that perceives the stimulus (temperature receptor). Stimulus: change that begins a response (touching a hot stove). Target: the cell or tissue that carries out the response (muscle).
16. Neural control is faster than endocrine and better for short-acting responses. Endocrine can affect widely separated tissues with a single signal and better for long-acting responses.
17. (a) negative, (b) positive, (c) negative, (d) negative
18. (a) tissues that respond to glucagon, such as liver, (b) breast, (c) bladder, (d) sweat glands
19. (a) pancreatic endocrine cells that secrete glucagon, (b)–(d) nervous system

Level Three  Problem Solving
20. (a) stimulus = decrease in body temperature to decrease; sensor = temperature receptors; input = sensory neurons; integrating center = CNS; output = efferent neurons; targets = muscles used to pull up afghan; response = afghan conserves heat (b) stimulus = smell of sticky buns; sensor = odor receptors in the nose; input = sensory neurons; integrating center = CNS; output = efferent neurons; target = skeletal muscles; response = walk to bakery, buy buns, and eat
21. (a) antagonistic (b) Neurotransmitters act on nearby cells (paracrine action). Neurohormones act on distant targets. (c) Epinephrine is secreted in larger amounts because it will be diluted by the blood volume before reaching its target.

Level Four  Quantitative Problems
22. (a) amplification and a cascade (b) (1000 \times 4000) or 4,000,000 GMP

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