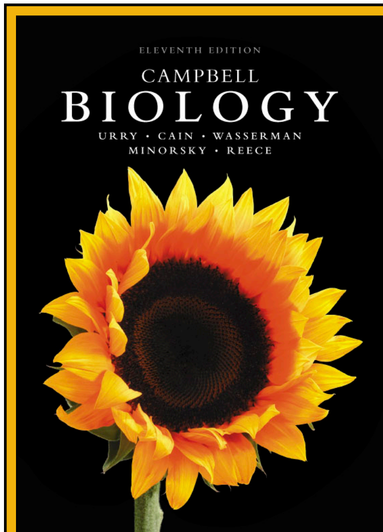

Chapter 11

Cell Communication

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

1

Cellular Messaging

- Cells can signal to each other and interpret the signals they receive from other cells and the environment
- Signals are most often chemicals
- The same small set of cell-signaling mechanisms shows up in diverse species and processes

2

Figure 11.1 How Does Cell Signaling Trigger the Desperate Flight of this Impala?

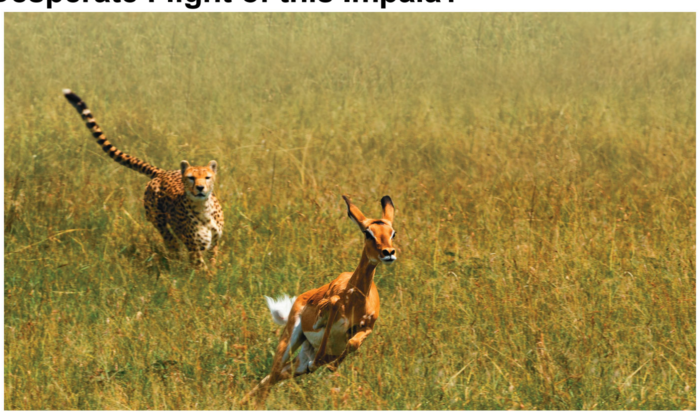

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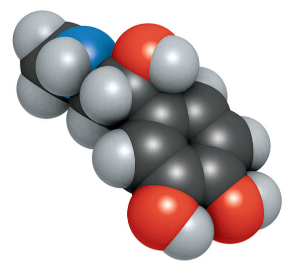
Figure 11.1a How Does Cell Signaling Trigger the Desperate Flight of this Impala? (Part 1: Epinephrine Molecule)



Epinephrine (adrenaline)

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Concept 11.1: External signals are converted to responses within the cell

- Communication among microorganisms provides some insight into how cells send, receive, and respond to signals

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Evolution of Cell Signaling

- The yeast *Saccharomyces cerevisiae* has two mating types, **a** and **α**
- Cells of different mating types locate each other via secreted factors specific to each type
- The binding of a mating factor at the cell surface initiates a series of steps called a signal transduction pathway
- Molecular details of signal transduction in yeasts and mammals are very similar.

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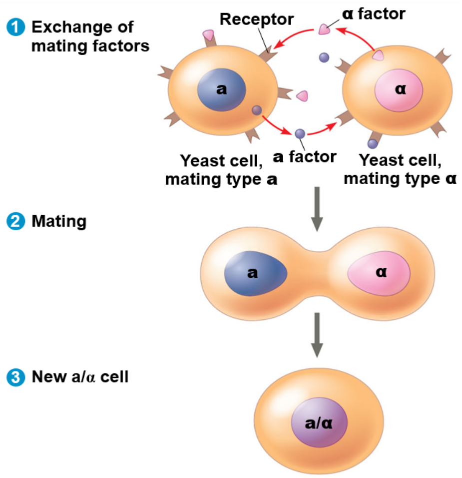
Figure 11.2_3 Communication Between Mating Yeast Cells (Step 3)



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Evolution of Cell Signaling, Continued

- Ancestral signaling molecules likely evolved in prokaryotes and single-celled eukaryotes and were adopted for use in their multicellular descendants
- Cell signaling is critical among prokaryotes
- A concentration of signaling molecules allows bacteria to sense local population density in a process called quorum sensing

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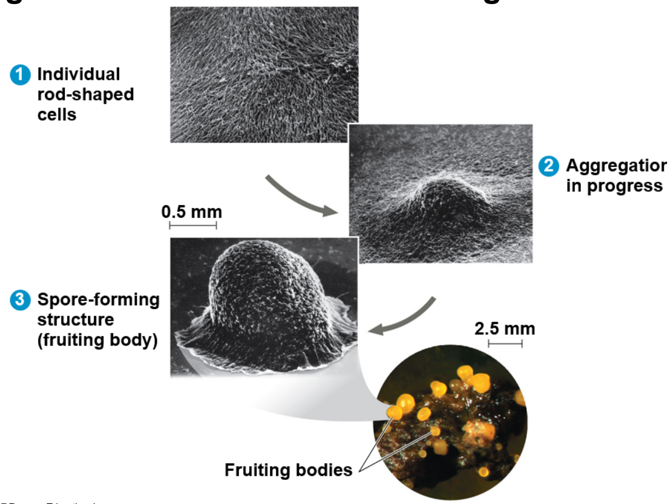
Figure 11.3 Communication Among Bacteria



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Evolution of Cell Signaling, Continued-1

- An example of quorum sensing is the formation of a biofilm
- A biofilm is an aggregation of bacterial cells adhered to a surface
- Another example of medical importance is the secretion of toxins by infectious bacteria
- Interfering with the signaling pathways used in quorum sensing may be a promising approach as an alternative to antibiotic treatment

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Local and Long-Distance Signaling

- Cells in a multicellular organism communicate via signaling molecules
- In local signaling, animal cells may communicate by direct contact
- Animal and plant cells have cell junctions that directly connect the cytoplasm of adjacent cells
- Signaling substances in the cytosol can pass freely between adjacent cells

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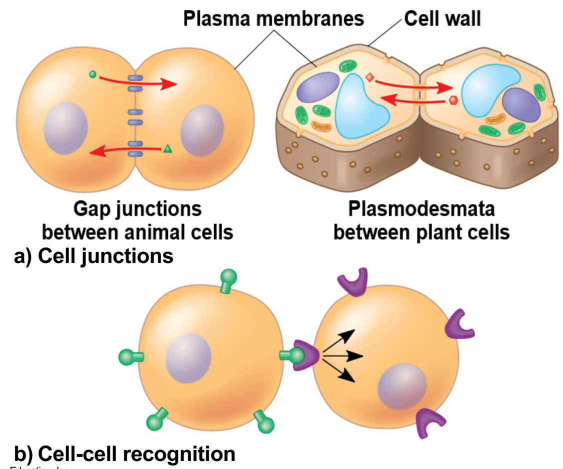
Figure 11.4 Communication by Direct Contact Between Cells



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Local and Long-Distance Signaling, Continued

- In other cases, animal cells communicate using secreted messenger molecules that travel only short distances
- Growth factors, which stimulate nearby target cells to grow and divide, are one class of such local regulators in animals
- This type of local signaling in animals is called paracrine signaling

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Local and Long-Distance Signaling, Continued-1

- Synaptic signaling occurs in the animal nervous system when a neurotransmitter is released in response to an electric signal
- Local signaling in plants is not well understood beyond communication between plasmodesmata

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Local and Long-Distance Signaling, Continued-2

- In long-distance signaling, plants and animals use chemicals called **hormones**
- Hormonal signaling in animals is called endocrine signaling; specialized cells release hormones, which travel to target cells via the circulatory system
- The ability of a cell to respond to a signal depends on whether or not it has a receptor specific to that signal

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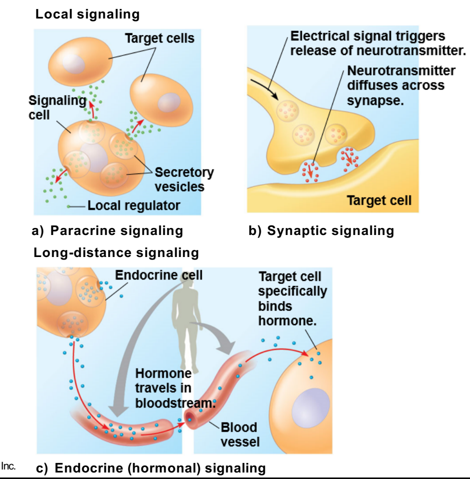
Figure 11.5 Local and Long-distance Cell Signaling by Secreted Molecules in Animals



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The Three Stages of Cell Signaling: *A Preview*

- Earl W. Sutherland and colleagues discovered how the hormone epinephrine acts on cells
- Sutherland suggested that cells receiving signals went through three processes
  - **Reception**
  - **Transduction**
  - **Response**

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The Three Stages of Cell Signaling: *A Preview,* Continued

- In reception, the target cell detects a signaling molecule that binds to a receptor protein on the cell surface
- In transduction, the binding of the signaling molecule alters the receptor and initiates a **signal transduction pathway**; transduction often occurs in a series of steps
- In response, the transduced signal triggers a specific response in the target cell

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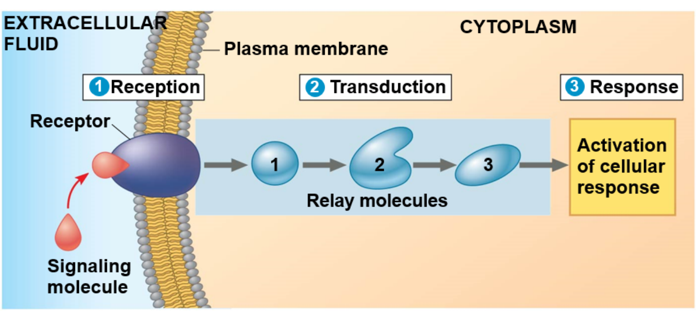
Figure 11.6_3 Overview of Cell Signaling (Step 3)



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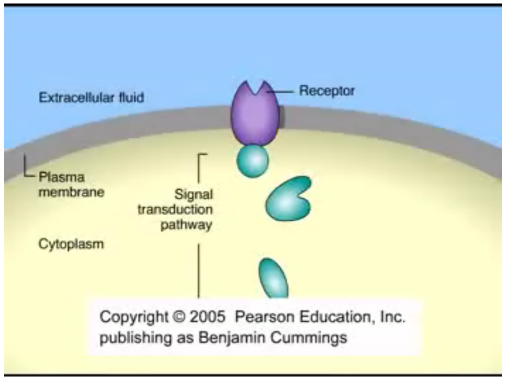
Animation: Overview of Cell Signaling



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

- The binding between a signal molecule (**ligand**) and receptor is highly specific
- A shape change in a receptor is often the initial transduction of the signal
- Most signal receptors are plasma membrane proteins

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Receptors in the Plasma Membrane

- G protein-coupled receptors (GPCRs) are the largest family of cell-surface receptors
- Most water-soluble signal molecules bind to specific sites on receptor proteins that span the plasma membrane

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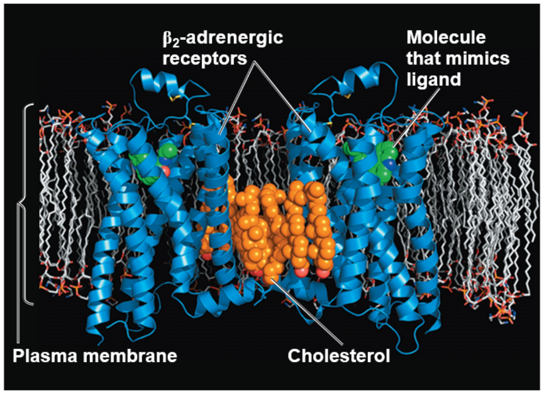
Figure 11.7 The Structure of a G Protein-coupled Receptor (GPCR)



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Receptors in the Plasma Membrane, Continued

- There are three main types of membrane receptors:
  - G protein-coupled receptors
  - Receptor tyrosine kinases
  - Ion channel receptors

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Receptors in the Plasma Membrane, Continued-1

- **G protein-coupled receptors** (GPCRs) are cell-surface transmembrane receptors that work with the help of a **G protein**
- G proteins bind the energy-rich GTP
- G proteins are all very similar in structure
- GPCR systems are extremely widespread and diverse in their functions

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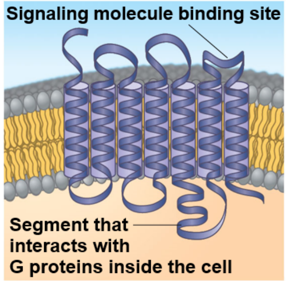
Figure 11.8a Exploring Cell-surface Transmembrane Receptors (Part 1: GPCR Ribbon Model)



G protein-coupled receptor

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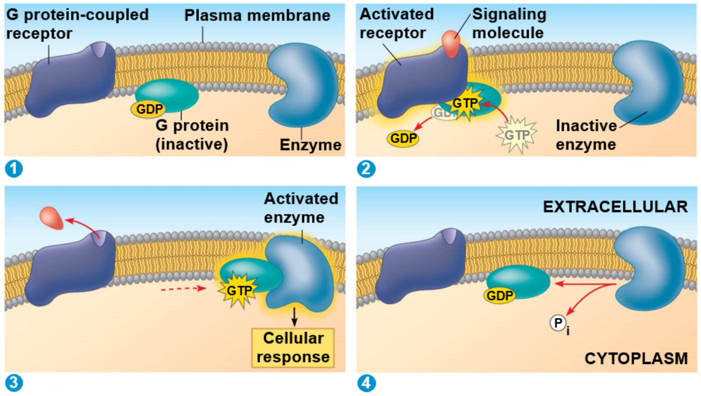
Figure 11.8b Exploring Cell-surface Transmembrane Receptors (Part 2: GPCR Signaling)



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Receptors in the Plasma Membrane, Continued-2

- **Receptor tyrosine kinases (RTKs)** are membrane receptors that transfer phosphate groups from ATP to another protein
- A receptor tyrosine kinase can trigger multiple signal transduction pathways at once
- Abnormal functioning of RTKs is associated with many types of cancers

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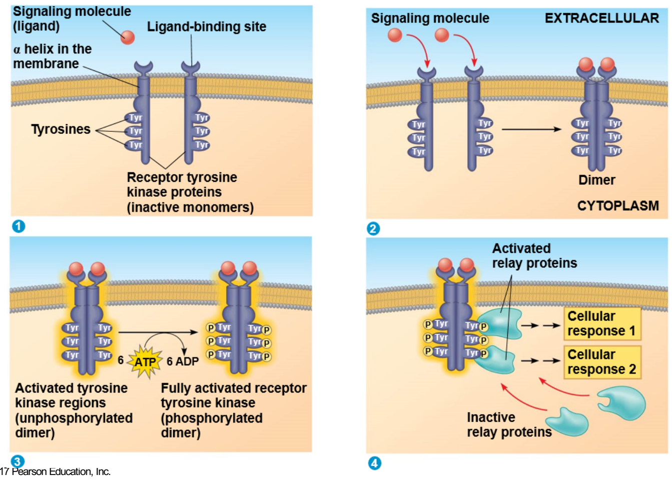
Figure 11.8c Exploring Cell-surface Transmembrane Receptors (Part 3: RTKs)



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Receptors in the Plasma Membrane, Continued-3

- A **ligand-gated ion channel** receptor acts as a gate that opens and closes when the receptor changes shape
- When a signal molecule binds as a ligand to the receptor, the gate allows specific ions, such as Na^+ or Ca^{2+}, through a channel in the receptor

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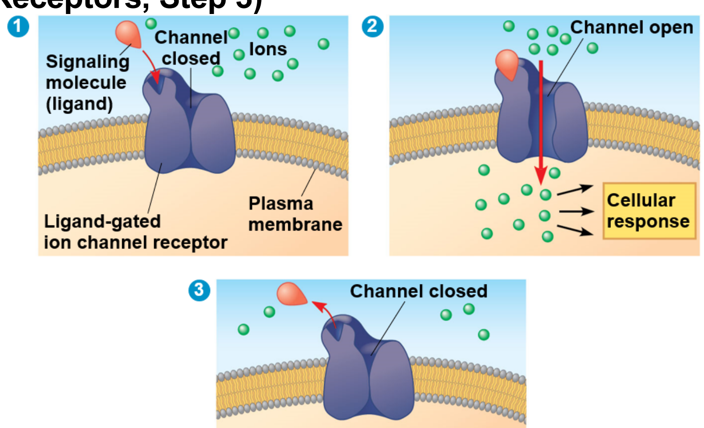
Figure 11.8d_3 Exploring Cell-surface Transmembrane Receptors (Part 4: Ion Channel Receptors, Step 3)



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Which correctly describes the use of ligand-gated ion channel receptors?

a) Ligand binding is irreversible, resulting in a permanent change in this ion channel's activity.
b) The binding site of this type of receptor is most often in the middle of the membrane.
c) Once activated, this receptor will cause G proteins to bind with GTP.
d) Once the ligand is bound, the ion channel activity can alter the local membrane potential and cytosolic concentration of the ion.
e) The ligand involved is often a phosphate group that is covalently added to the cytosolic side of this ion channel.

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Intracellular Receptors

- Intracellular receptor proteins are found in the cytoplasm or nucleus of target cells
- Small or hydrophobic chemical messengers can readily cross the membrane and activate receptors
- Examples of hydrophobic messengers are the steroid and thyroid hormones of animals
- An activated hormone-receptor complex can act as a transcription factor, turning on or off specific genes

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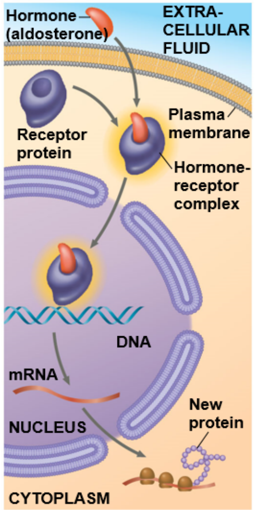
Figure 11.9 Steroid Hormone Interacting with an Intracellular Receptor



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

- Cell signaling is usually a multistep process
- Multistep pathways can greatly amplify a signal
- Multistep pathways provide more opportunities for coordination and regulation of the cellular response

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Signal Transduction Pathways

- The binding of a signaling molecule to a receptor triggers the first step in a chain of molecular interactions
- The receptor activates another protein, which activates another, and so on, until the protein producing the response is activated
- At each step, the signal is transduced into a different form, usually a shape change in a protein

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Protein Phosphorylation and Dephosphorylation

- Phosphorylation and dephosphorylation of proteins is a widespread cellular mechanism for regulating protein activity
- **Protein kinases** transfer phosphates from ATP to protein, a process called phosphorylation
- Many relay molecules in signal transduction pathways are protein kinases, creating a **phosphorylation cascade**

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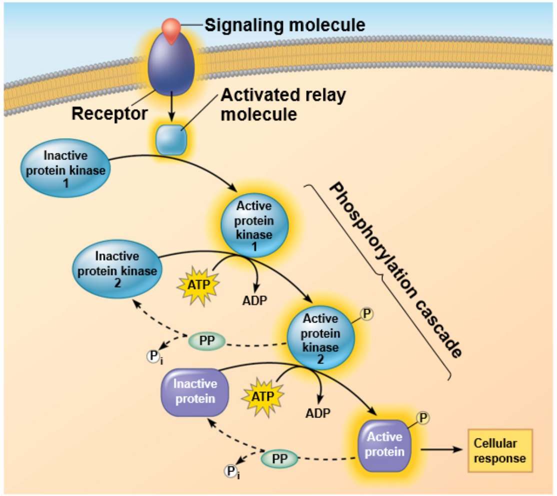
Figure 11.10 A Phosphorylation Cascade



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Protein Phosphorylation and Dephosphorylation, Continued

- **Protein phosphatases** rapidly remove the phosphates from proteins, a process called dephosphorylation
- This phosphorylation and dephosphorylation system acts as a molecular switch, turning activities on and off or up or down, as required

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Phosphorylation of proteins in a kinase cascade does what?

a) makes functional ATP
b) distorts a protein from one functional state to another
c) activates phosphatases to remove the phosphate group
d) alters the permeability of the cell's membranes
e) produces an increase in the cell's store of inorganic phosphates

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Small Molecules and Ions as Second Messengers

- Many signaling pathways involve **second messengers**
- These are small, nonprotein, water-soluble molecules or ions that spread throughout a cell by diffusion
- Second messengers participate in pathways initiated by GPCRs and RTKs
- Cyclic AMP and calcium ions are common second messengers

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Cyclic AMP

- **Cyclic AMP (cAMP)** is one of the most widely used second messengers
- **Adenylyl cyclase**, an enzyme in the plasma membrane, converts ATP to cAMP in response to an extracellular signal

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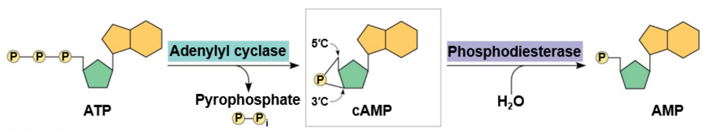
Figure 11.11 Cyclic AMP



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Cyclic AMP, Continued

- Many signal molecules trigger formation of cAMP
- Other components of cAMP pathways are G proteins, G protein-coupled receptors, and protein kinases
- cAMP usually activates protein kinase A, which phosphorylates various other proteins
- Further regulation of cell metabolism is provided by G protein systems that inhibit adenylyl cyclase

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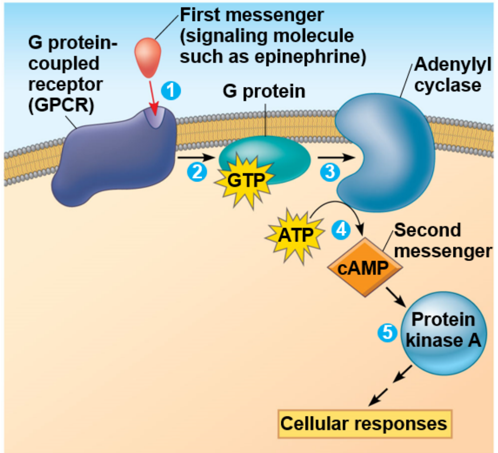
Figure 11.12 cAMP as a Second Messenger in a G Protein Signaling Pathway



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Cyclic AMP, Continued-1

- Understanding of the role of cAMP in G protein signaling pathways helps explain how certain microbes cause disease
- The cholera bacterium, *Vibrio cholerae*, produces a toxin that modifies a G protein so that it is stuck in its active form
- This protein continually makes cAMP, causing intestinal cells to secrete large amounts of salt into the intestines
- Water follows by osmosis, and an untreated person can soon die from loss of water and salt

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Calcium Ions and Inositol Triphosphate (IP_3)

- Calcium ions (Ca^{2+}) are used widely as a second messenger
- Ca^{2+} can function as a second messenger because its concentration in the cytosol is normally much lower than the concentration outside the cell
- A small change in number of calcium ions thus represents a relatively large percentage change in calcium concentration

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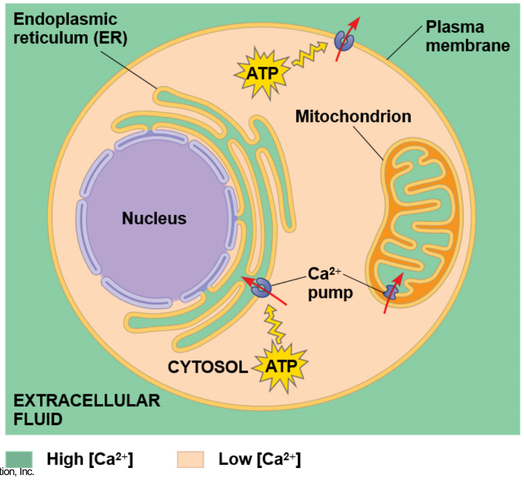
Figure 11.13 The Maintenance of Calcium Ion Concentrations in an Animal Cell



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Calcium Ions and Inositol Triphosphate (IP_3), Continued

- A signal relayed by a signal transduction pathway may trigger an increase in calcium in the cytosol
- Pathways leading to the release of calcium involve **inositol triphosphate (IP_3)** and **diacylglycerol (DAG)** as additional second messengers
- These two are produced by cleavage of a certain phospholipid in the plasma membrane

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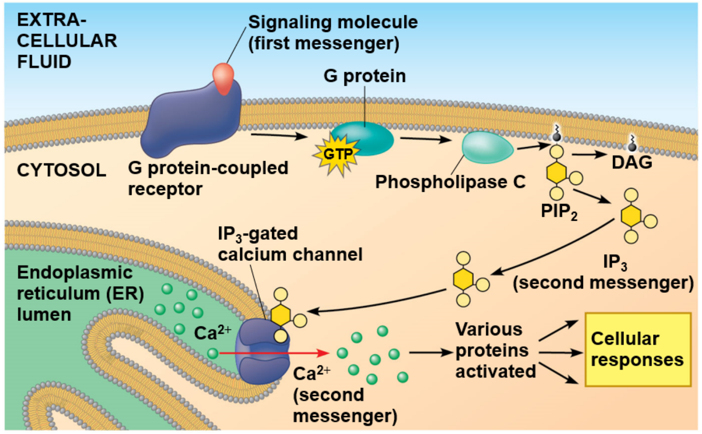
Figure 11.14_3 Calcium and IP_3 in Signaling Pathways (Step 3)



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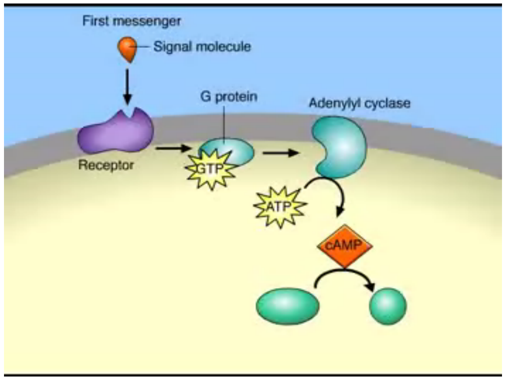
Animation: Signal Transduction Pathways



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

- The cell's response to an extracellular signal is called the "output response"

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Nuclear and Cytoplasmic Responses

- Ultimately, a signal transduction pathway leads to regulation of one or more cellular activities
- The response may occur in the nucleus or in the cytoplasm
- Many signaling pathways regulate the synthesis of enzymes or other proteins, usually by turning genes on or off in the nucleus
- The final activated molecule in the signaling pathway may function as a transcription factor

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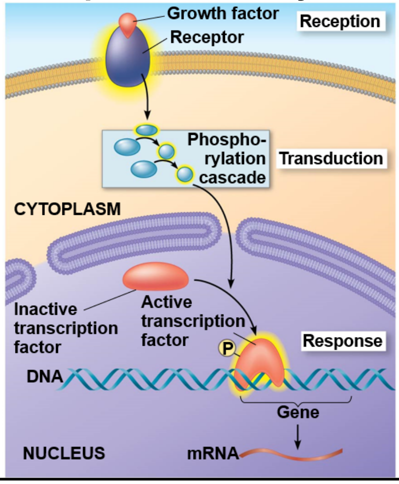
Figure 11.15 Nuclear Responses to a Signal: The Activation of a Specific Gene by a Growth Factor



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Nuclear and Cytoplasmic Responses, Continued

- Other pathways may regulate the activity of enzymes rather than their synthesis
- For example, a signal could cause opening or closing of an ion channel in the plasma membrane or a change in cell metabolism

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Nuclear and Cytoplasmic Responses, Continued-1

- Signaling pathways can also affect the overall behavior of a cell; for example, a signal could lead to cell division

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Regulation of the Response

- A response to a signal may not be simply “on” or “off”
- There are four aspects of signal regulation:
  - Amplification of the signal (and thus the response)
  - Specificity of the response
  - Overall efficiency of response, enhanced by scaffolding proteins
  - Termination of the signal

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Signal Amplification

- Enzyme cascades amplify the cell’s response to the signal
- At each step, the number of activated products can be much greater than in the preceding step

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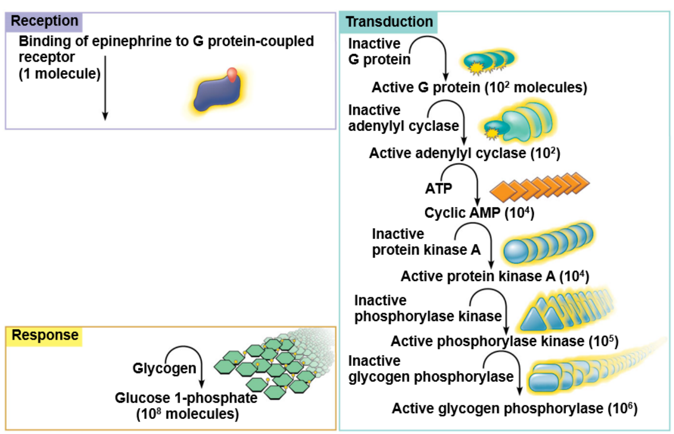
Figure 11.16 Cytoplasmic Response to a Signal: The Stimulation of Glycogen Breakdown by Epinephrine (Adrenaline)



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Which is the best example of amplification of signal?

a) production of many molecules by many signal molecules
b) activation of 100 molecules by a single signal binding event
c) activation of a specific gene by a transcription factor
d) conversion of the signal into many other types of molecules
e) activation of a receptor by a hormone

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The Specificity of Cell Signaling and Coordination of the Response

- Different kinds of cells have different collections of proteins
- These different proteins allow cells to detect and respond to different signals
- The same signal can have different effects in cells with different proteins and pathways
- Pathway branching and "cross-talk" further help the cell coordinate incoming signals

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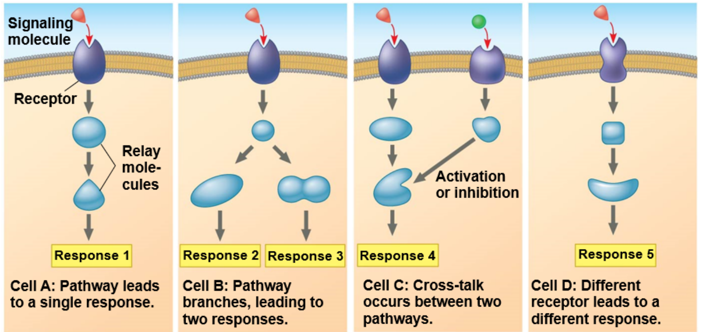
Figure 11.17 The Specificity of Cell Signaling



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Signaling Efficiency: Scaffolding Proteins and Signaling Complexes

- **Scaffolding proteins** are large relay proteins to which other relay proteins are attached
- Scaffolding proteins can increase the signal transduction efficiency by grouping together different proteins involved in the same pathway
- In some cases, scaffolding proteins may also help activate some of the relay proteins

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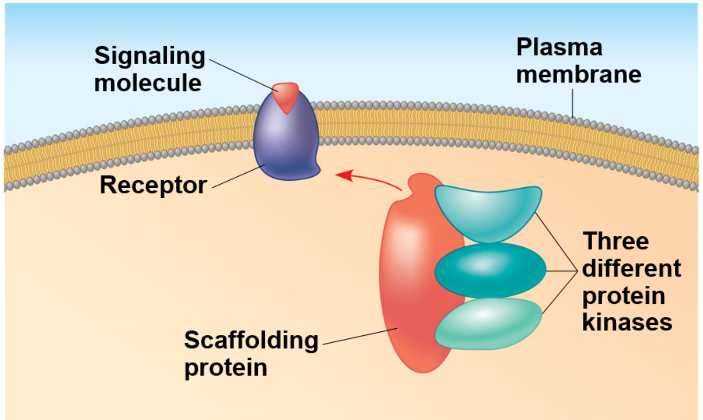
Figure 11.18 A Scaffolding Protein



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Termination of the Signal

- Inactivation mechanisms are an essential aspect of cell signaling
- If the concentration of external signaling molecules falls, fewer receptors will be bound
- Unbound receptors revert to an inactive state

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Concept 11.5: Apoptosis integrates multiple cell-signaling pathways

- Cells that are infected, damaged, or at the end of their functional lives often undergo "programmed cell death"
- **Apoptosis** is the best-understood type
- Components of the cell are chopped up and packaged into vesicles that are digested by scavenger cells
- Apoptosis prevents enzymes from leaking out of a dying cell and damaging neighboring cells

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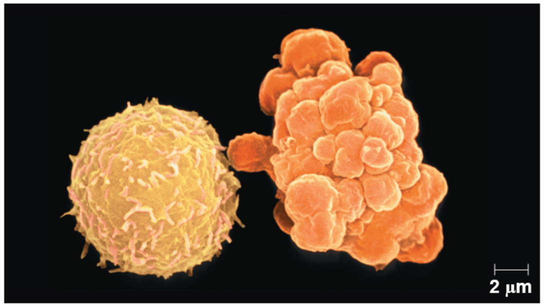
Figure 11.19 Apoptosis of a Human White Blood Cell



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Apoptosis in the Soil Worm *Caenorhabditis elegans*

- In worms and other organisms, apoptosis is triggered by signals that activate a cascade of "suicide" proteins in the cells programmed to die
- When the death signal is received, an apoptosis-inhibiting protein (Ced-9) is inactivated, triggering a cascade of caspase proteins that promote apoptosis
- The chief caspase in the nematode is called Ced-3

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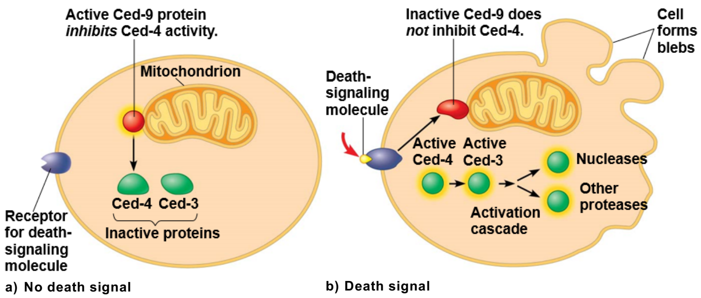
Figure 11.20 Molecular Basis of Apoptosis in *C. Elegans*



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Apoptotic Pathways and the Signals That Trigger Them

- In humans and other mammals, several different pathways, including about 15 caspases, can carry out apoptosis
- Apoptosis can be triggered by signals from outside the cell or inside it
- Internal signals can result from irreparable DNA damage or excessive protein misfolding

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Apoptotic Pathways and the Signals That Trigger Them, Continued

- Apoptosis evolved early in animal evolution and is essential for the development and maintenance of all animals
- For example, apoptosis is a normal part of development of hands and feet in humans (and paws in other mammals)
- Apoptosis may be involved in some diseases (for example, Parkinson's and Alzheimer's); interference with apoptosis may contribute to some cancers

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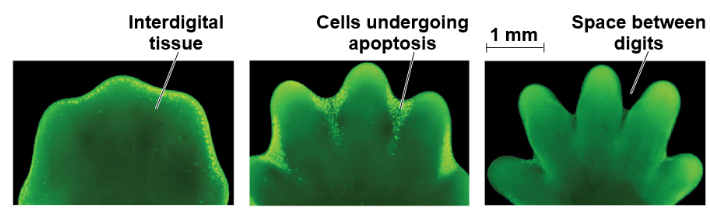
Figure 11.21 Effect of Apoptosis During Paw Development in the Mouse



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What is the best explanation for the disappearance of cells between segments of a palm leaf?

a) action of a G protein
b) amplification
c) apoptosis
d) a steroid receptor
e) none of the above

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