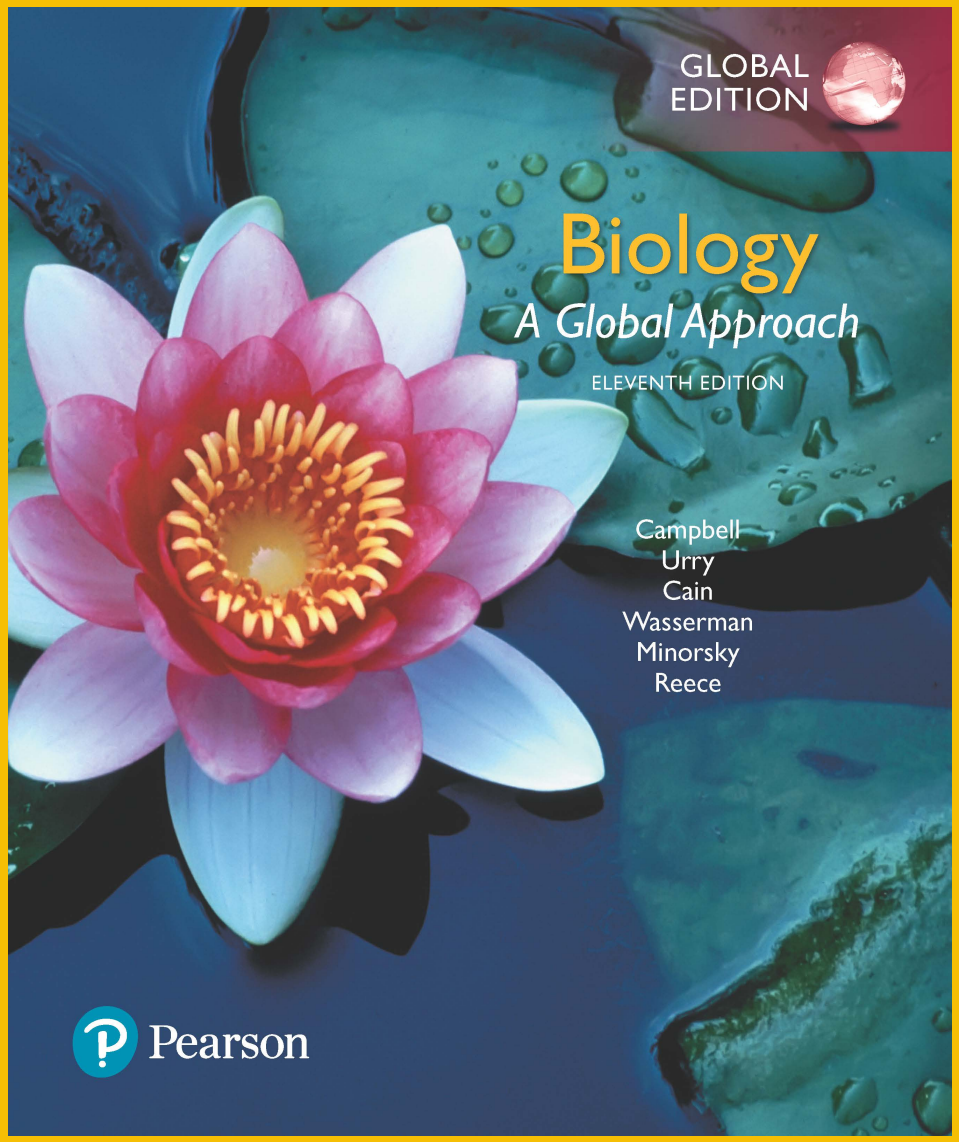


Chapter 9

Cellular Signaling

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

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

Figure 9.1

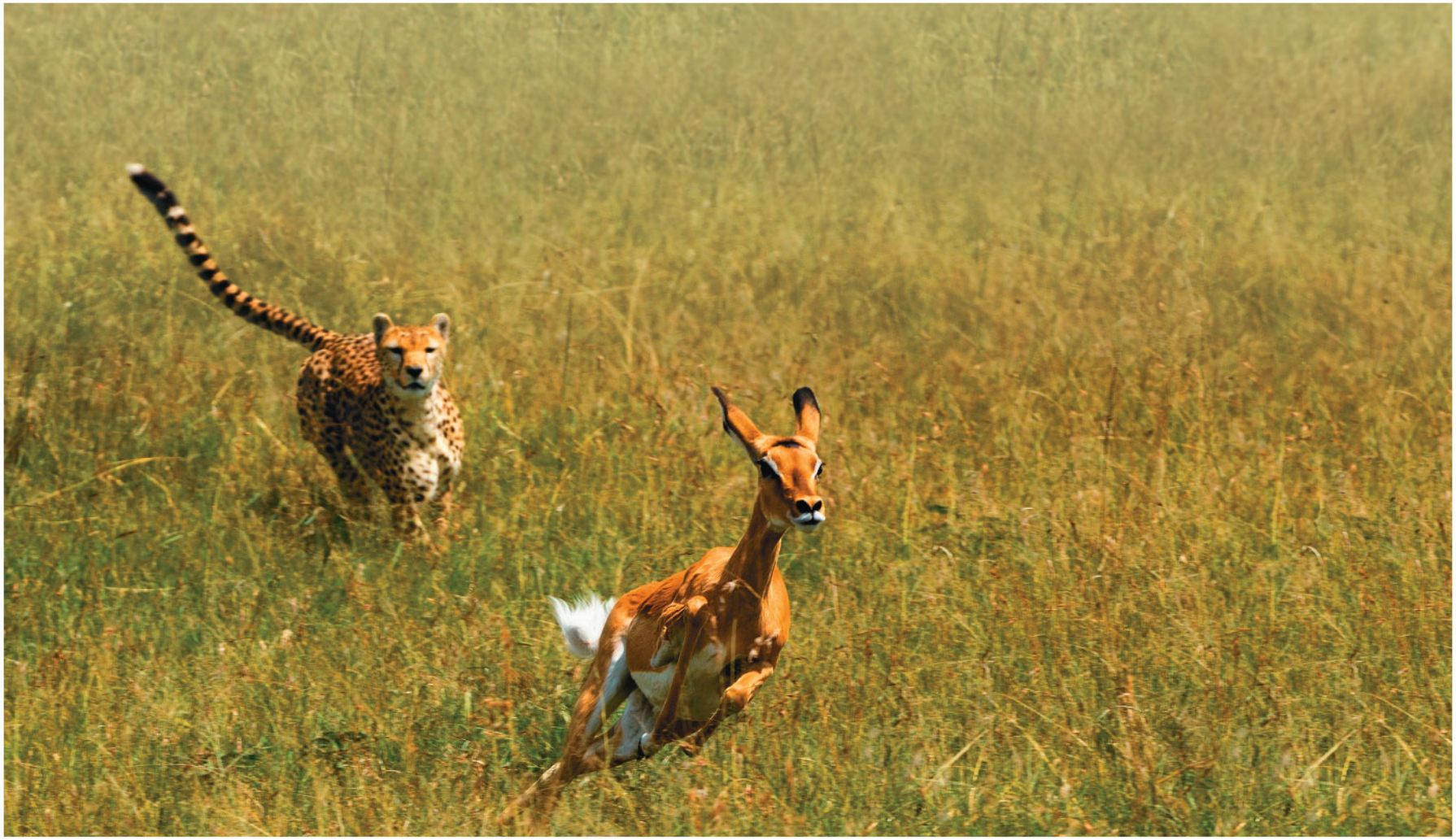
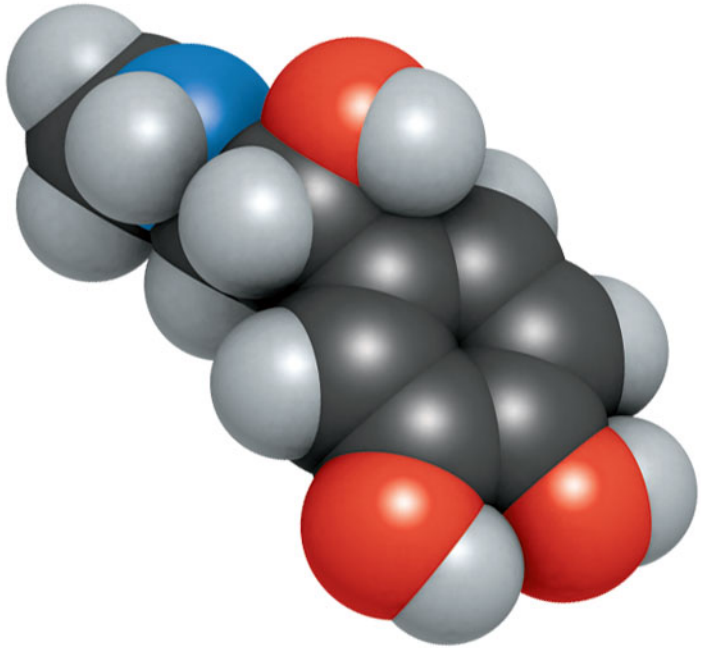


Figure 9.1a



Epinephrine (adrenaline)

Concept 9.1: External signals are converted to responses within the cell

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

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.

Figure 9.2_1

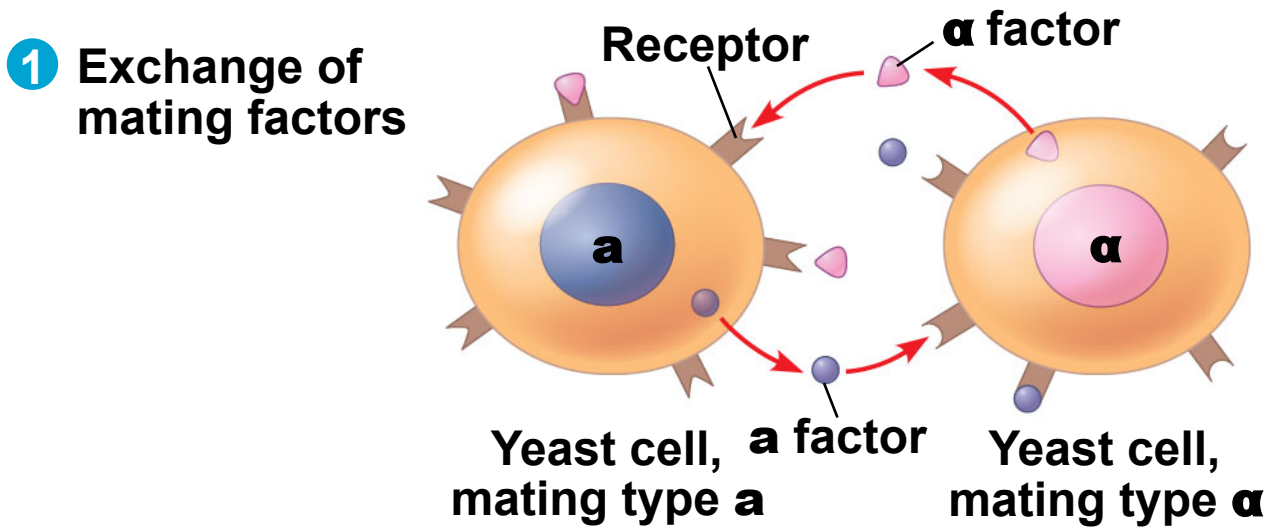


Figure 9.2_2

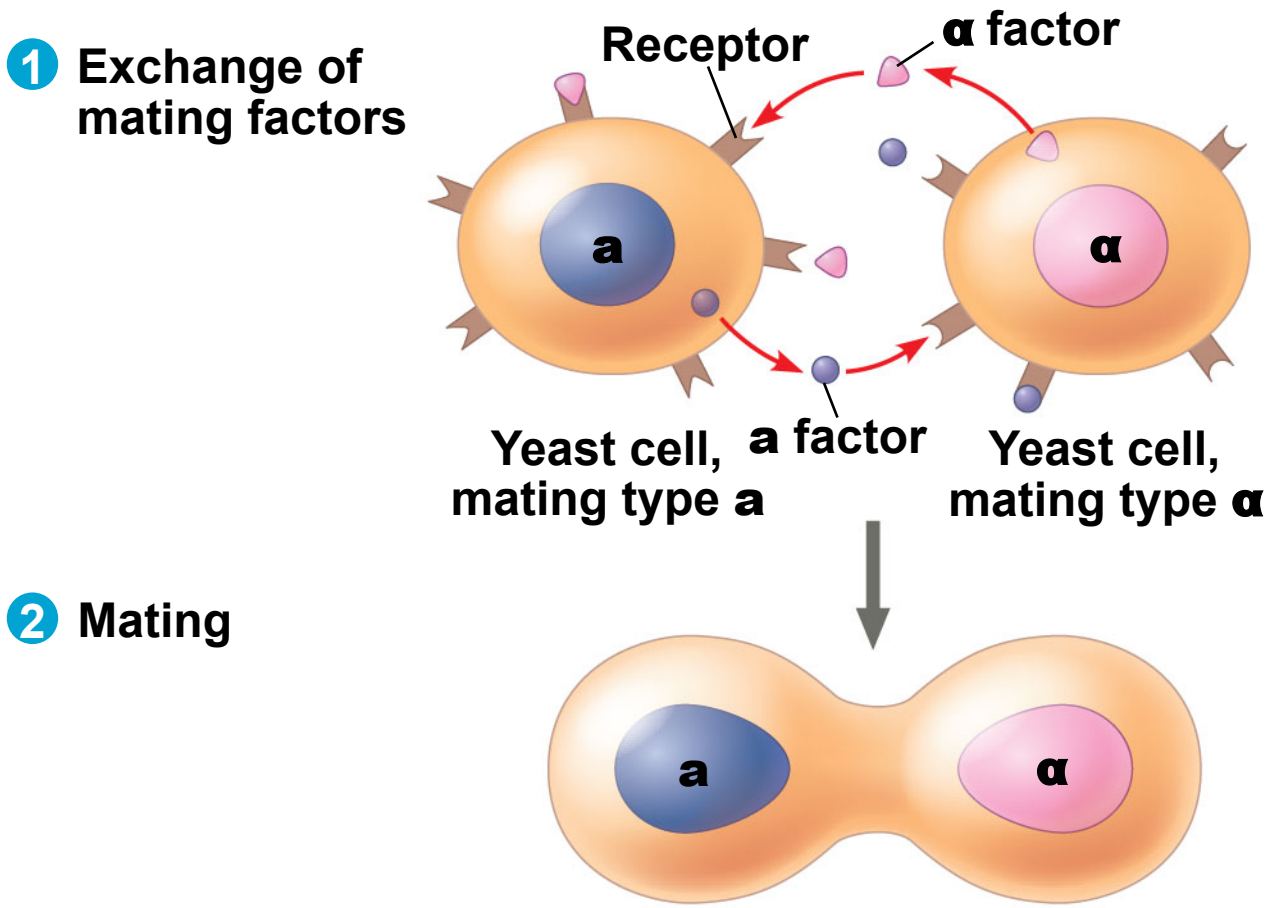
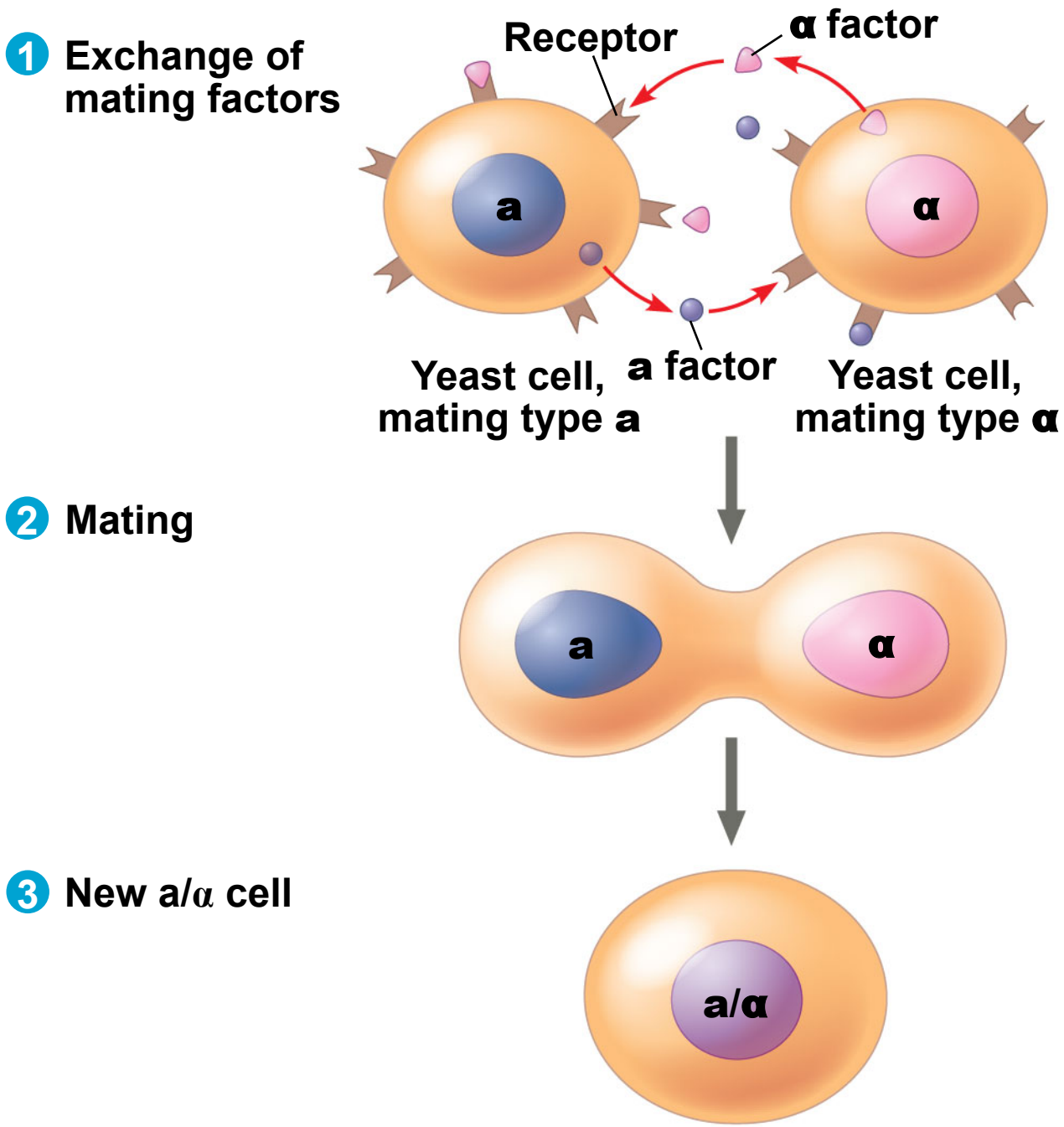
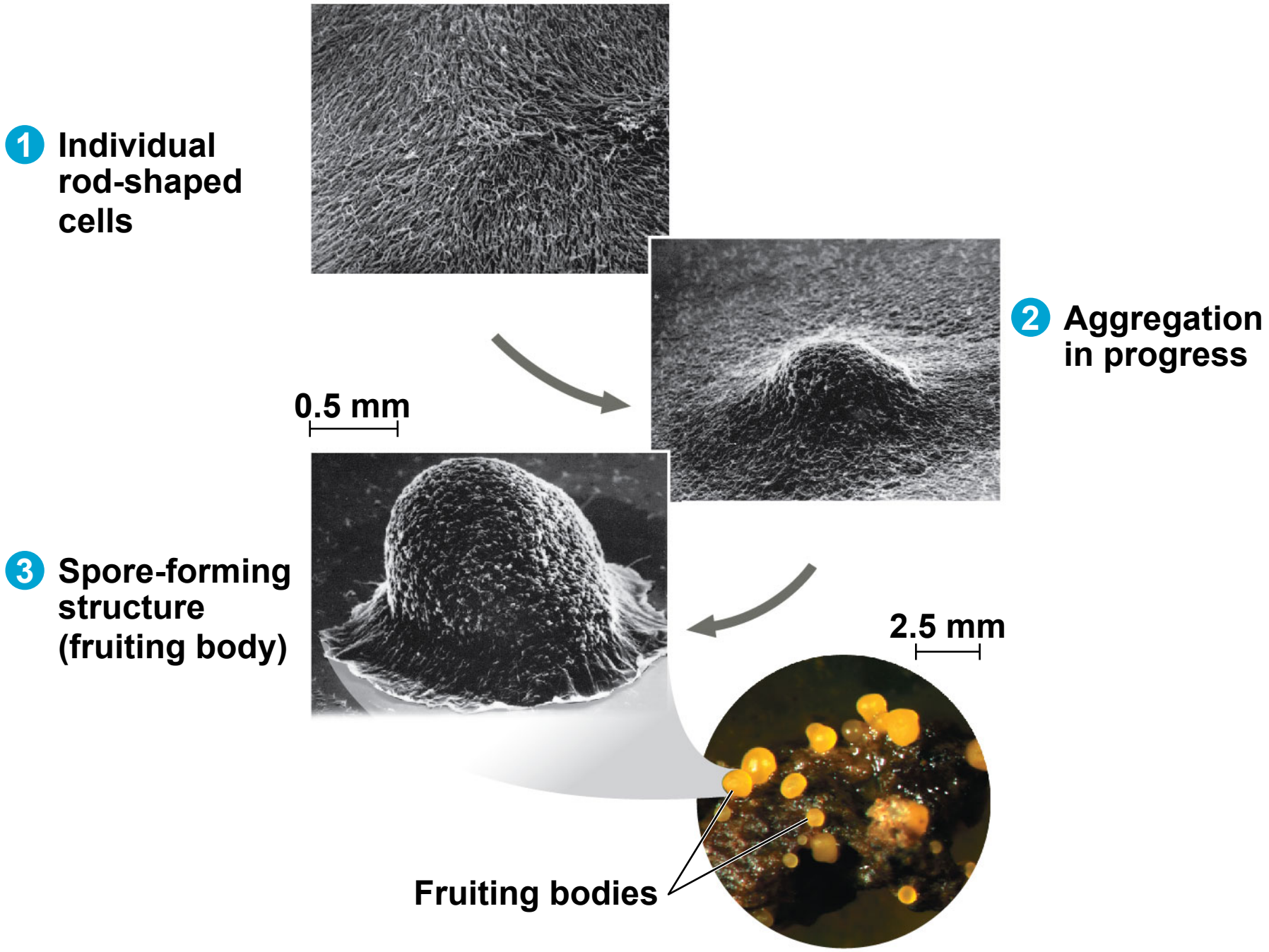


Figure 9.2_3



- 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

Figure 9.3



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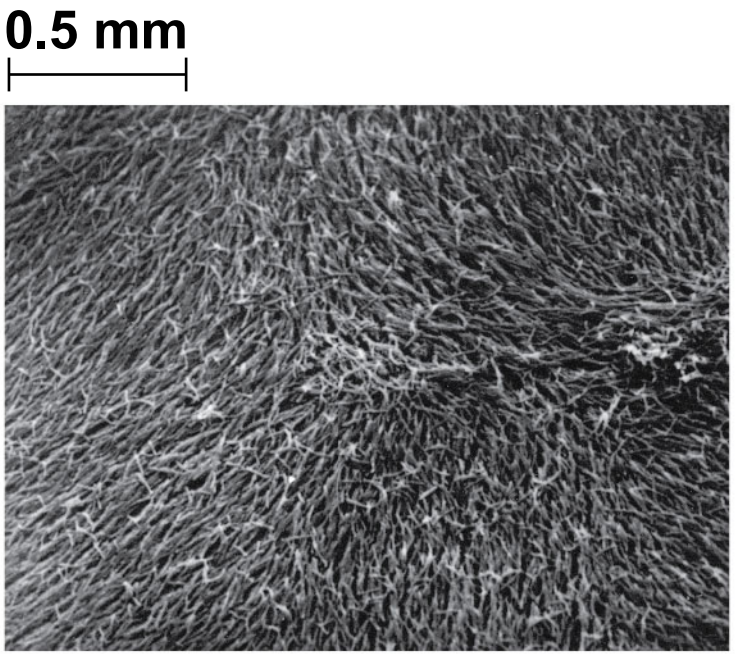


Figure 9.3b

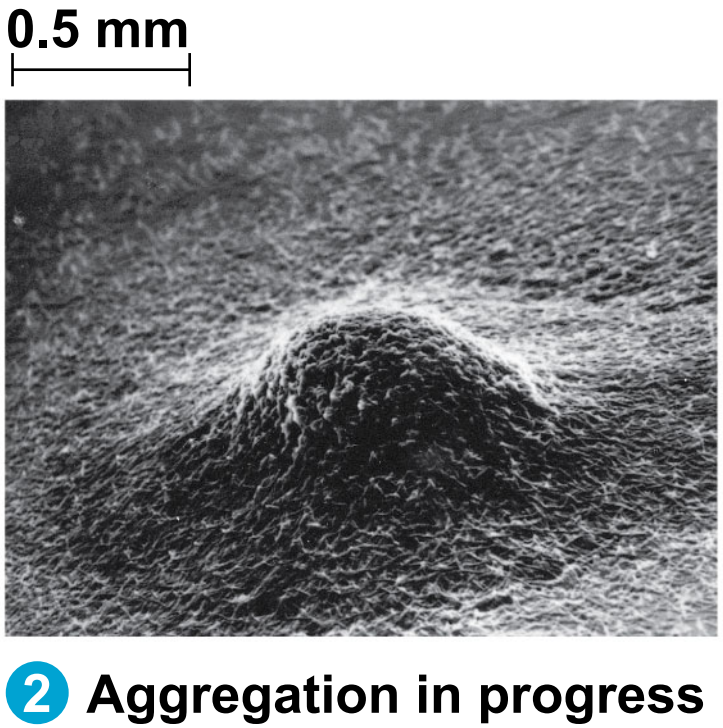


Figure 9.3c

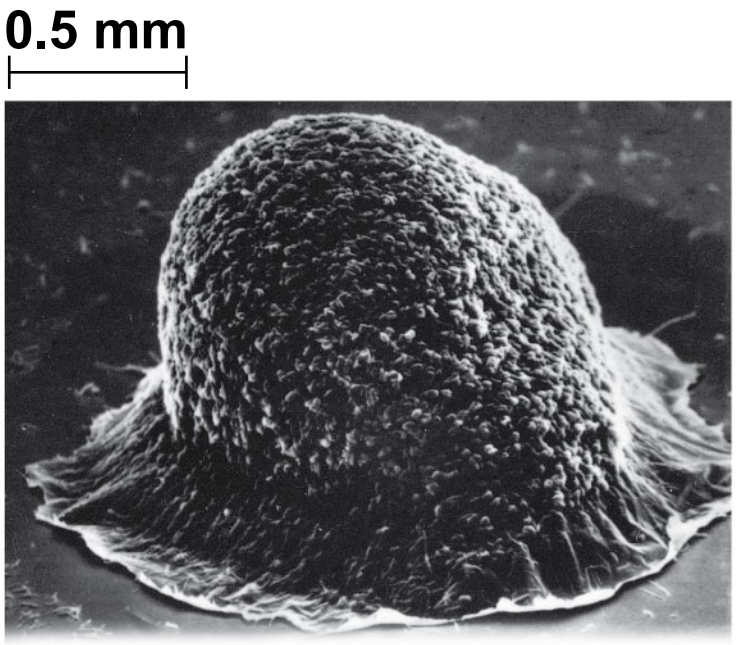
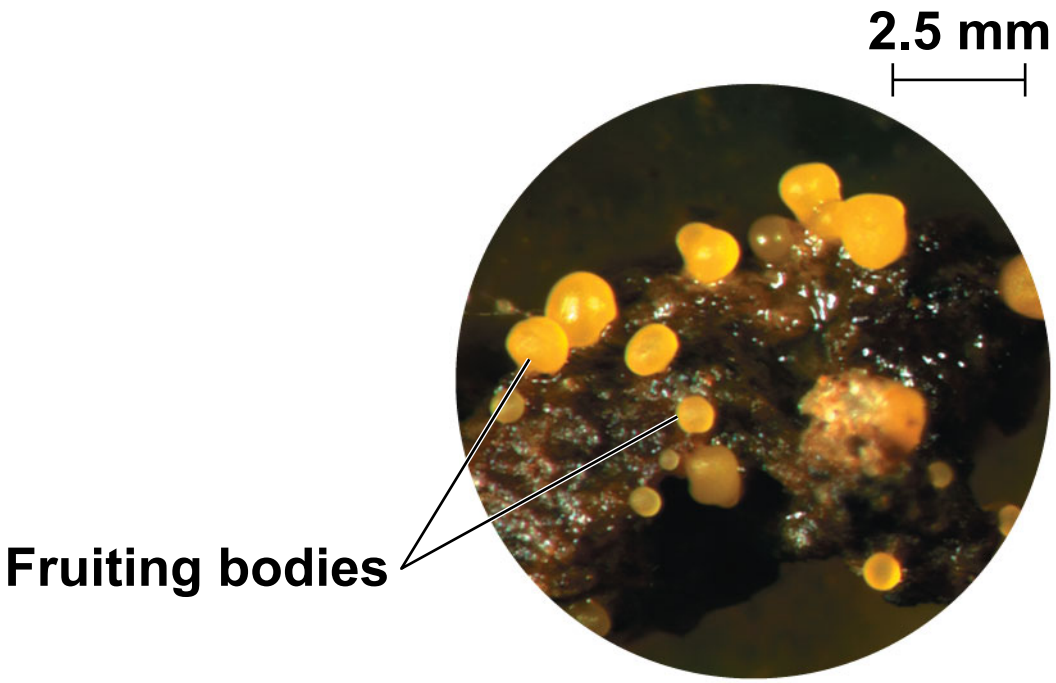


Figure 9.3d

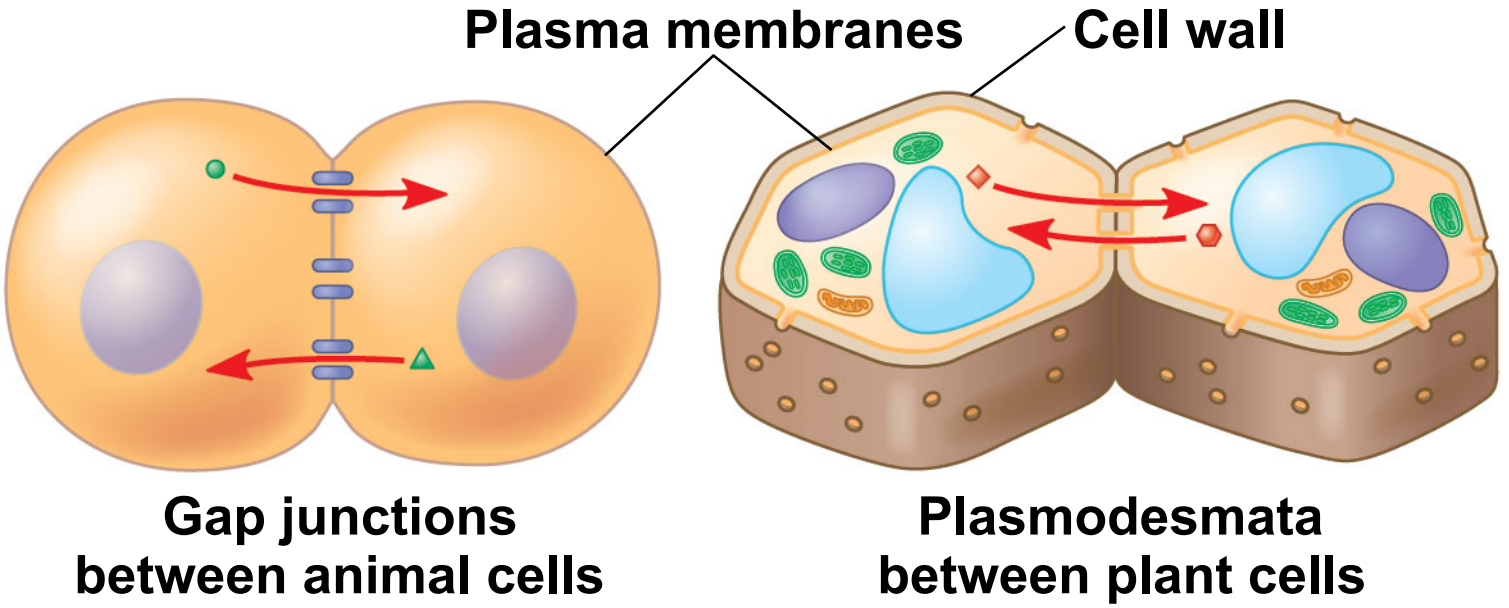


- An example of quorum sensing is the formation of a biofilm
- A biofilm is an aggregation of bacterial cells adhered to a surface
- Another example of medical importance is the secretion of toxins by infectious bacteria
- Interfering with the signaling pathways used in quorum sensing may be a promising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

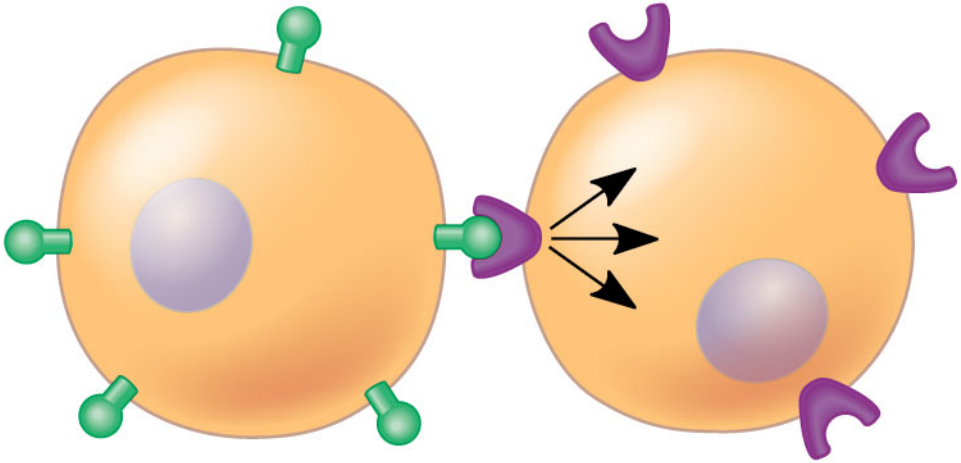
Local and Long-Distance Signaling

- 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

Figure 9.4



(a) Cell junctions



(b) Cell-cell recognition

- 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

- 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

- 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

Figure 9.5

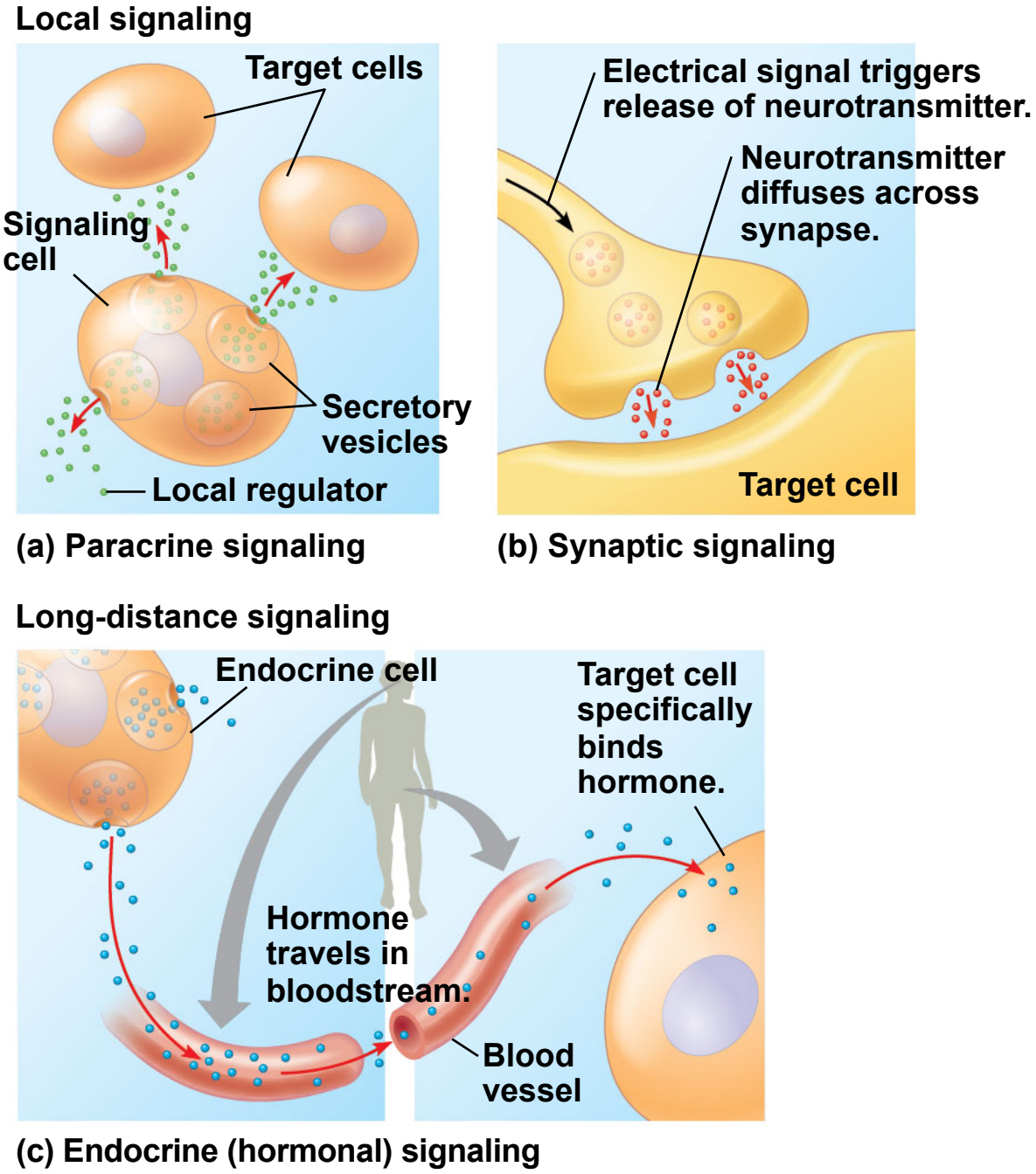


Figure 9.5a

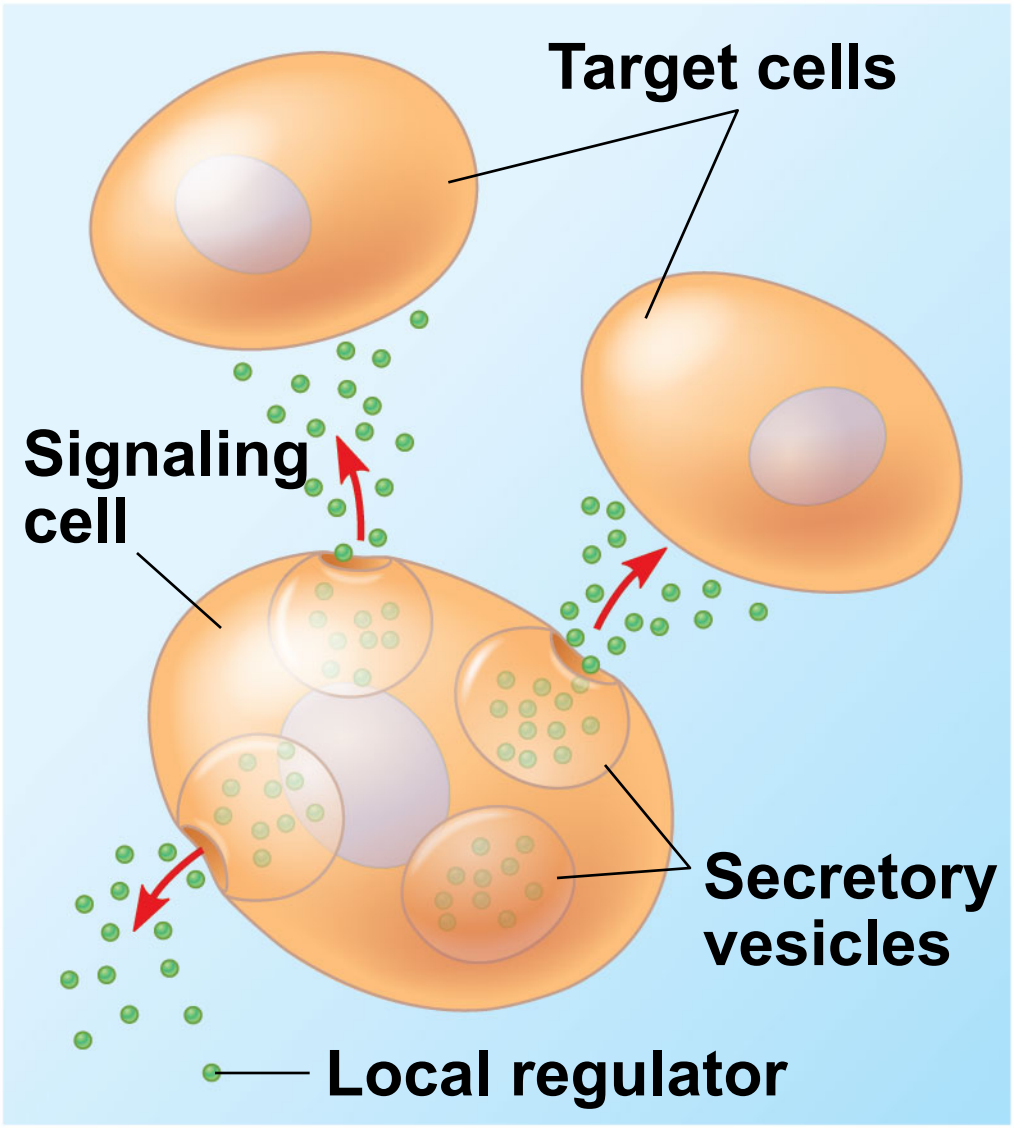
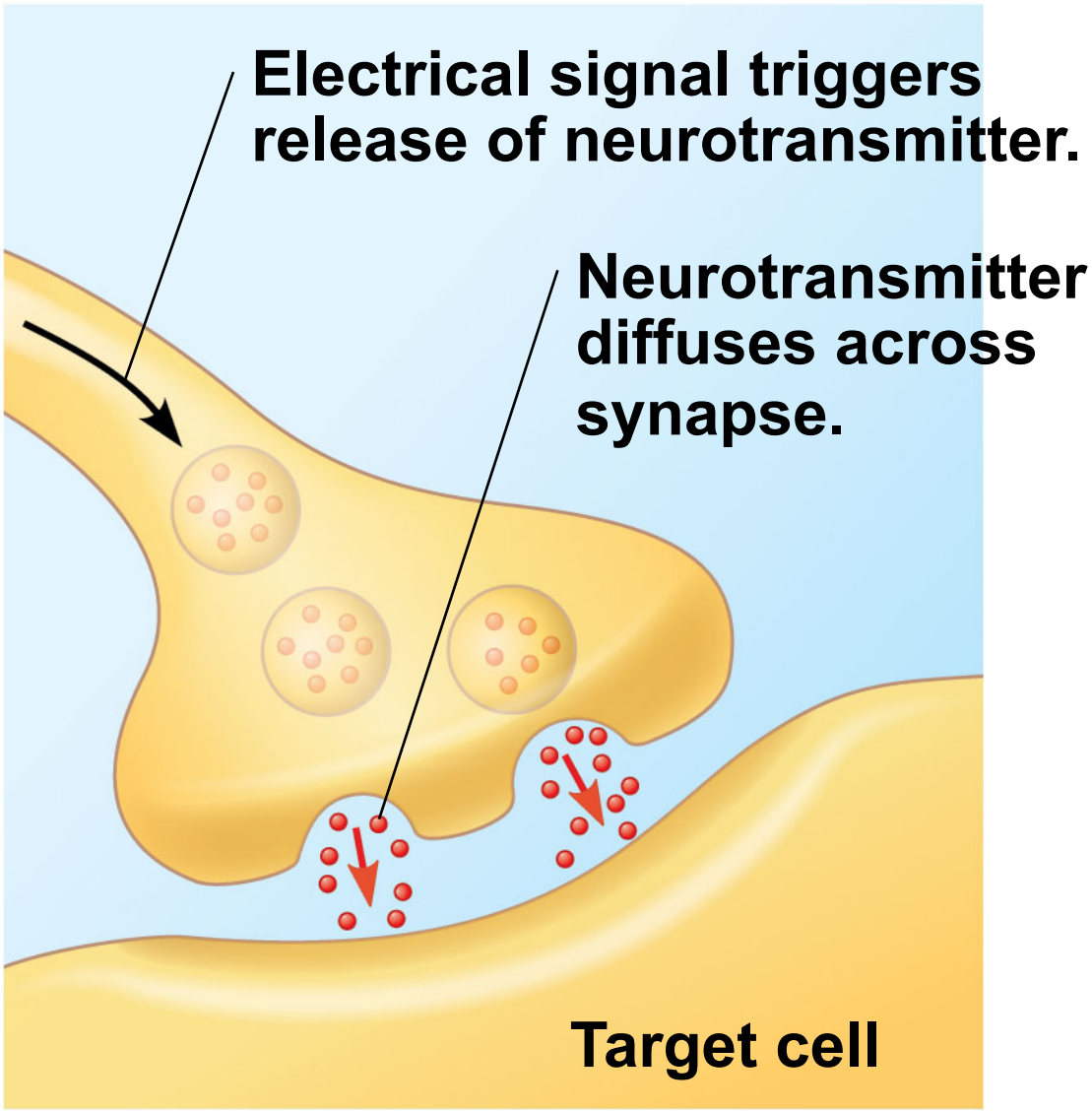
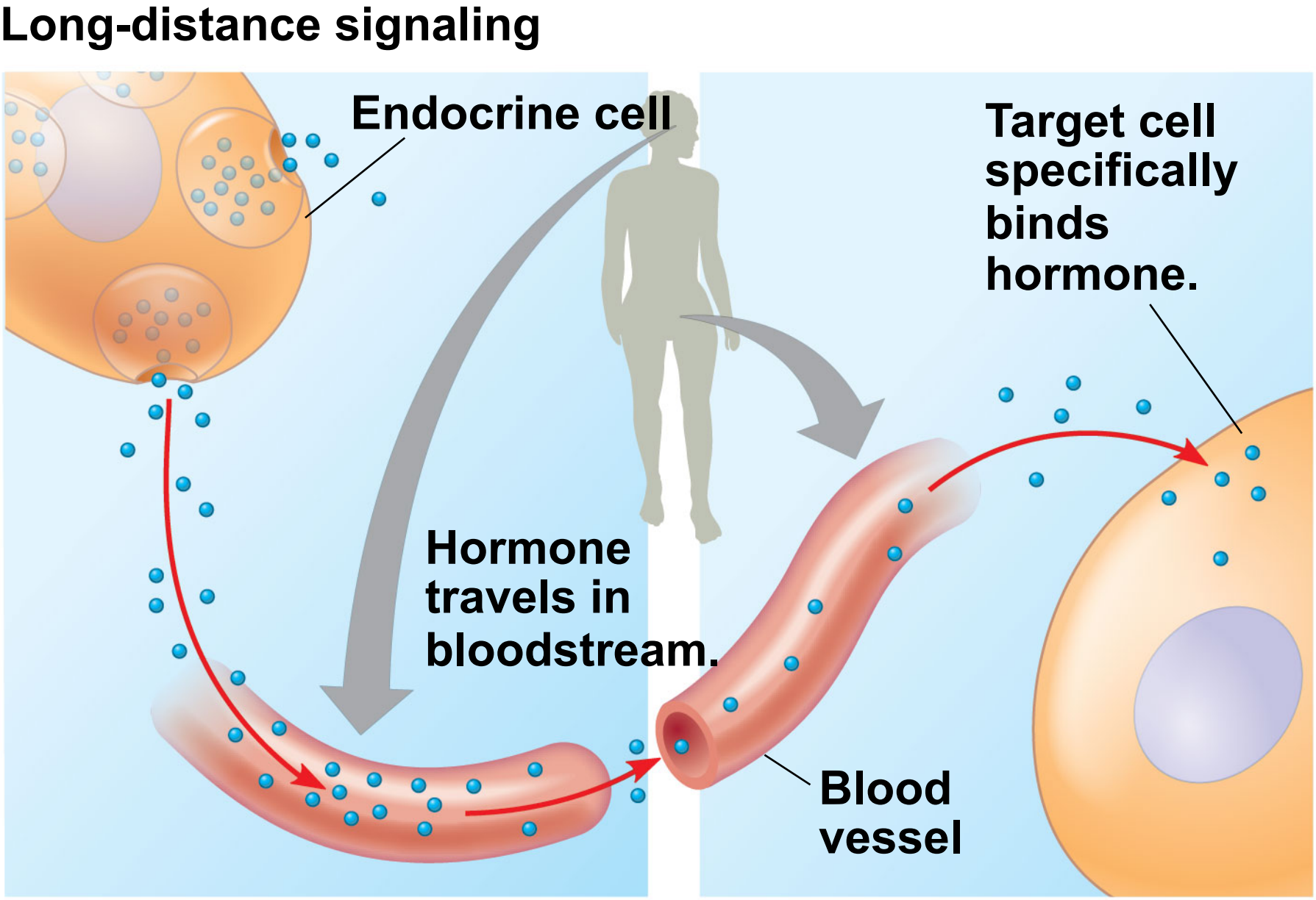


Figure 9.5b



(b) Synaptic signaling

Figure 9.5c



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**

- 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

Figure 9.6_1

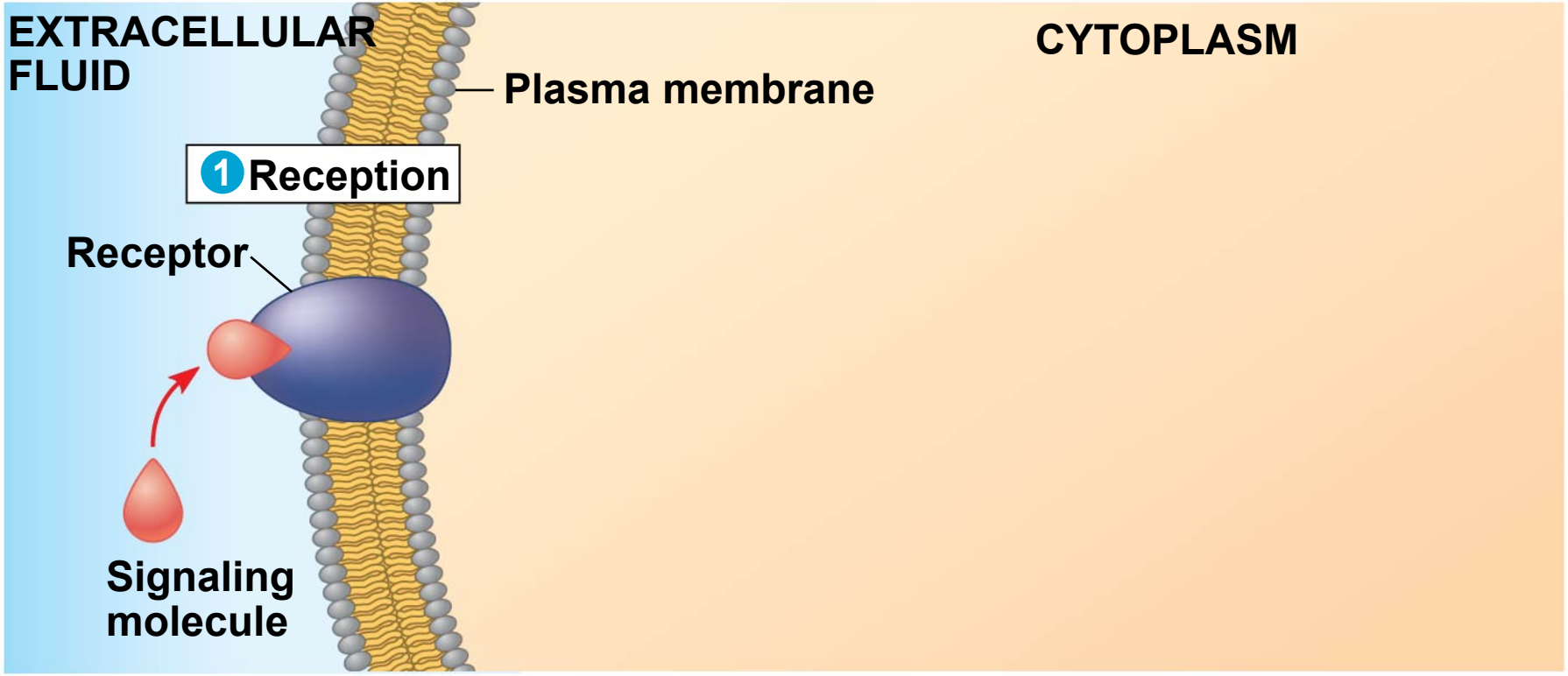


Figure 9.6_2

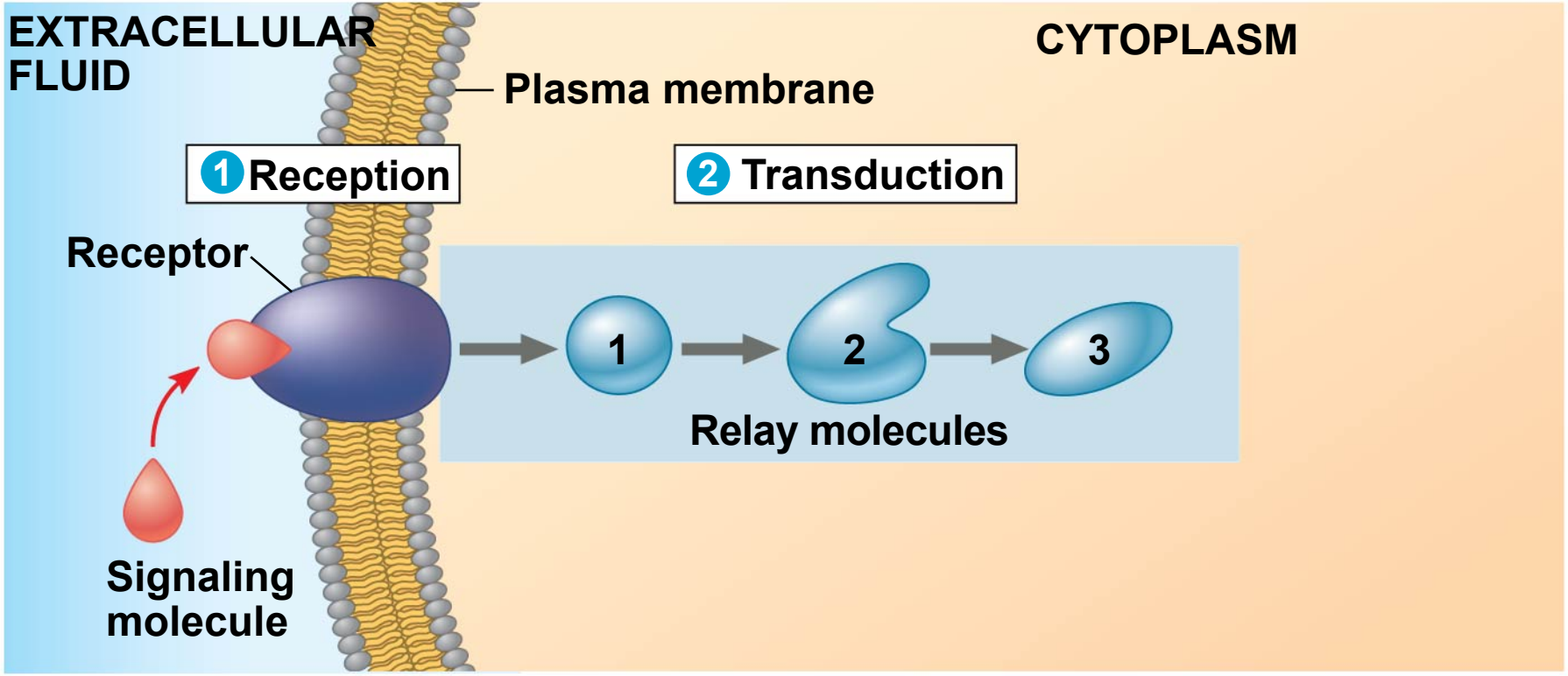
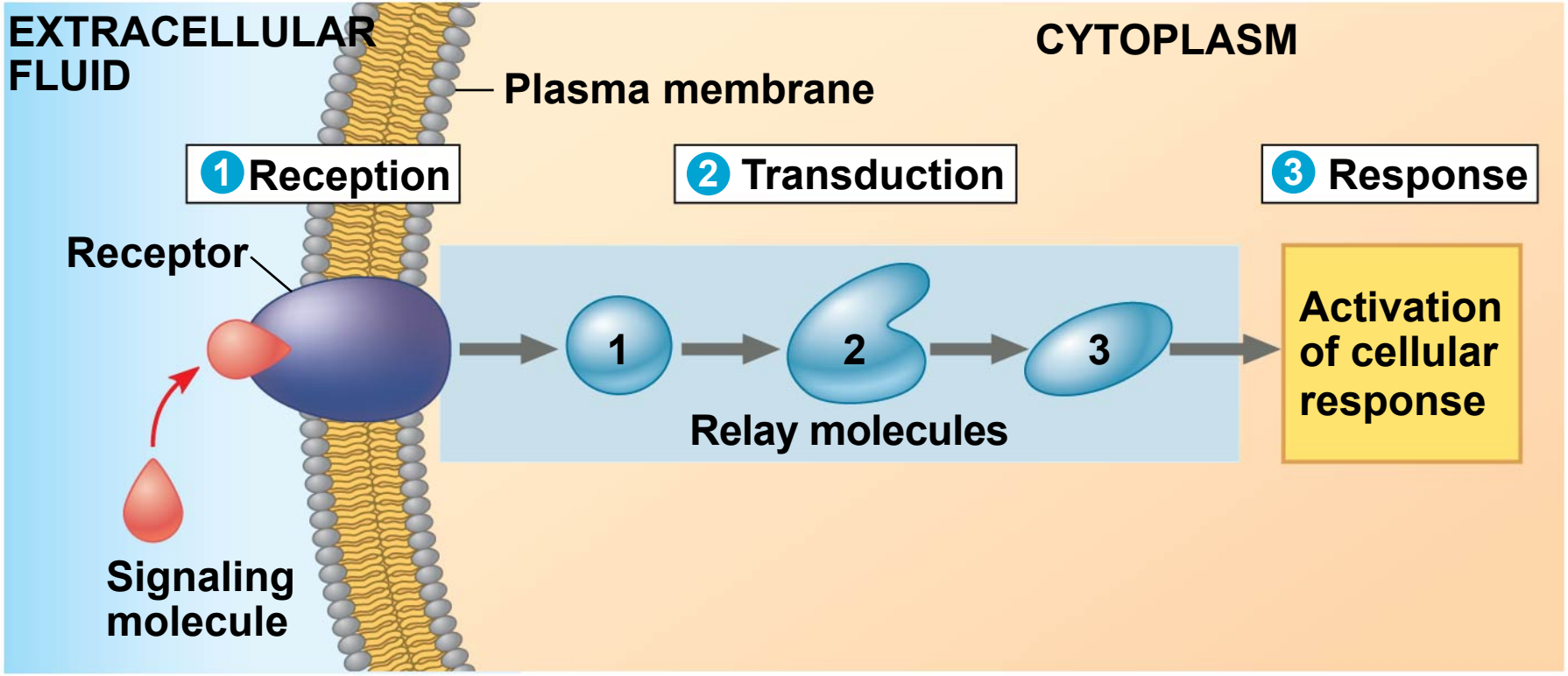
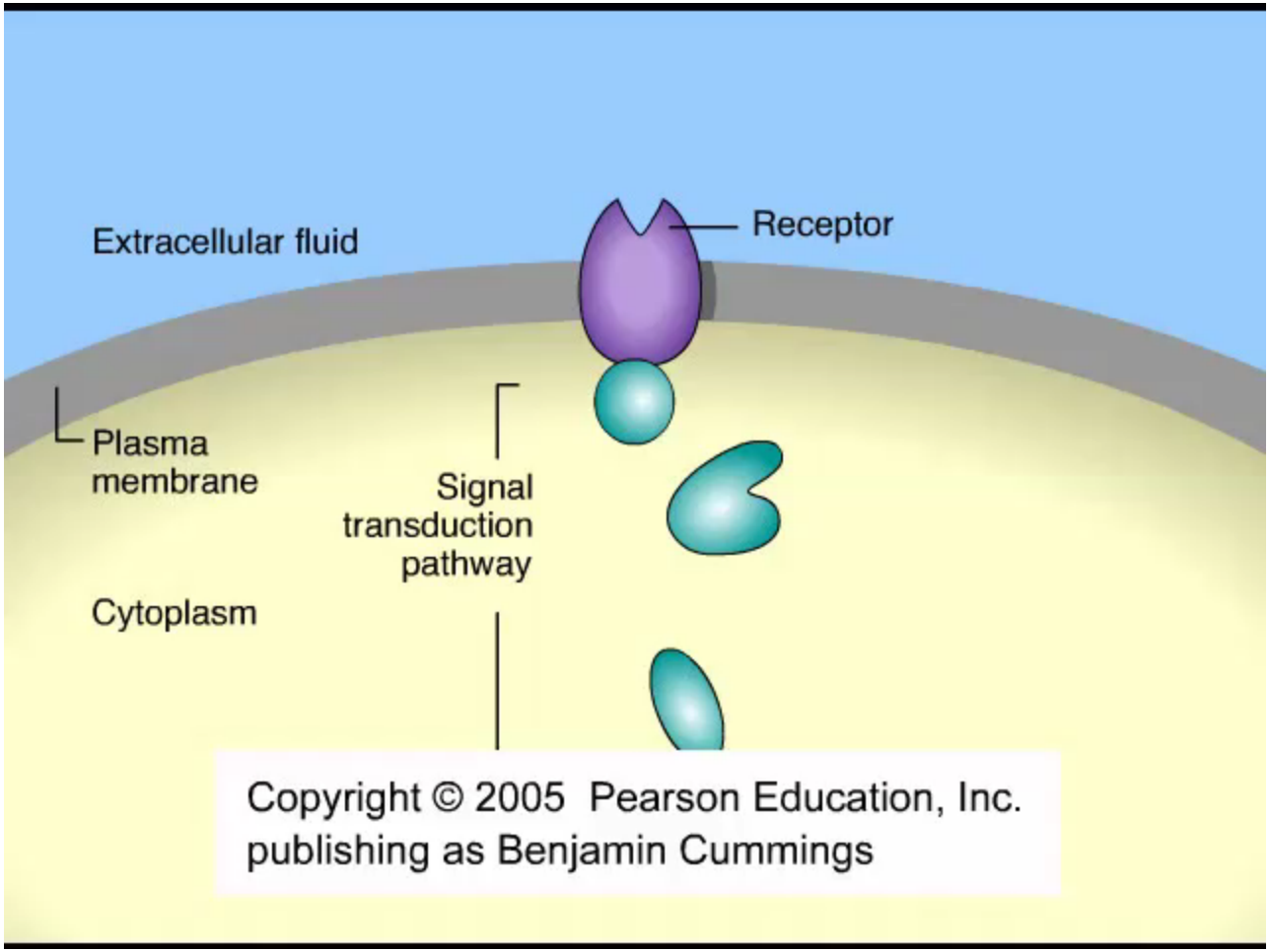


Figure 9.6_3



Animation: Overview of Cell Signaling



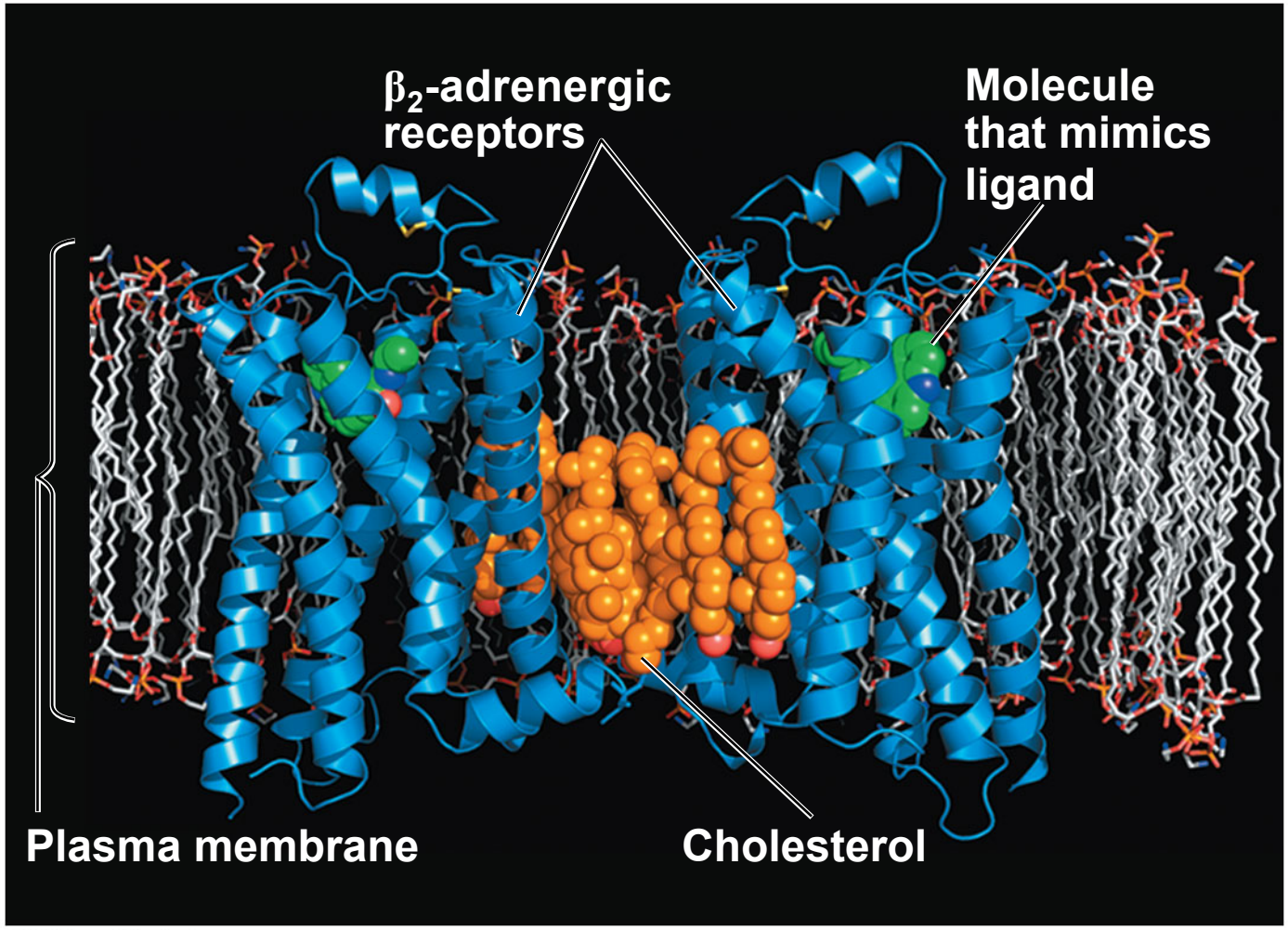
Concept 9.2: Reception: A signaling molecule binds to a receptor protein, causing it to change shape

- 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

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

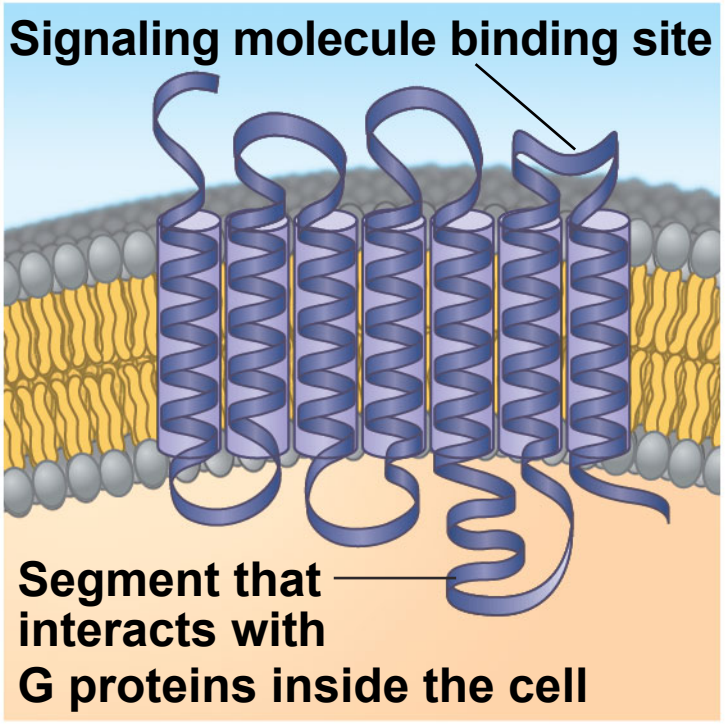
Figure 9.7



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

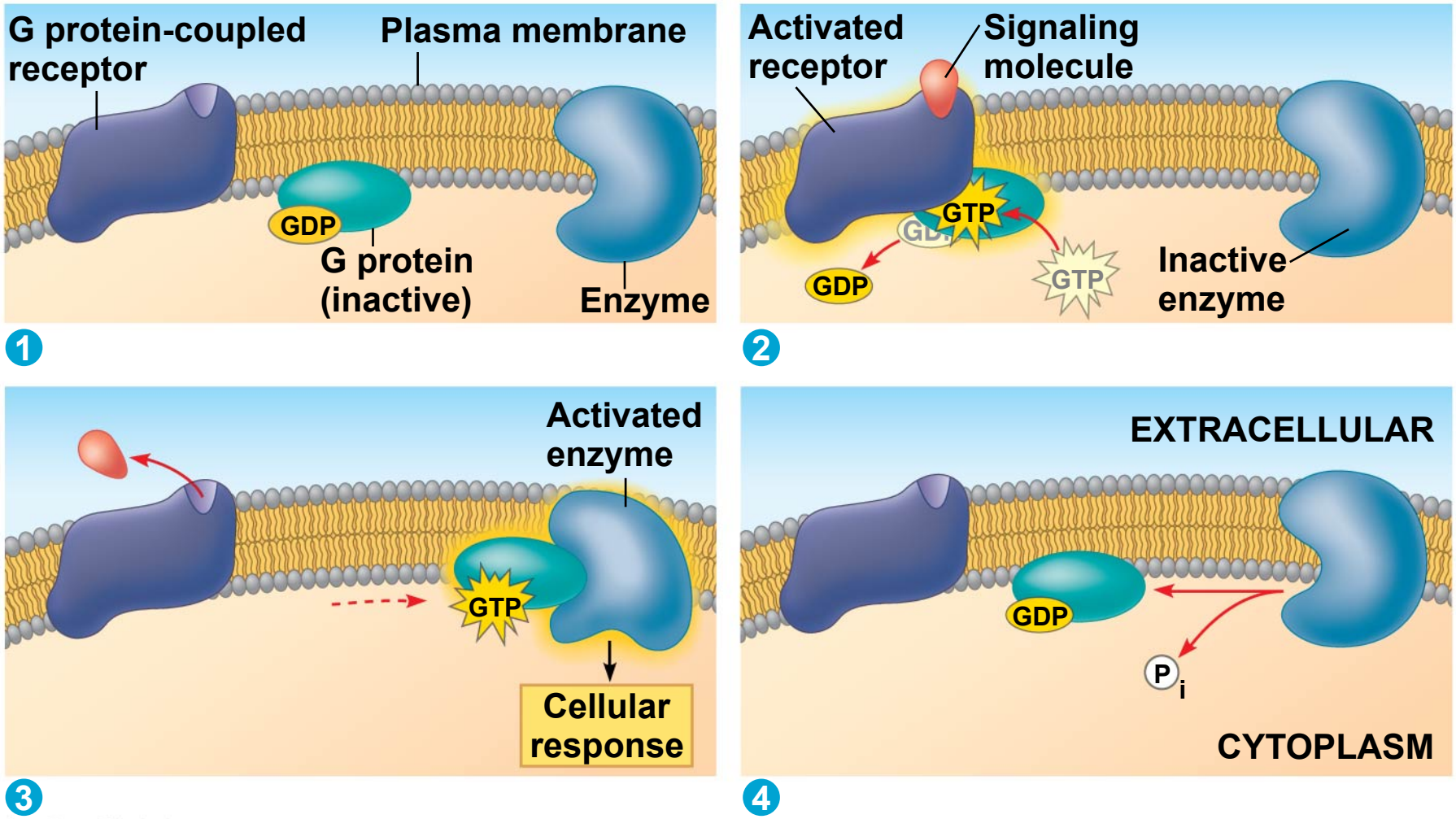
- **G protein-coupled receptors** (GPCRs) are cell-surface transmembrane receptors that work with the help of a **G protein**
- G proteins bind the energy-rich GTP
- G proteins are all very similar in structure
- GPCR systems are extremely widespread and diverse in their functions

Figure 9.8a



- **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

Figure 9.8b



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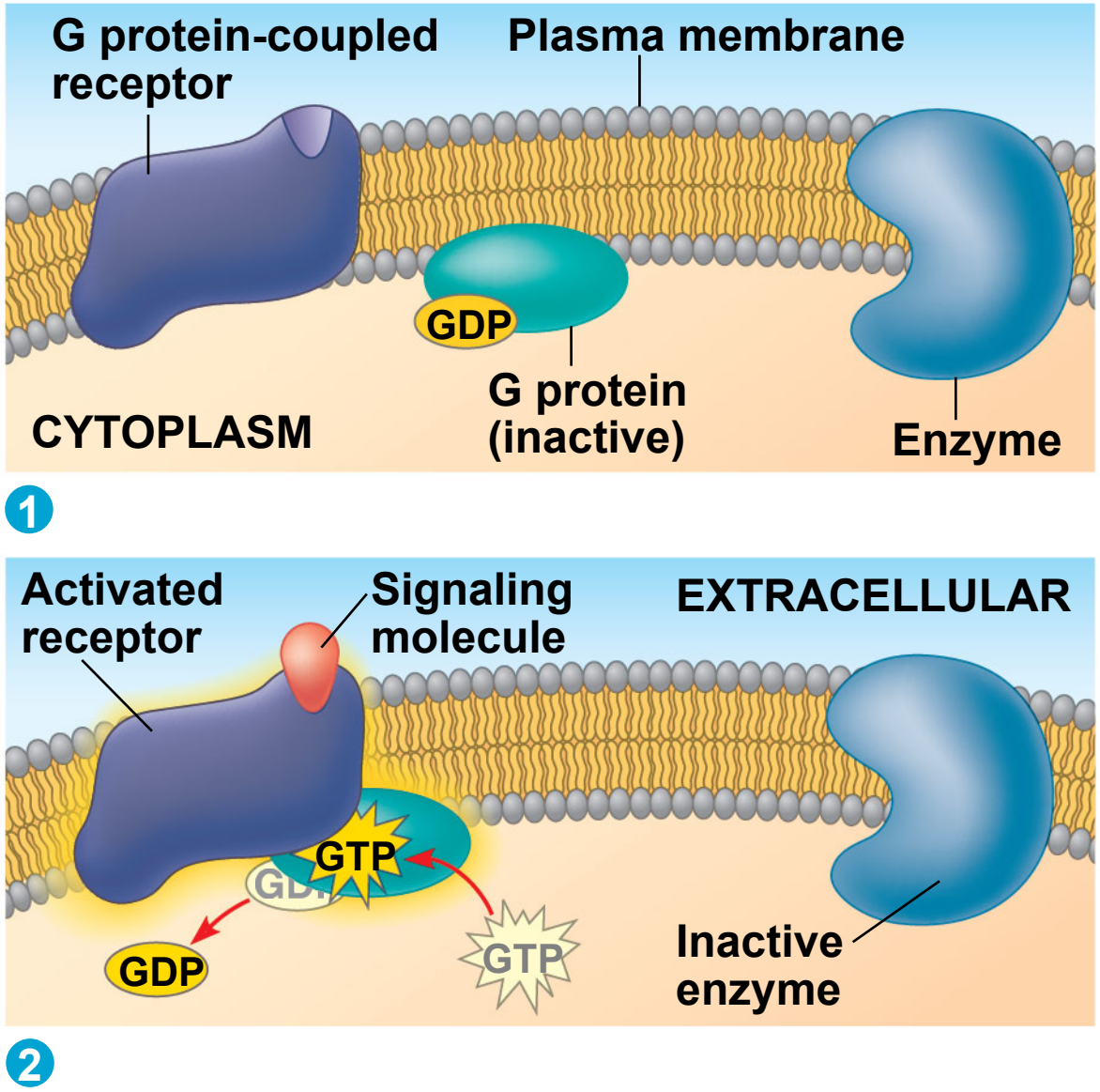

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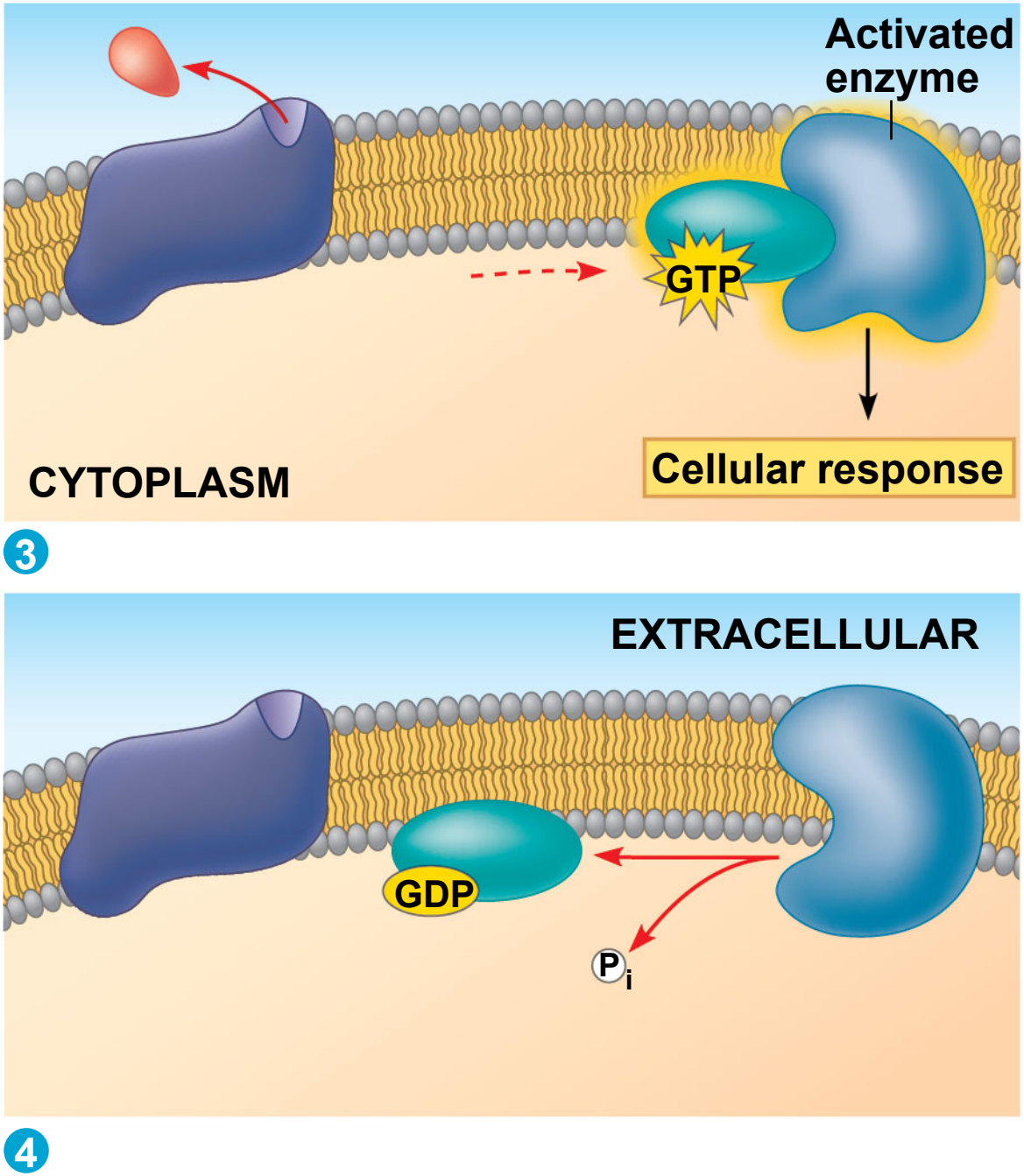
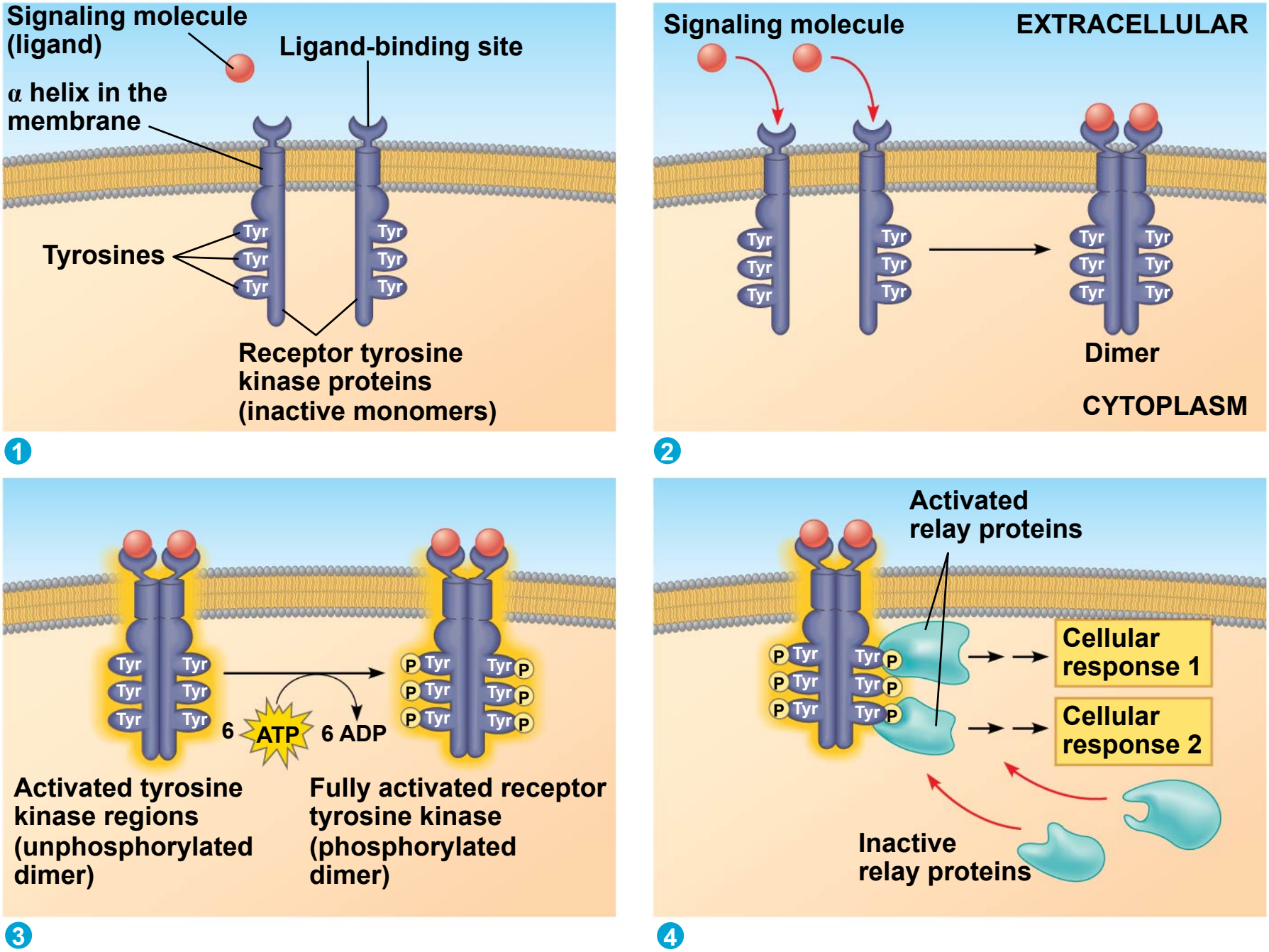


- A **ligand-gated ion channel** receptor acts as a gate that opens and closes when the receptor changes shape
- When a signal molecule binds as a ligand to the receptor, the gate allows specific ions, such as Na^+ or Ca^{2+}, through a channel in the receptor

Figure 9.8c



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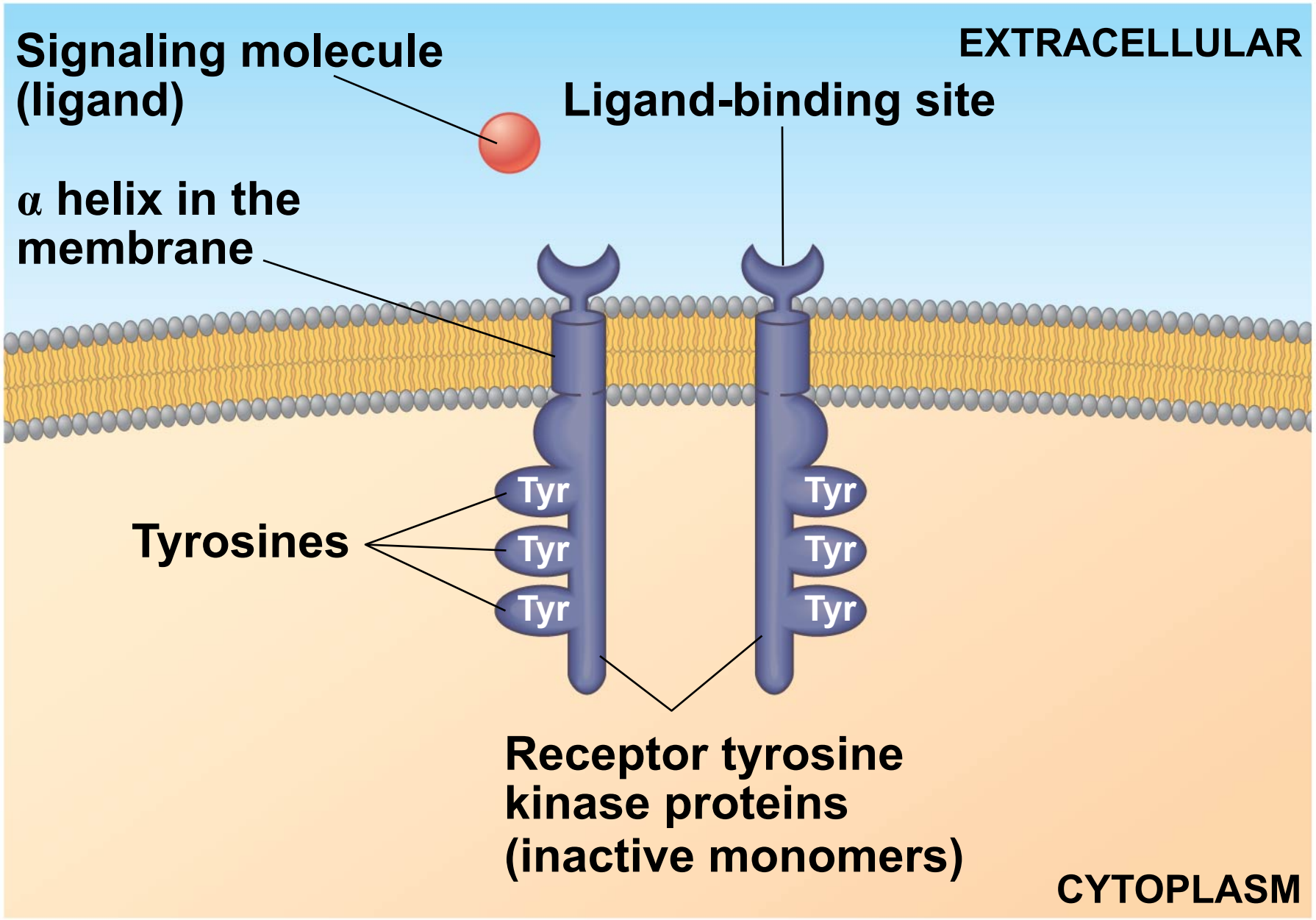

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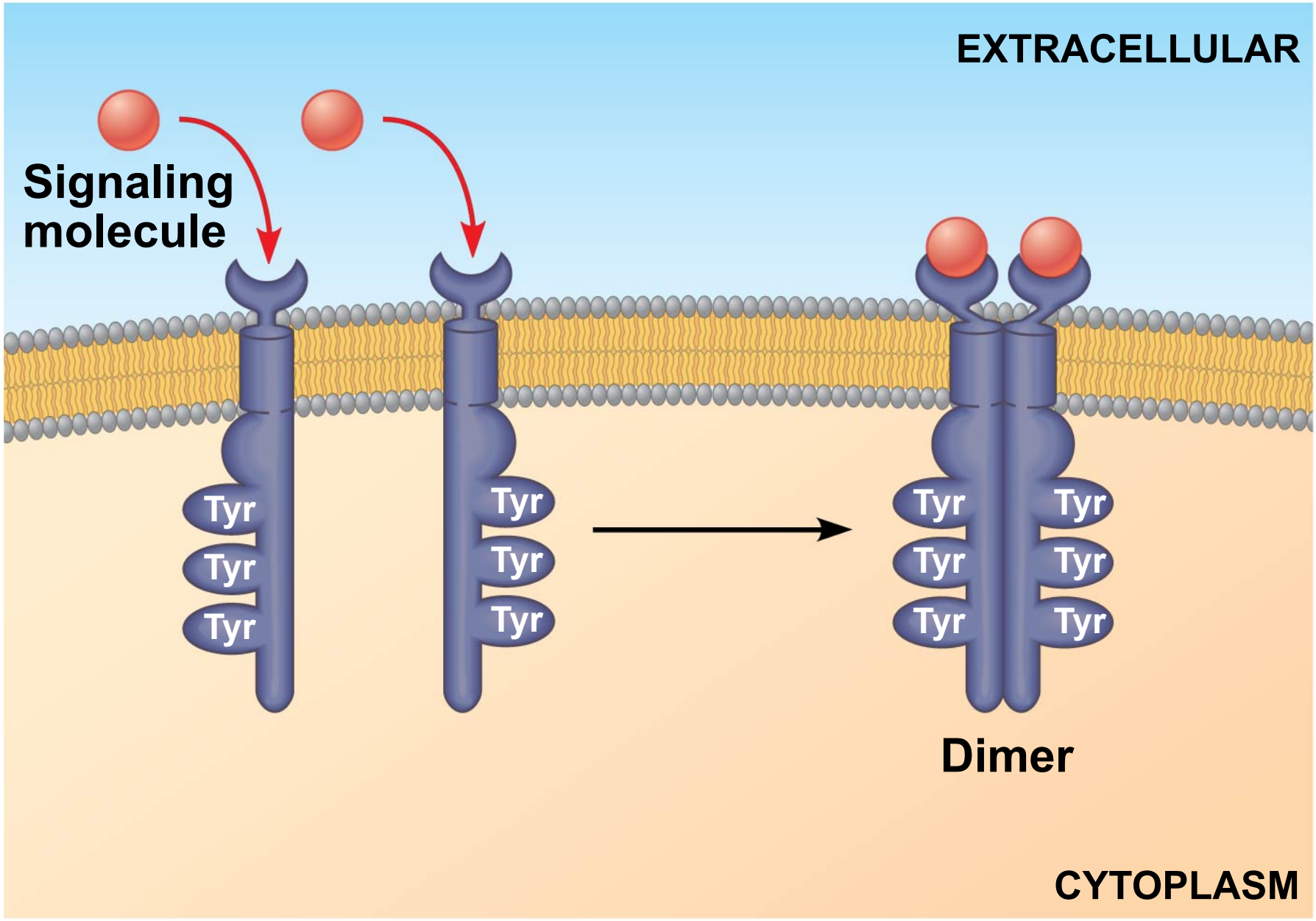

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Figure 9.8cc

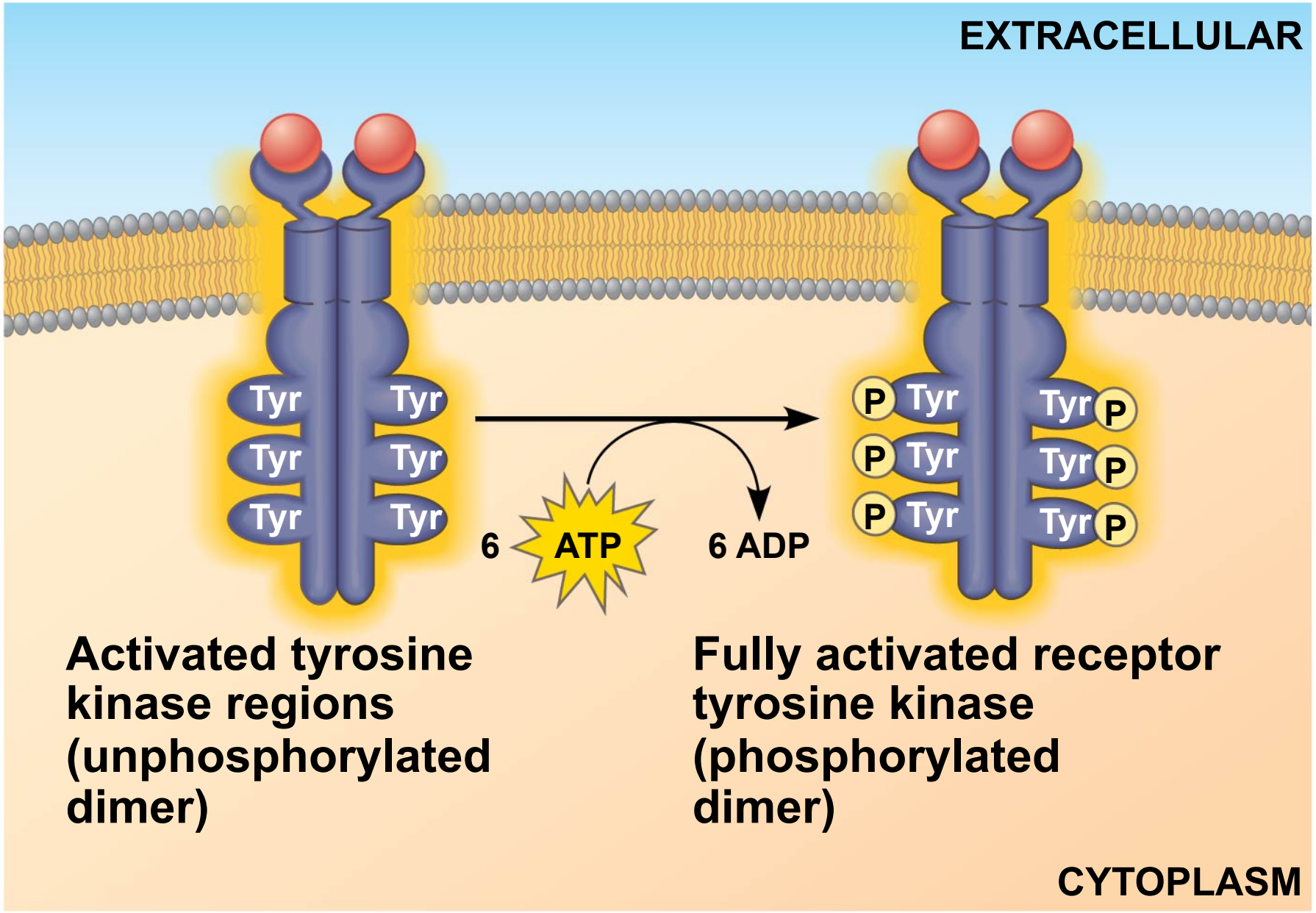

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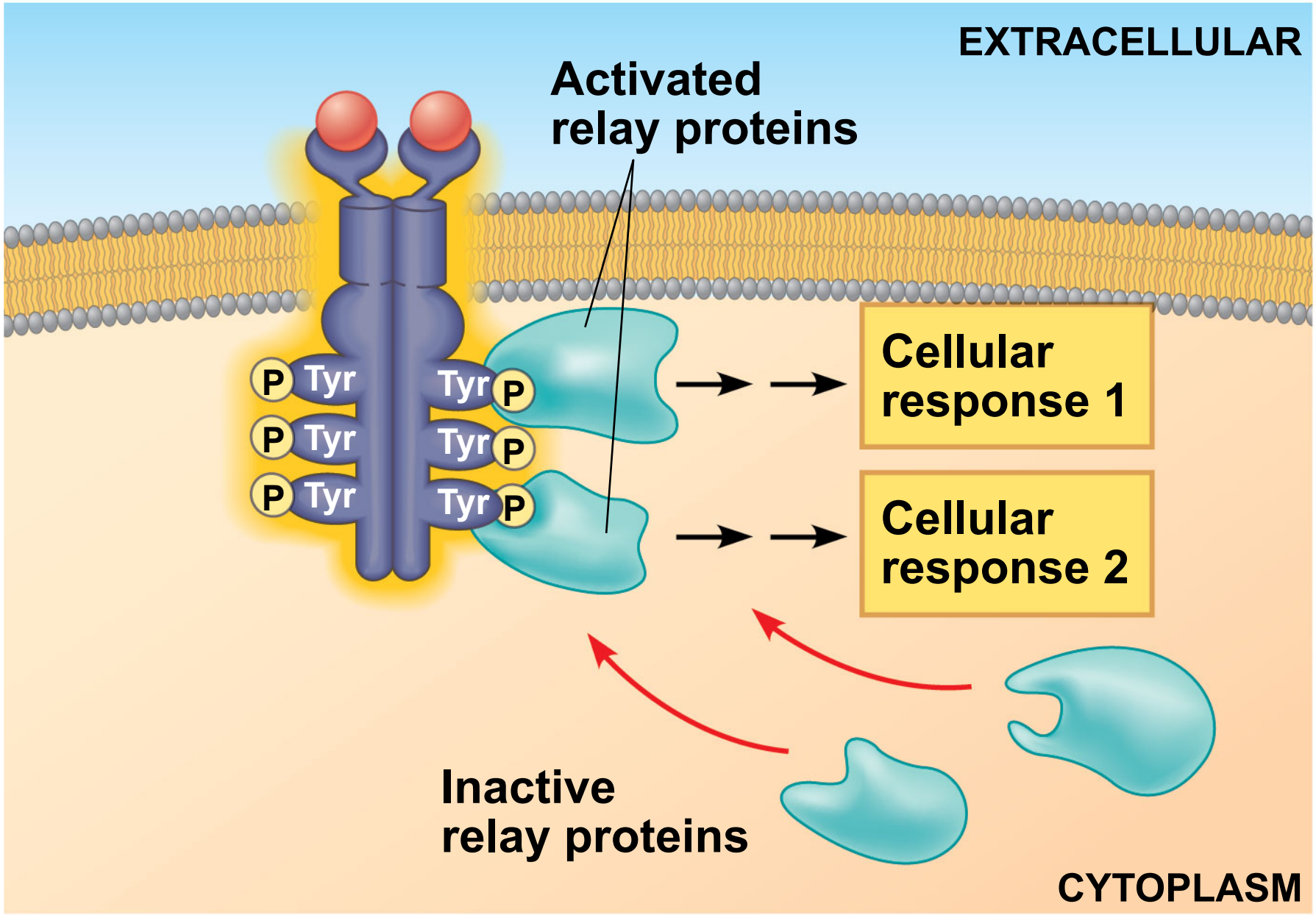
Figure 9.8cd



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

Figure 9.9

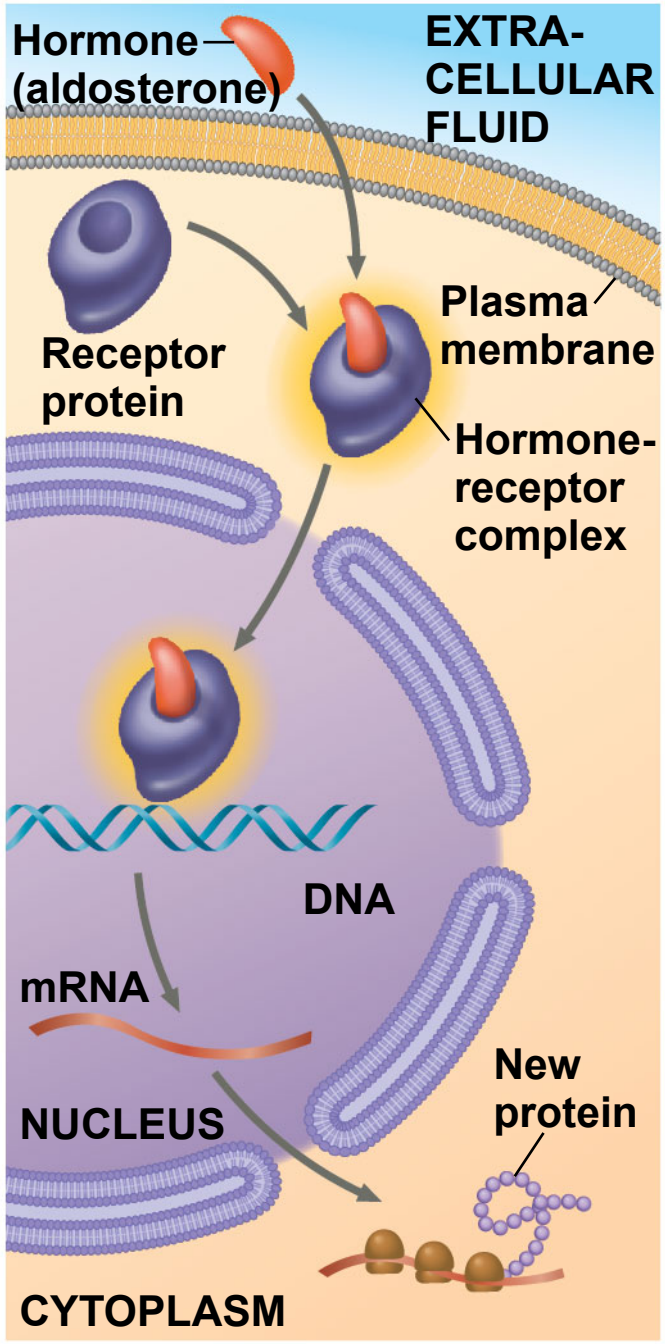


Figure 9.9a

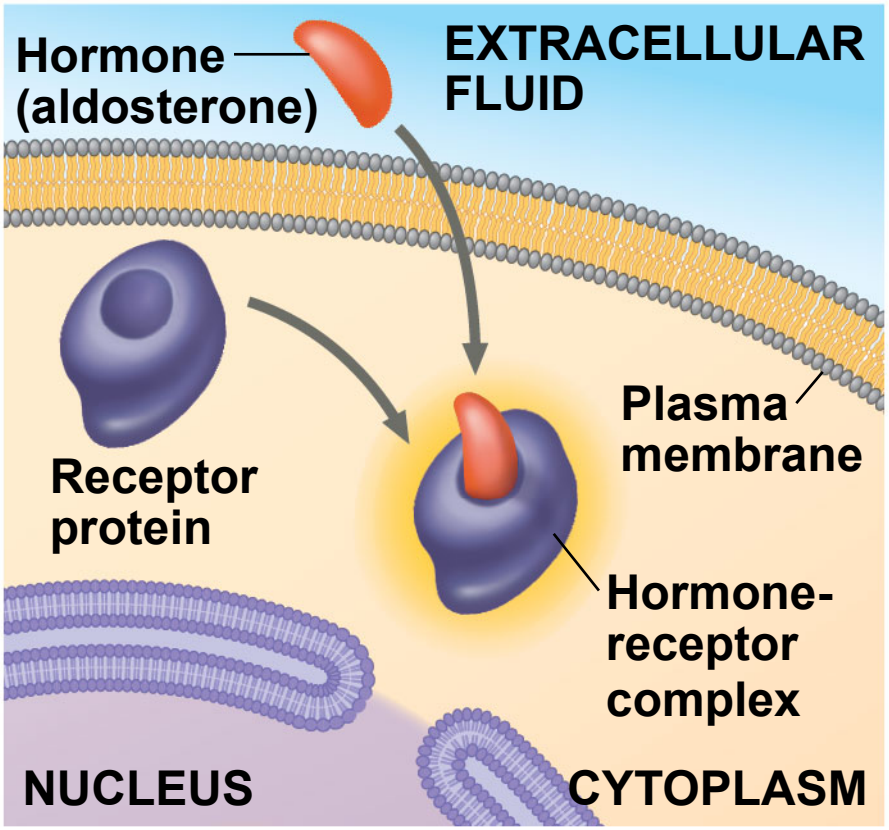
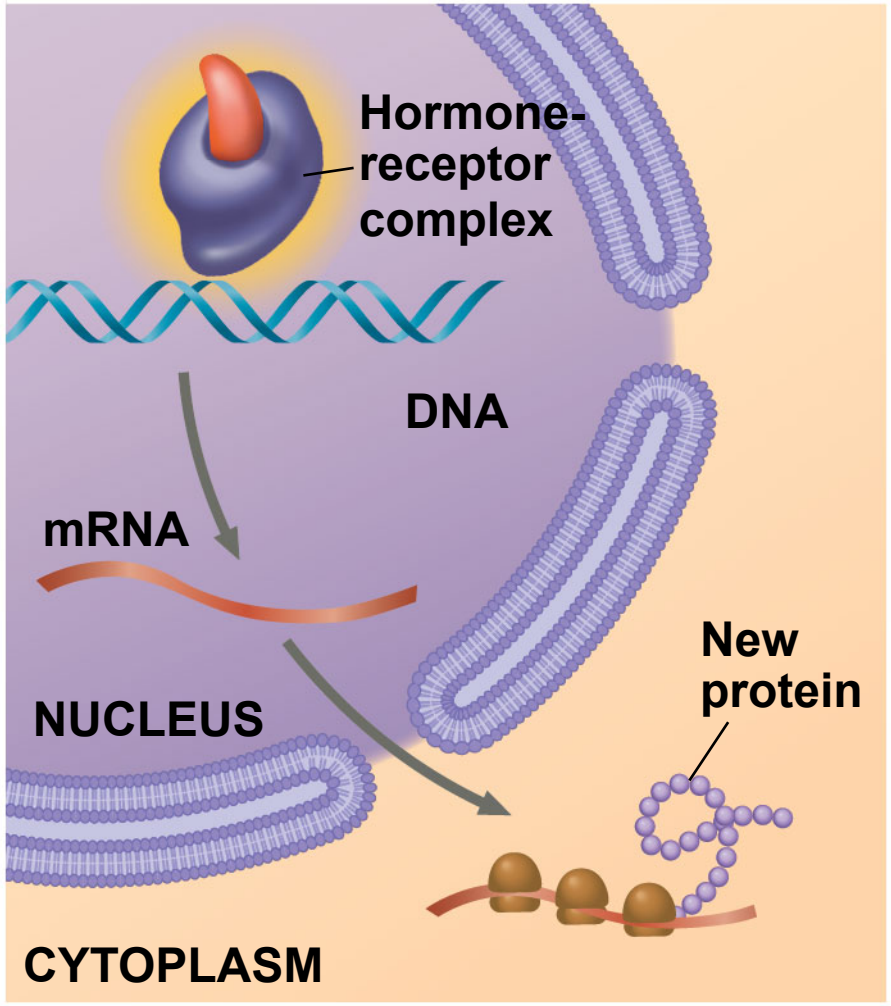


Figure 9.9b



Concept 9.3: 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

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

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**

Figure 9.10

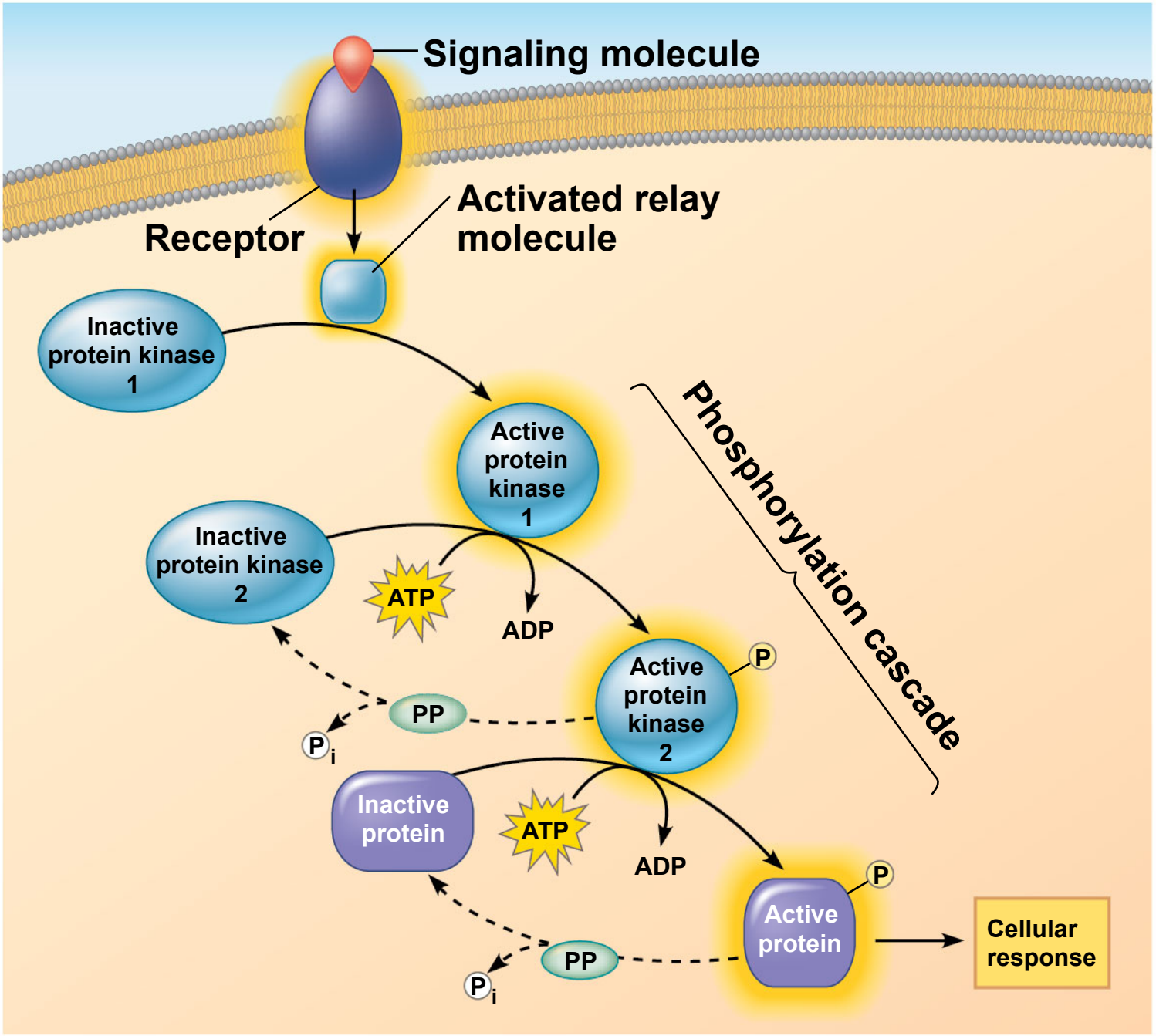


Figure 9.10a

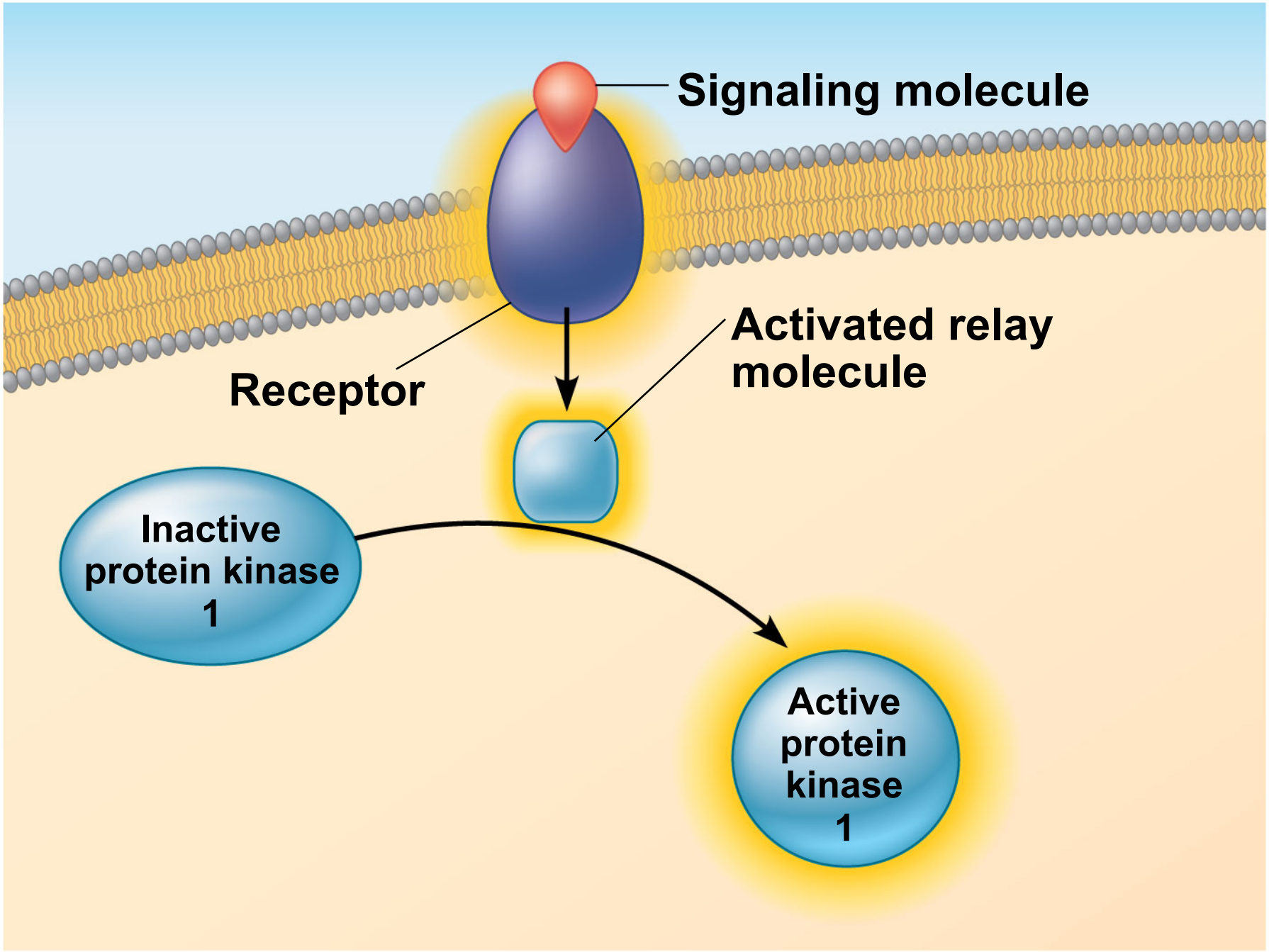


Figure 9.10b

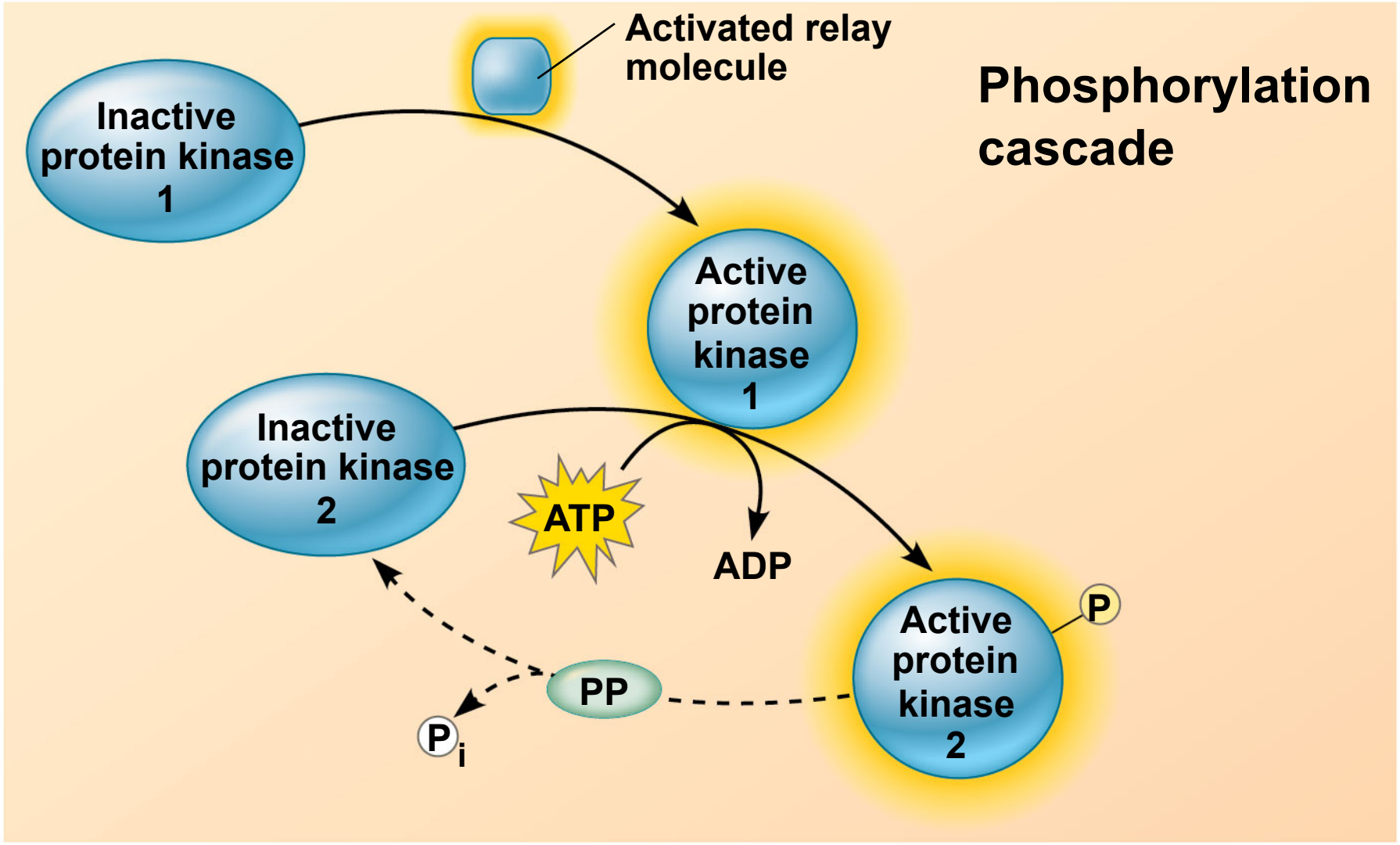
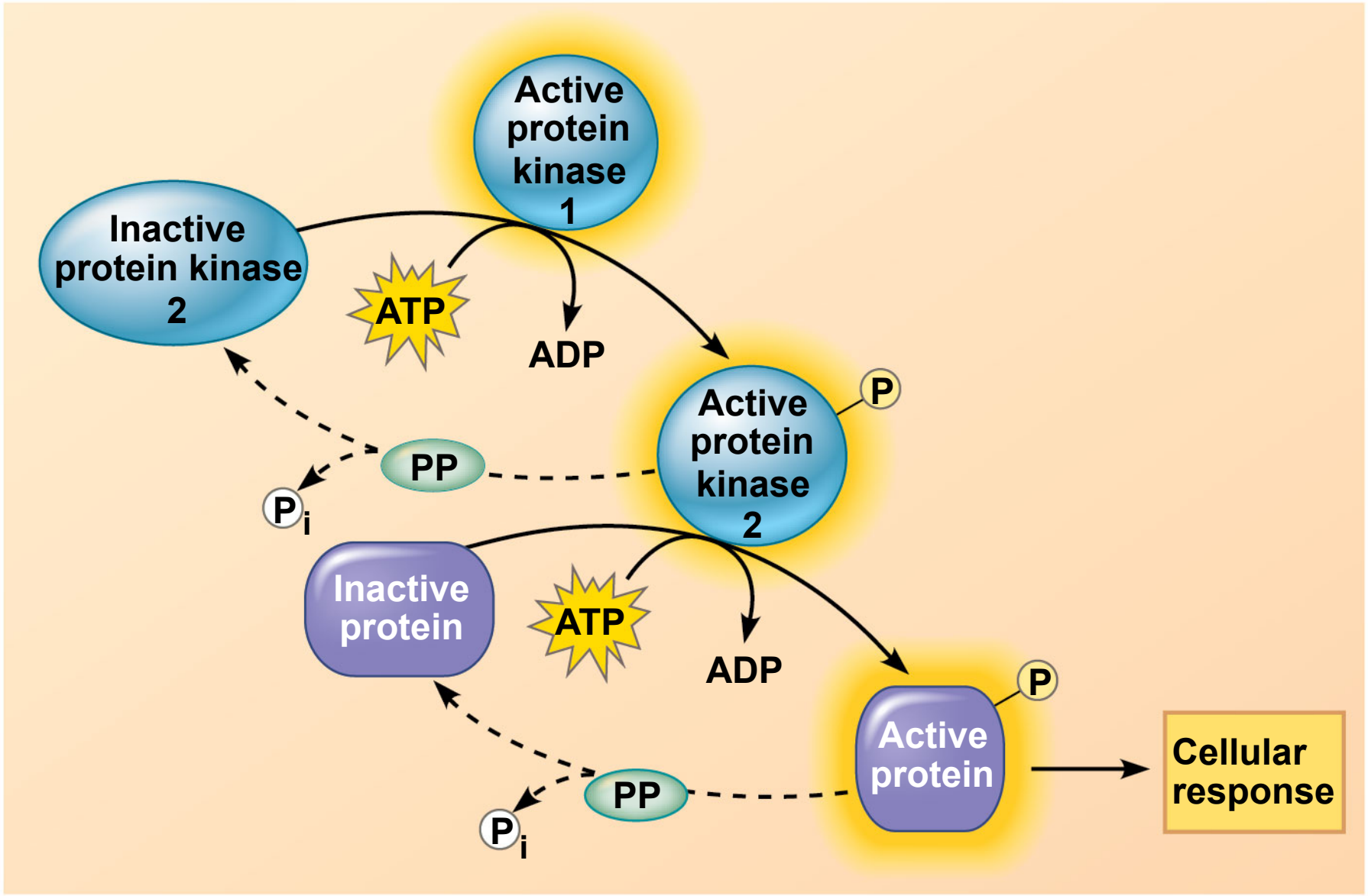


Figure 9.10c



- **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

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

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

Figure 9.11

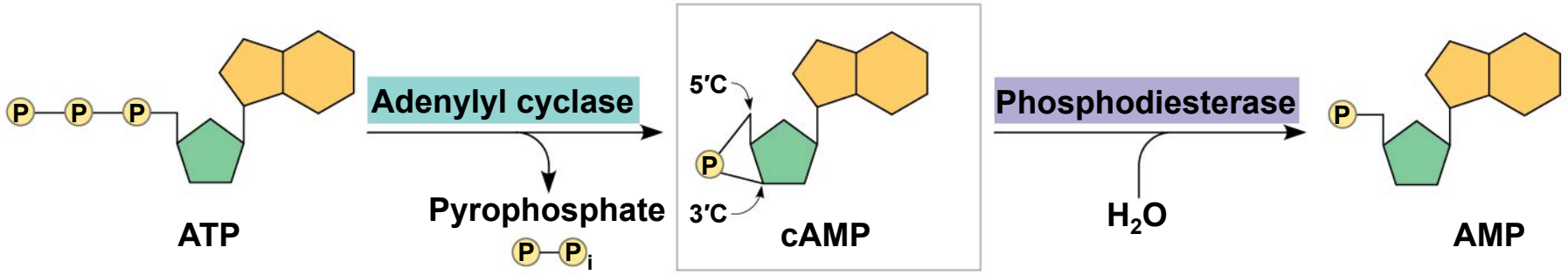


Figure 9.11a

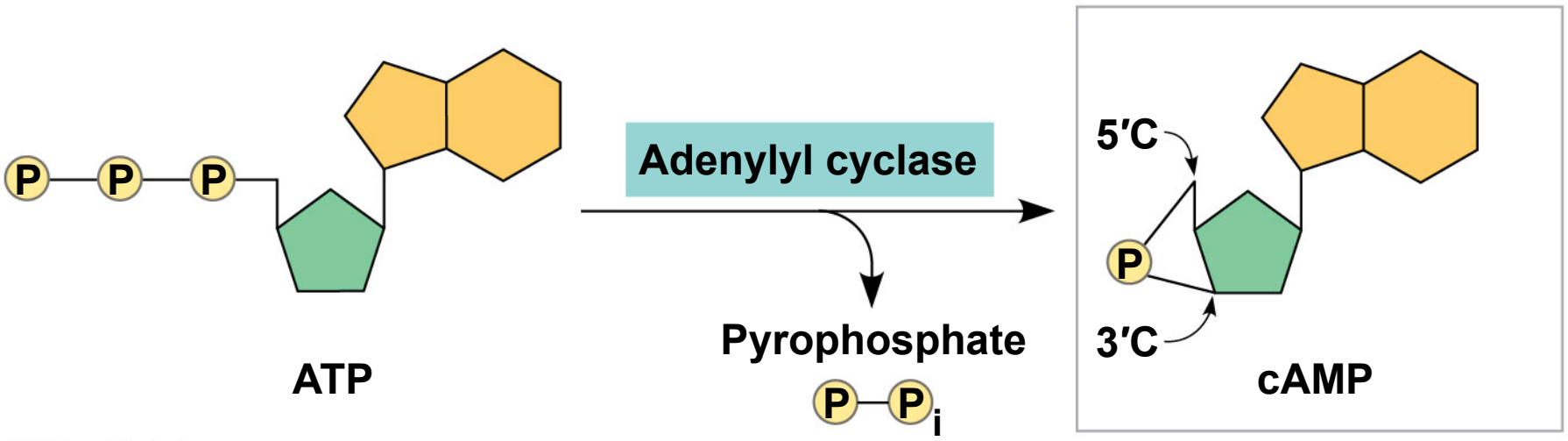
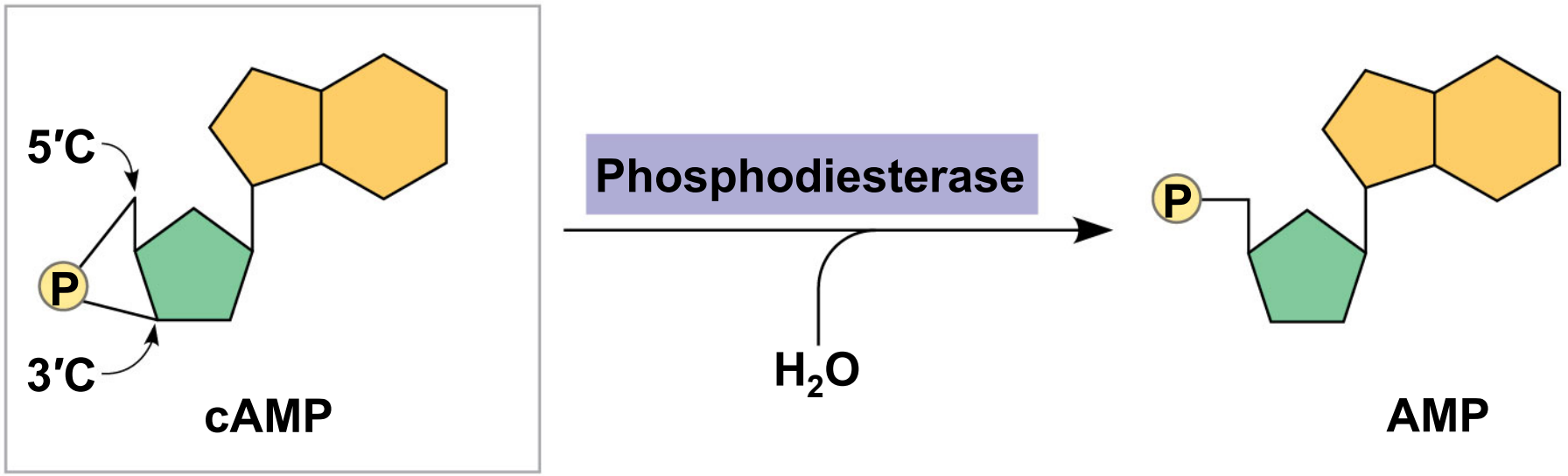
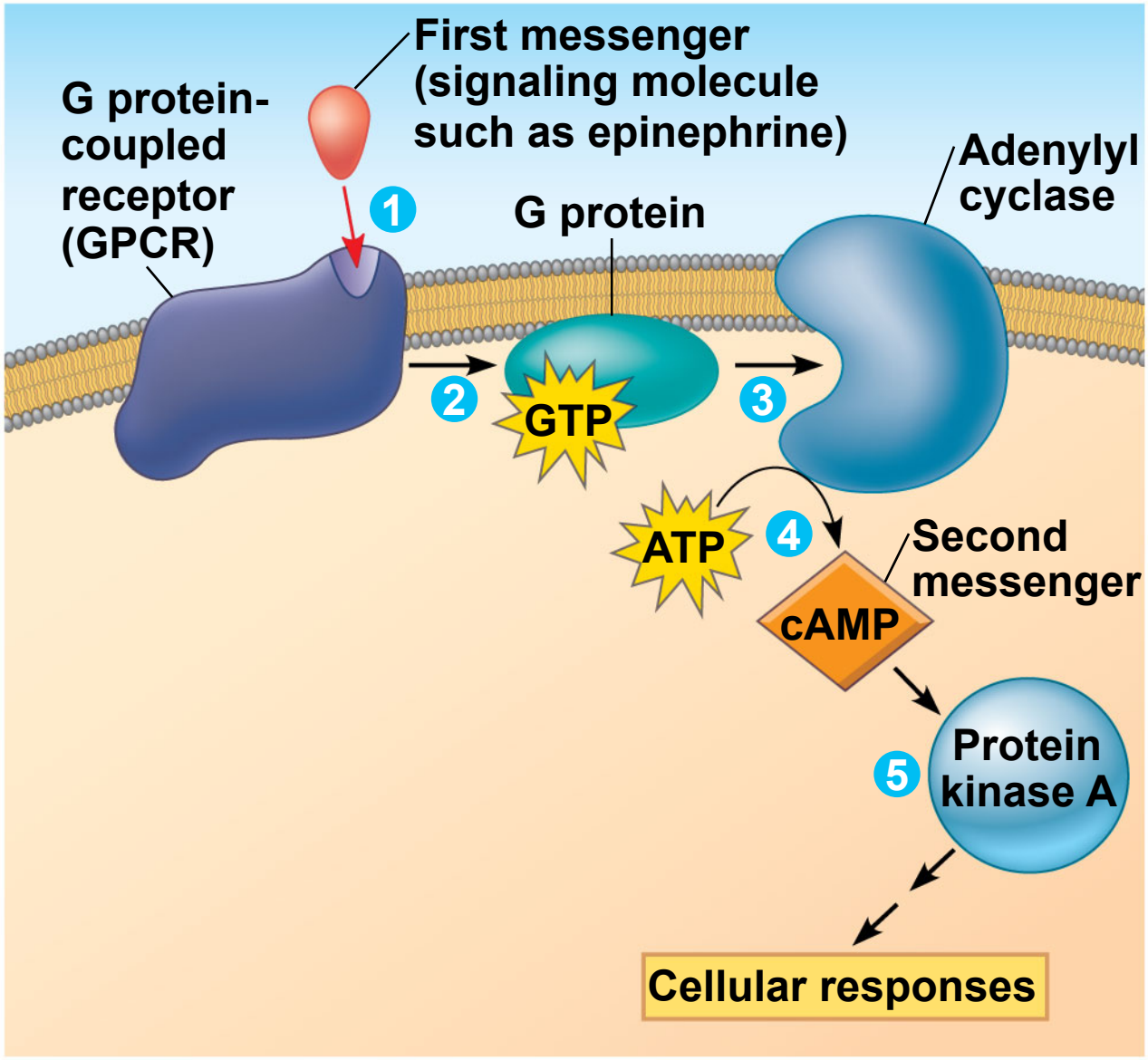


Figure 9.11b



- 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

Figure 9.12

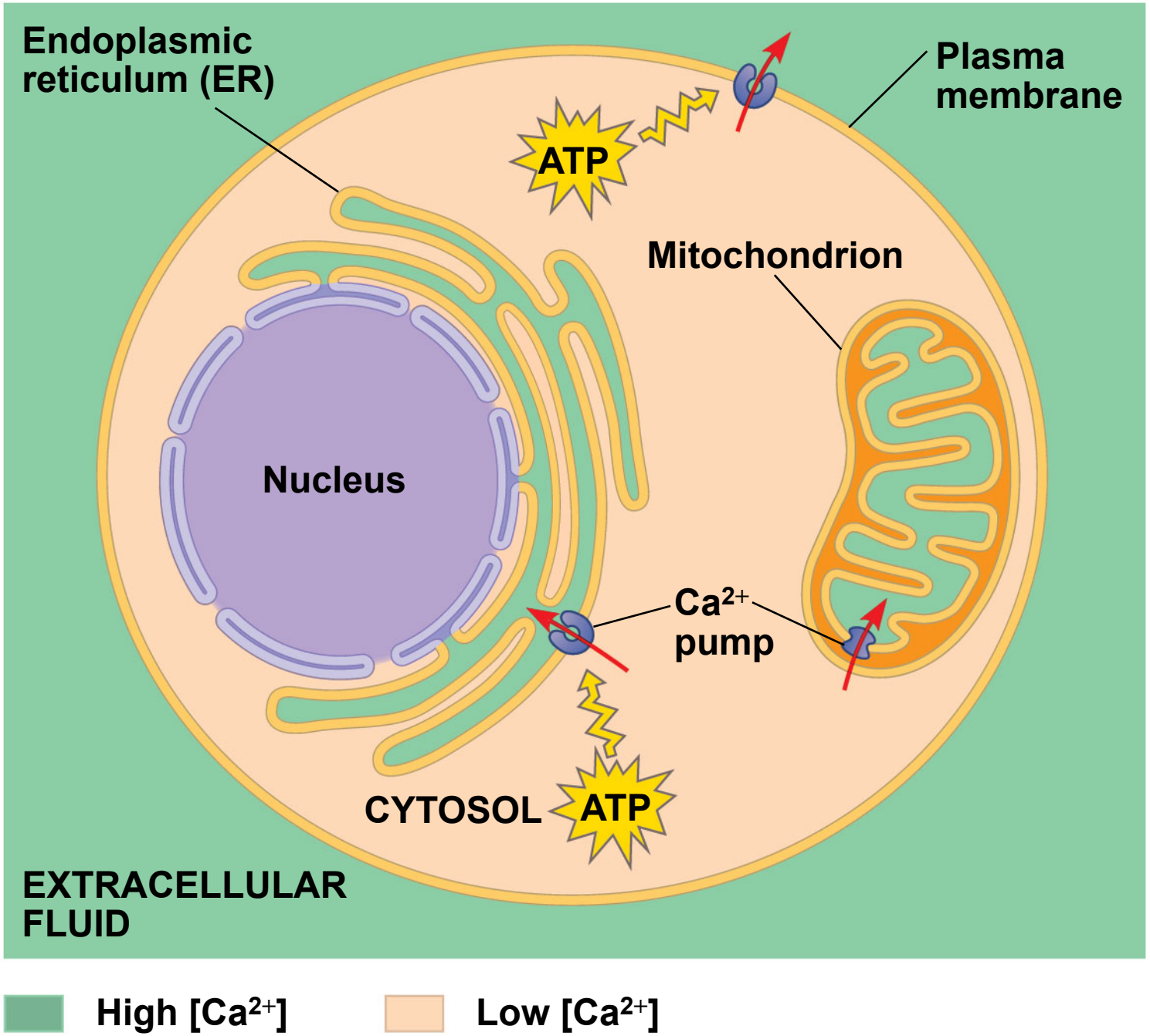


- Understanding of the role of cAMP in G protein signaling pathways helps explain how certain microbes cause disease
- The cholera bacterium, *Vibrio cholerae*, produces a toxin that modifies a G protein so that it is stuck in its active form
- This protein continually makes cAMP, causing intestinal 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

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

Figure 9.13



- 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

Figure 9.14_1

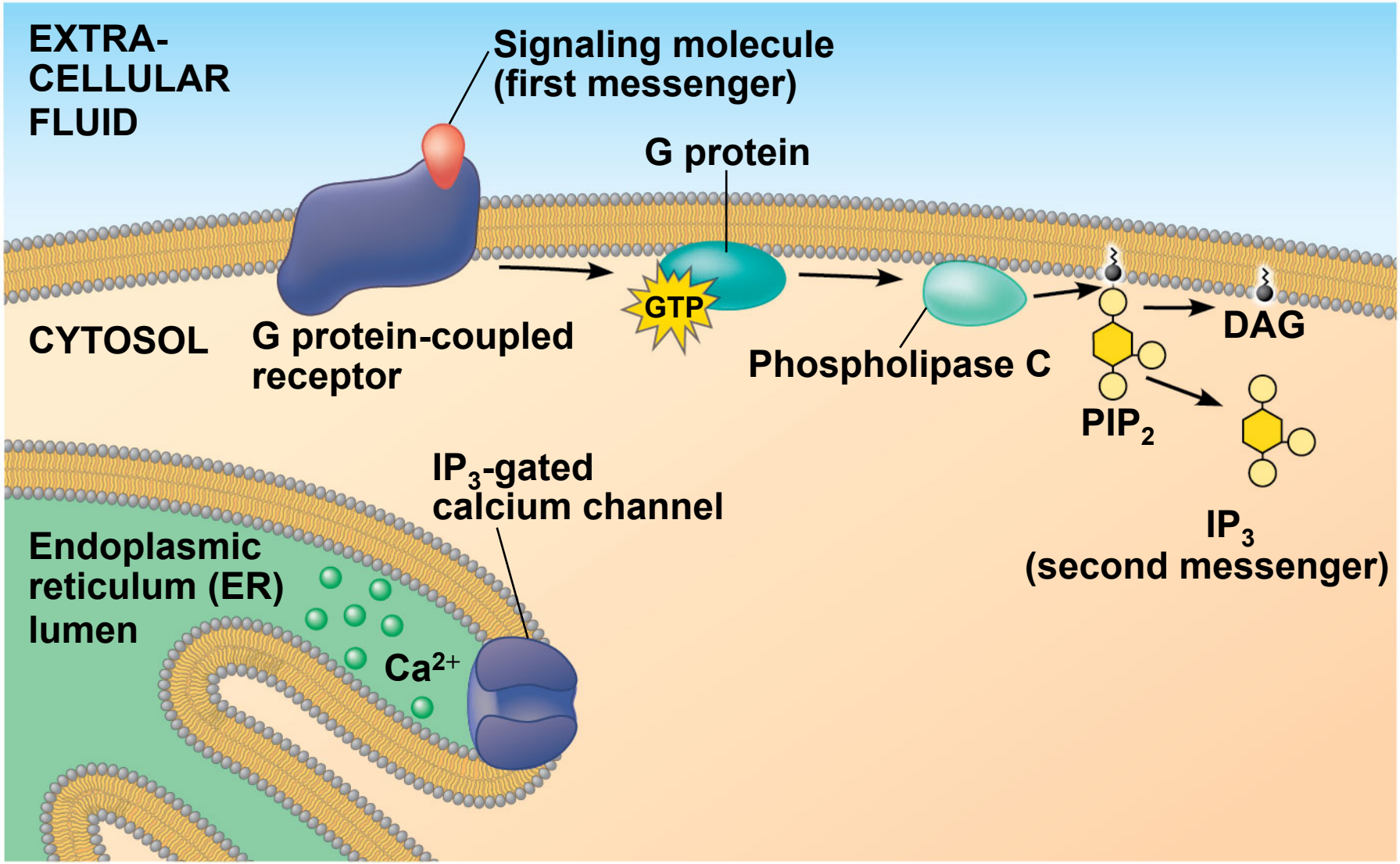


Figure 9.14_2

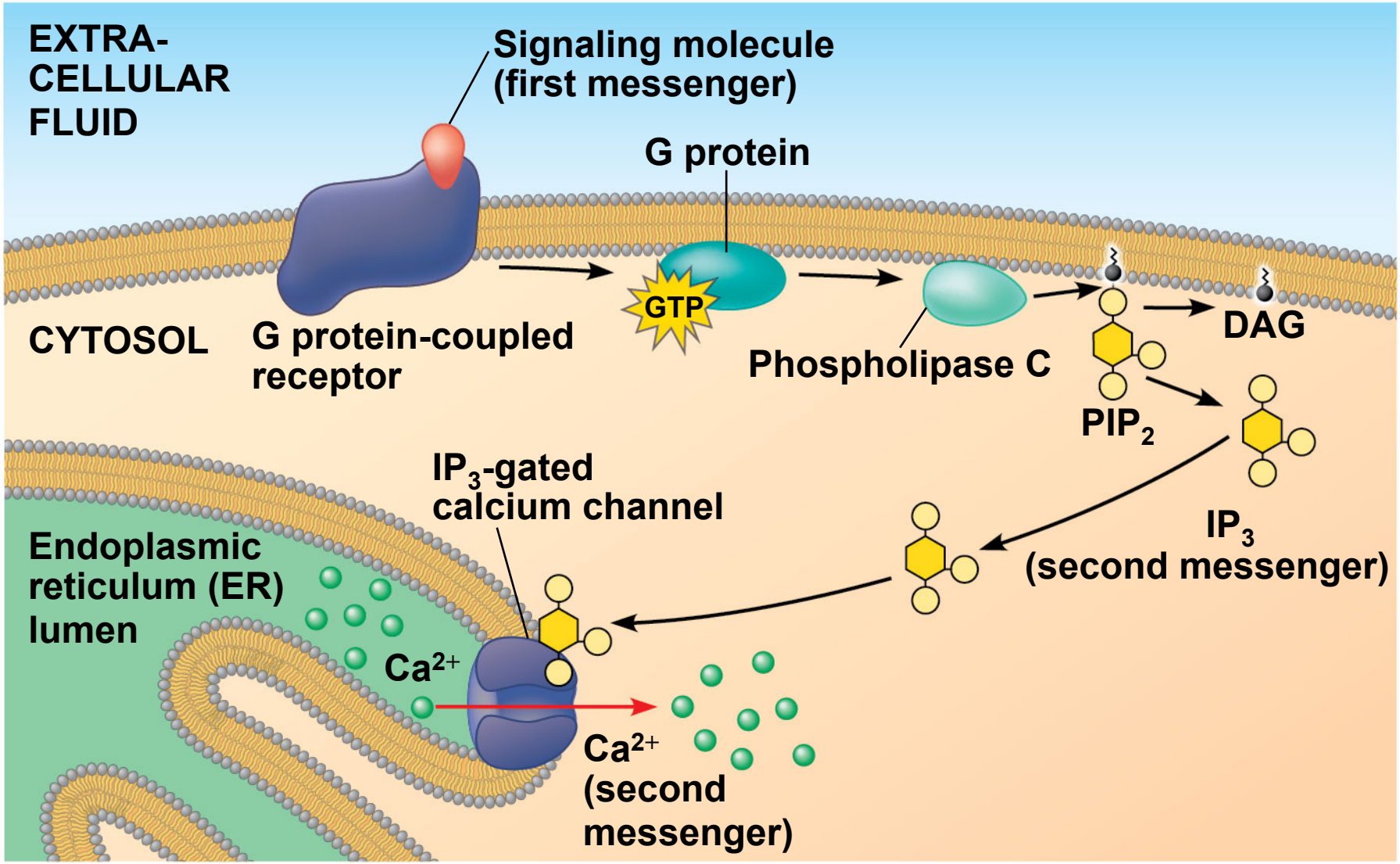
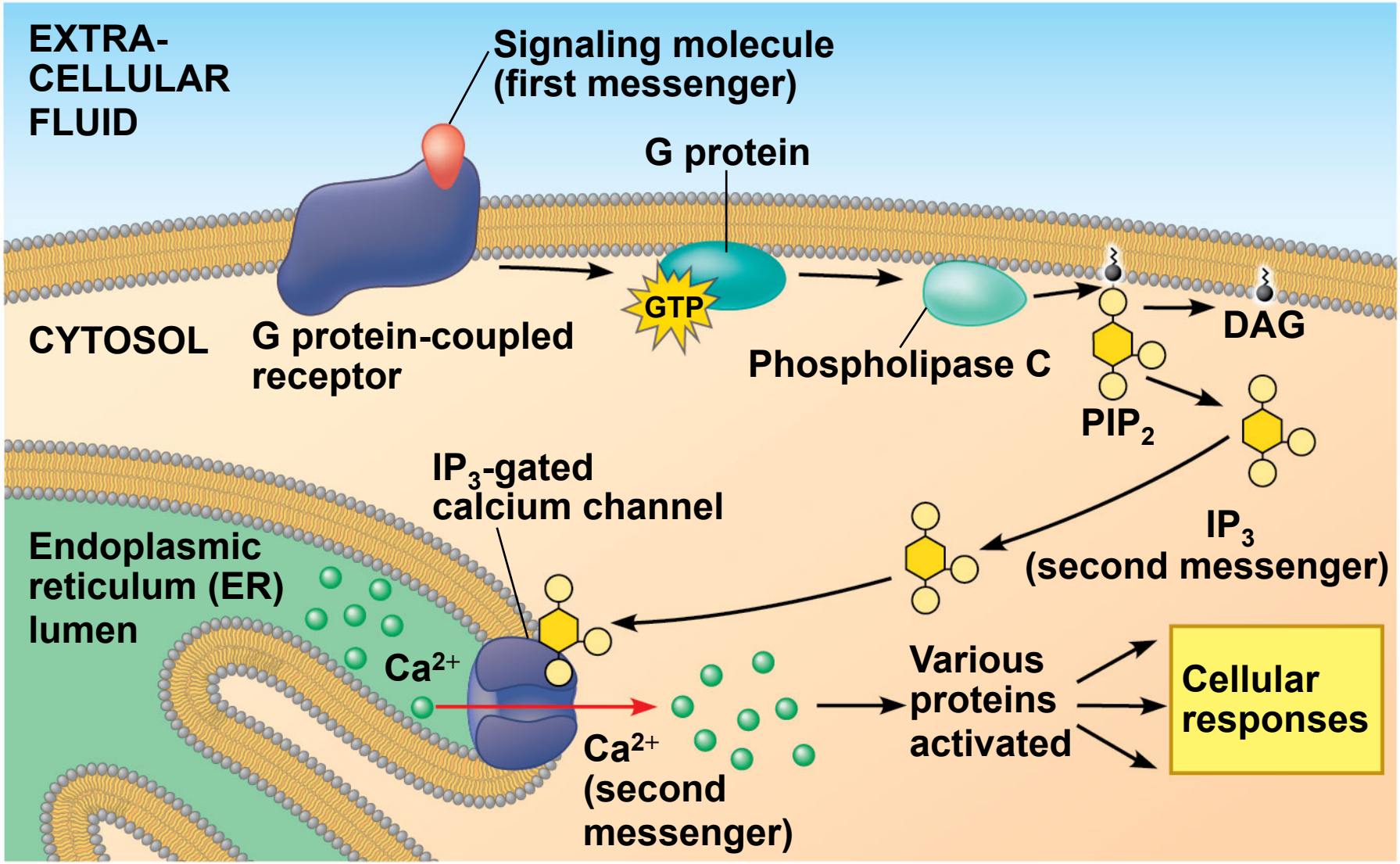
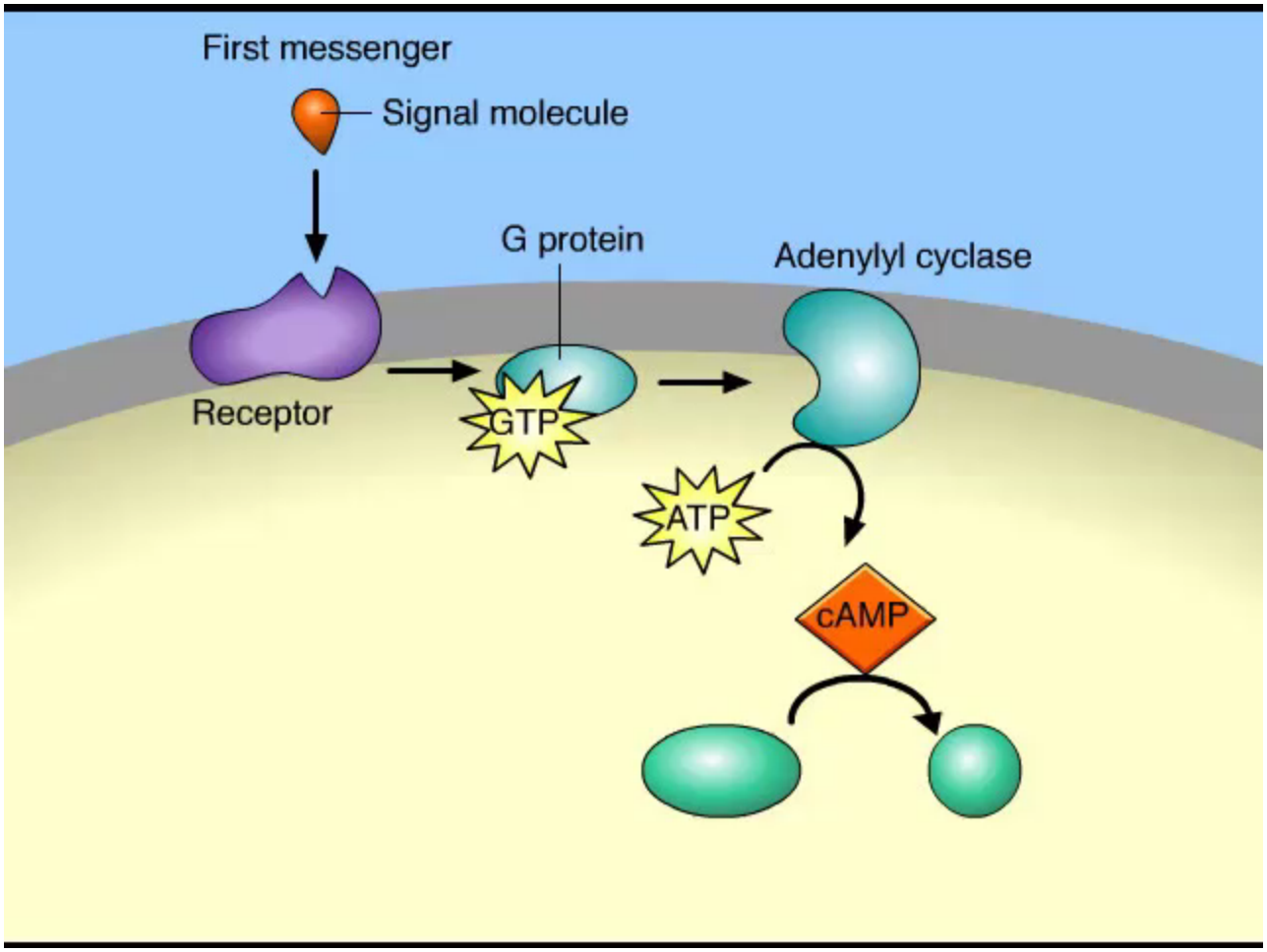


Figure 9.14_3



Animation: Signal Transduction Pathways



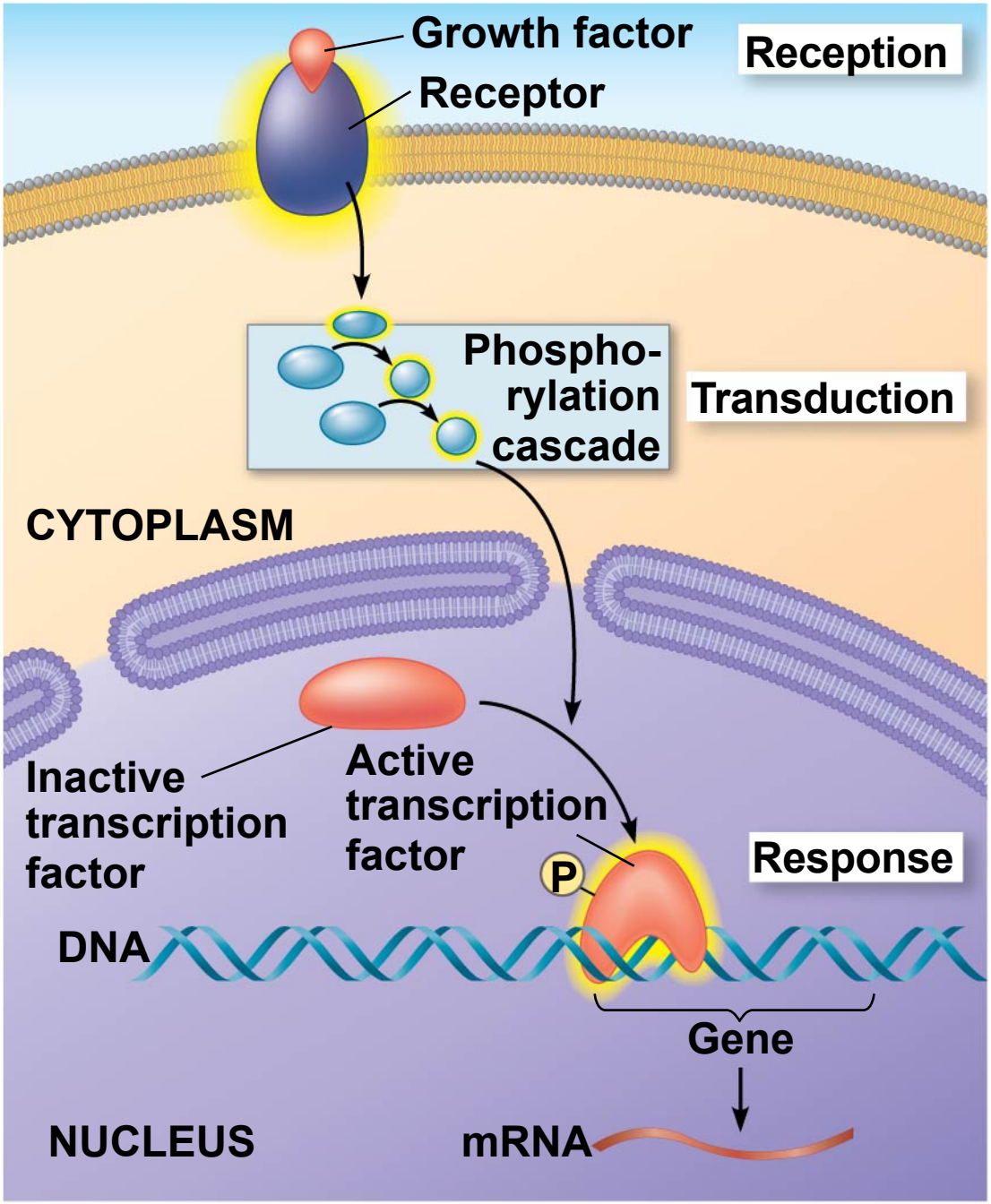
Concept 9.4: Response: Cell signaling leads to regulation of transcription or cytoplasmic activities

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

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

Figure 9.15



- 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

Figure 9.16

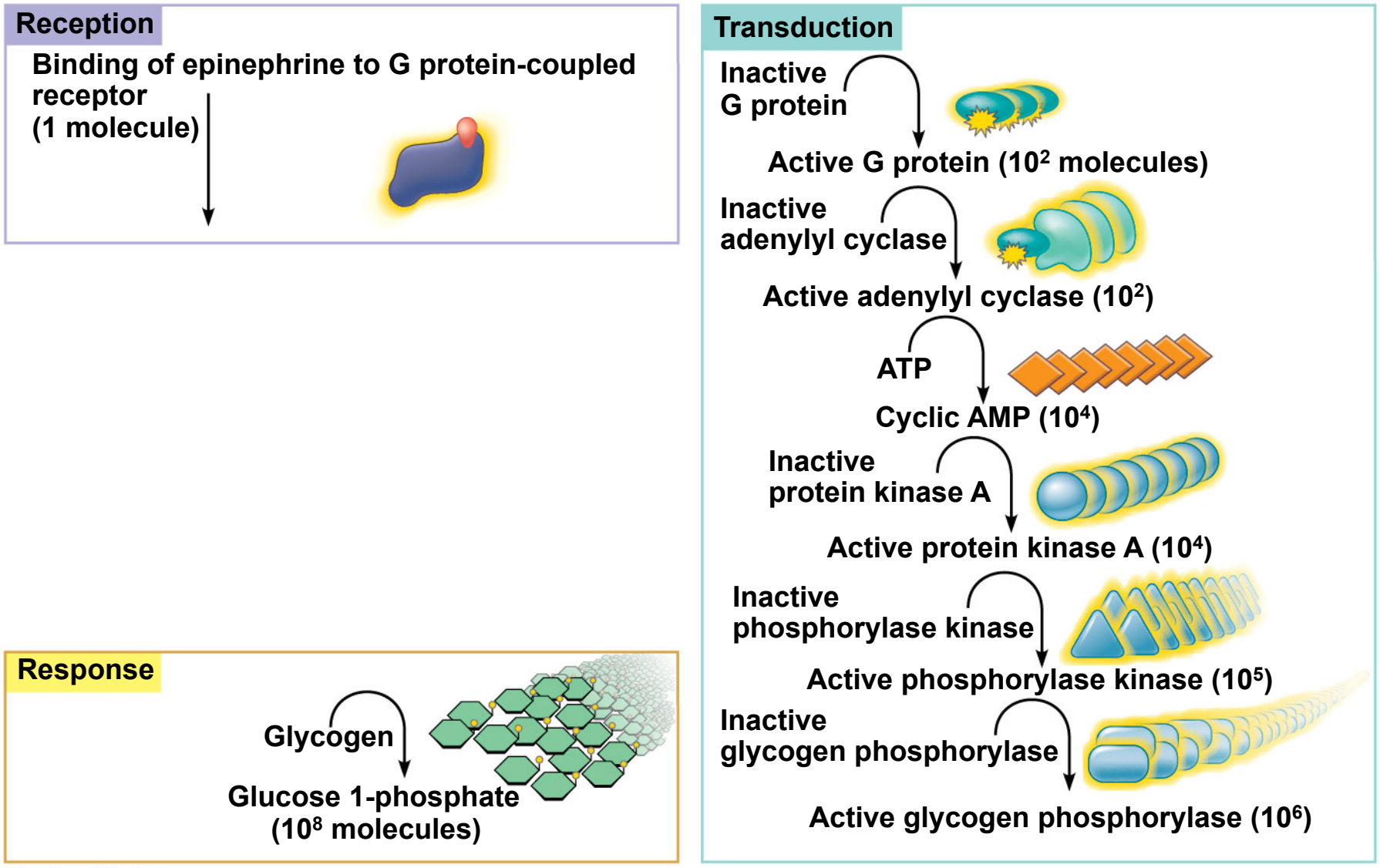
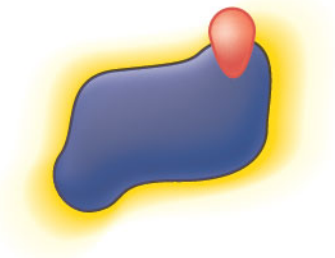


Figure 9.16a

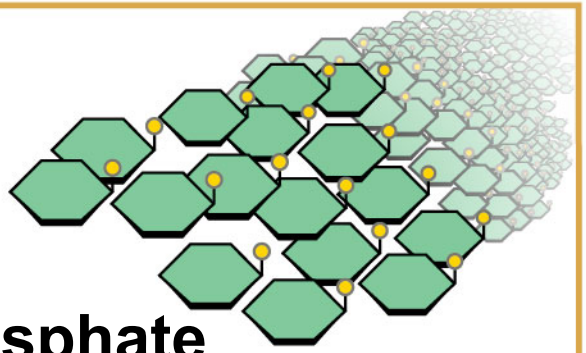
Reception

Binding of epinephrine to G protein-coupled receptor
(1 molecule)



Response

Glycogen



Glucose 1-phosphate
(10^8 molecules)

Figure 9.16b

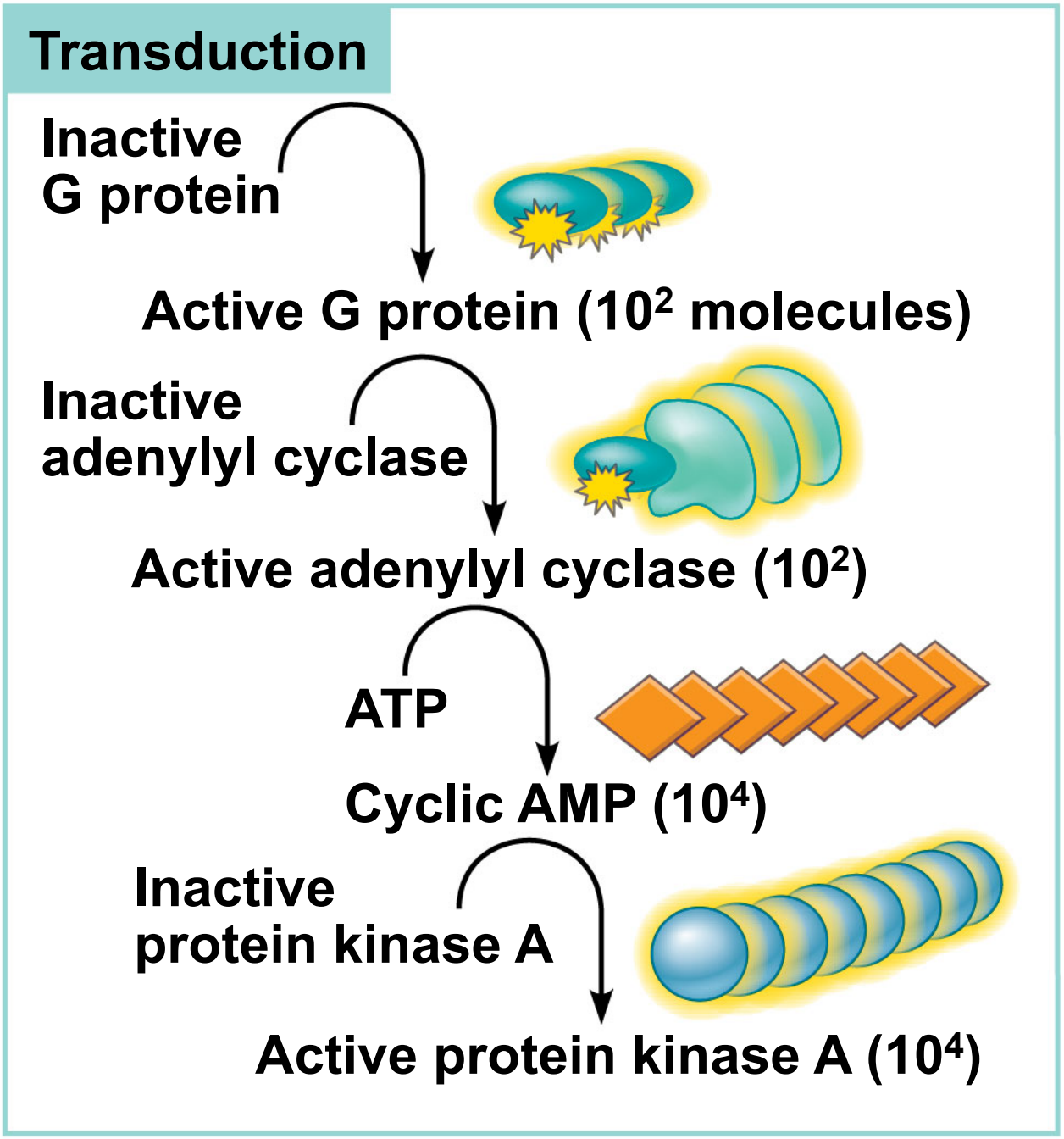
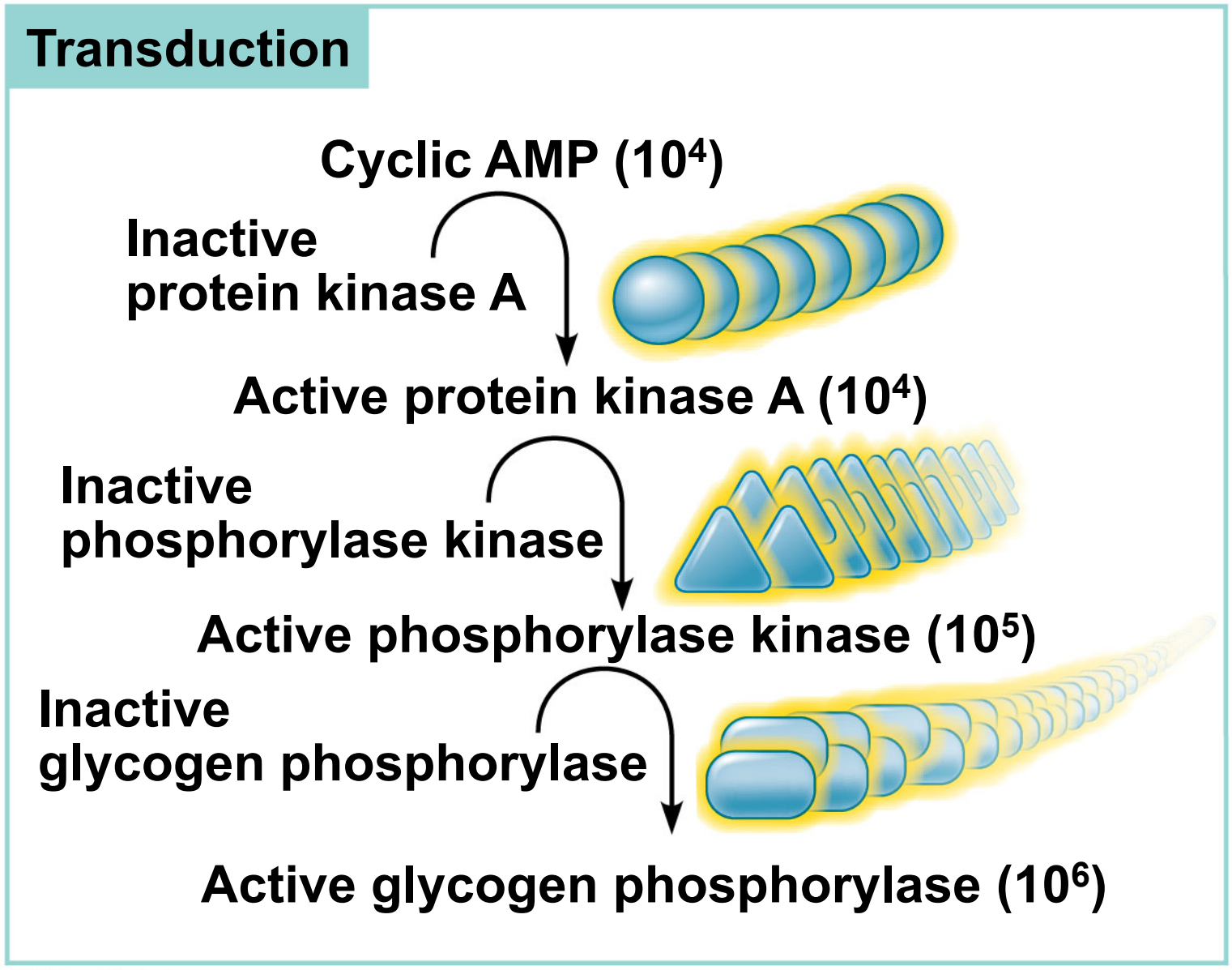


Figure 9.16c



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

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

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

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

Figure 9.17

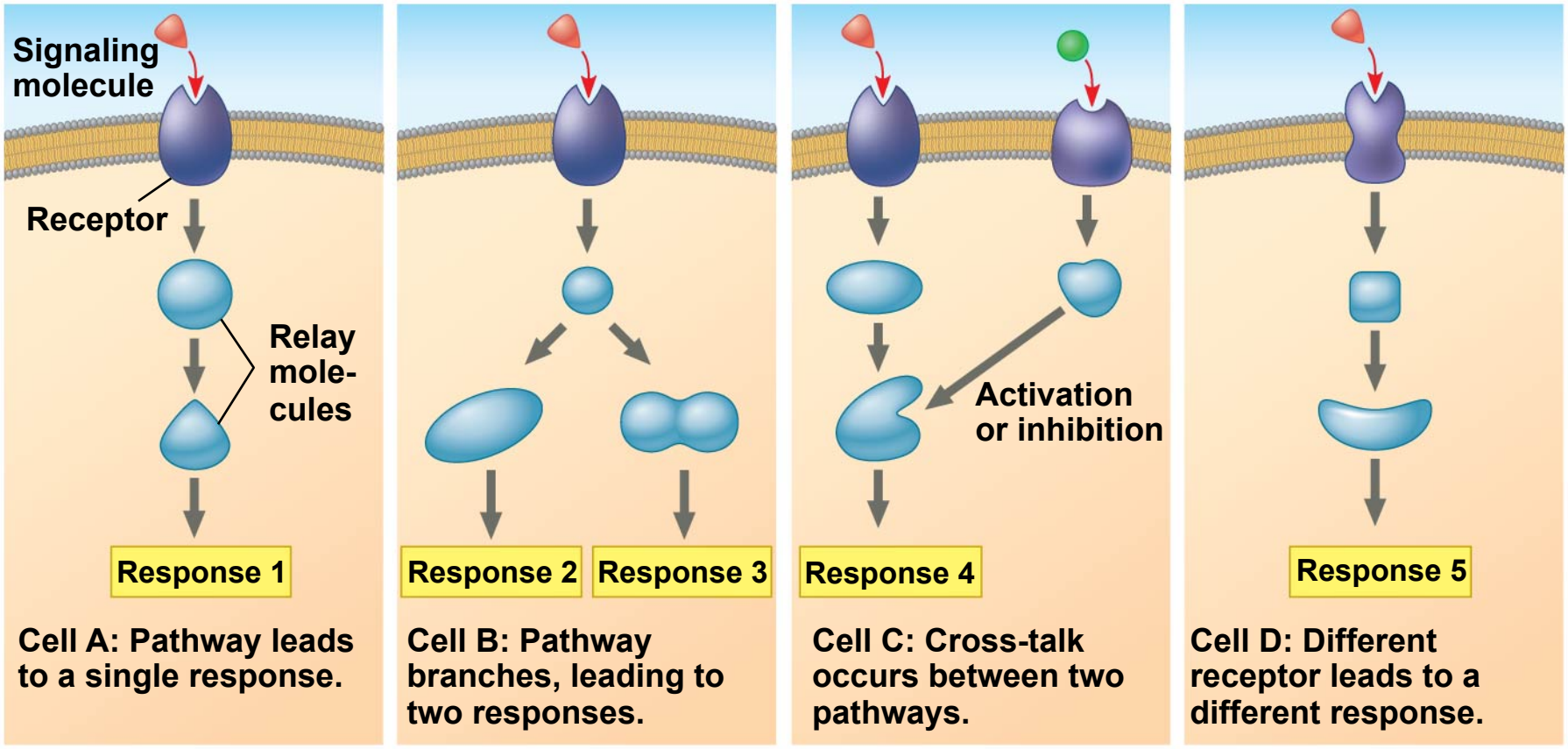


Figure 9.17a

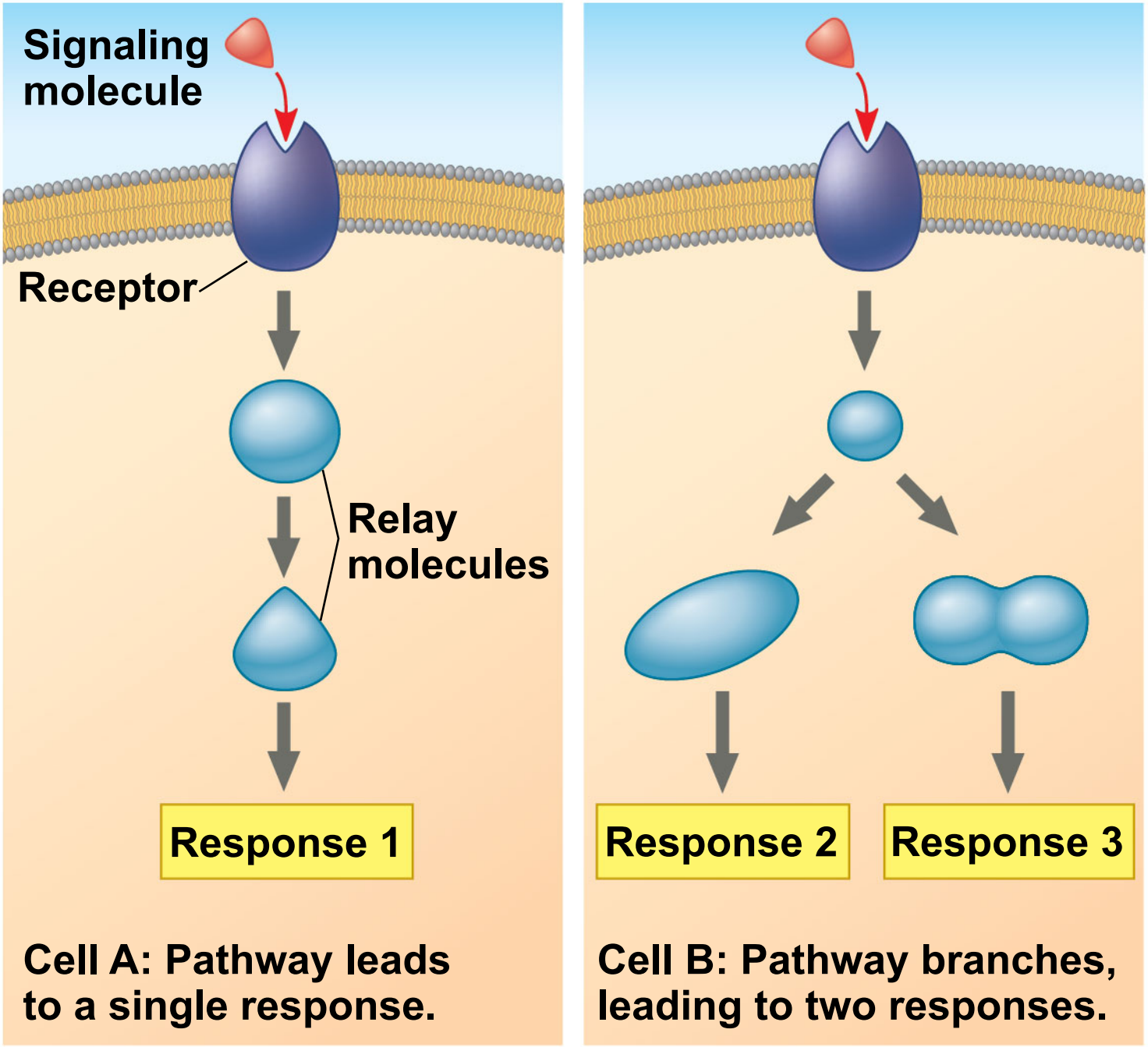
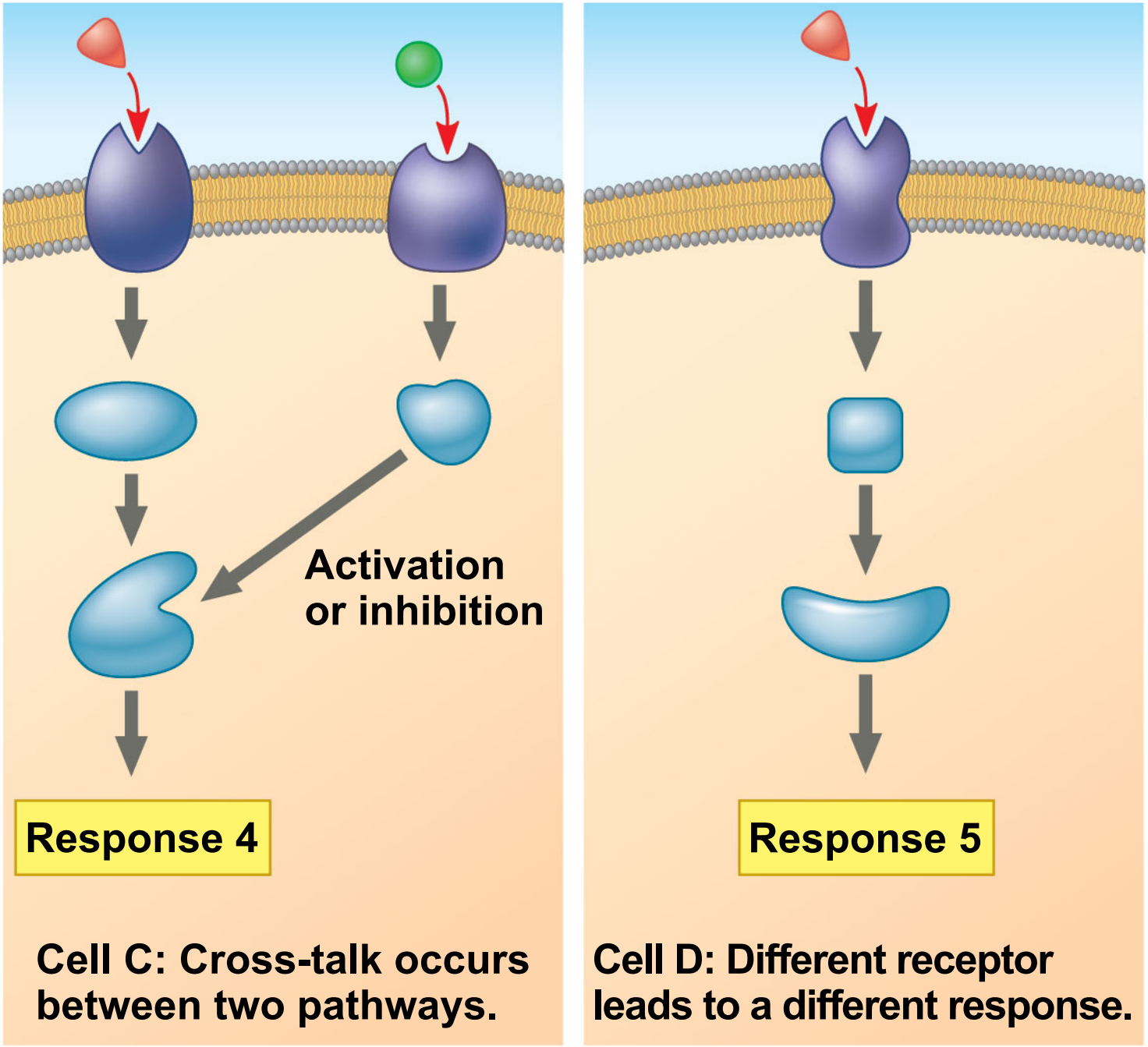


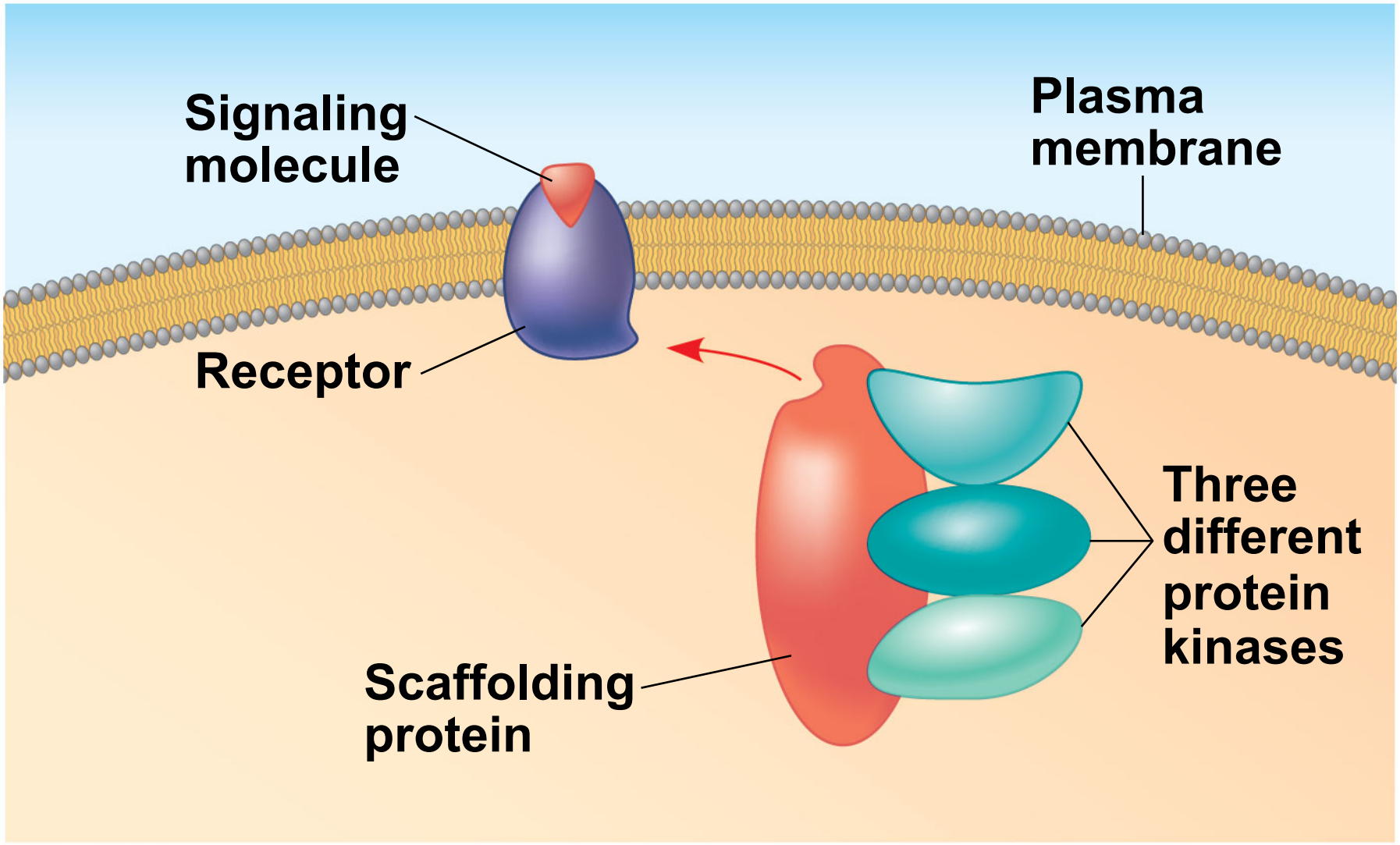
Figure 9.17b



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

Figure 9.18



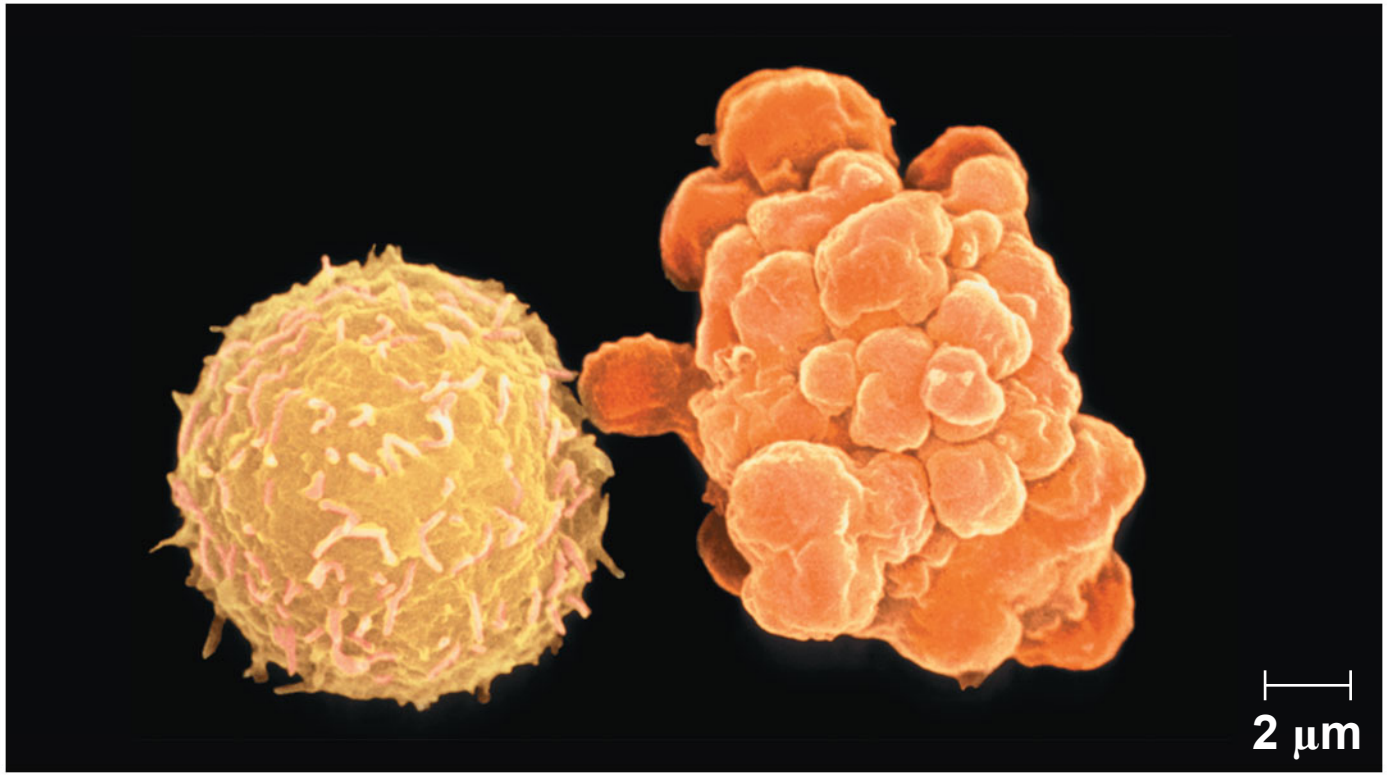
Termination of the Signal

- 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

Concept 9.5: 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

Figure 9.19



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

Figure 9.20

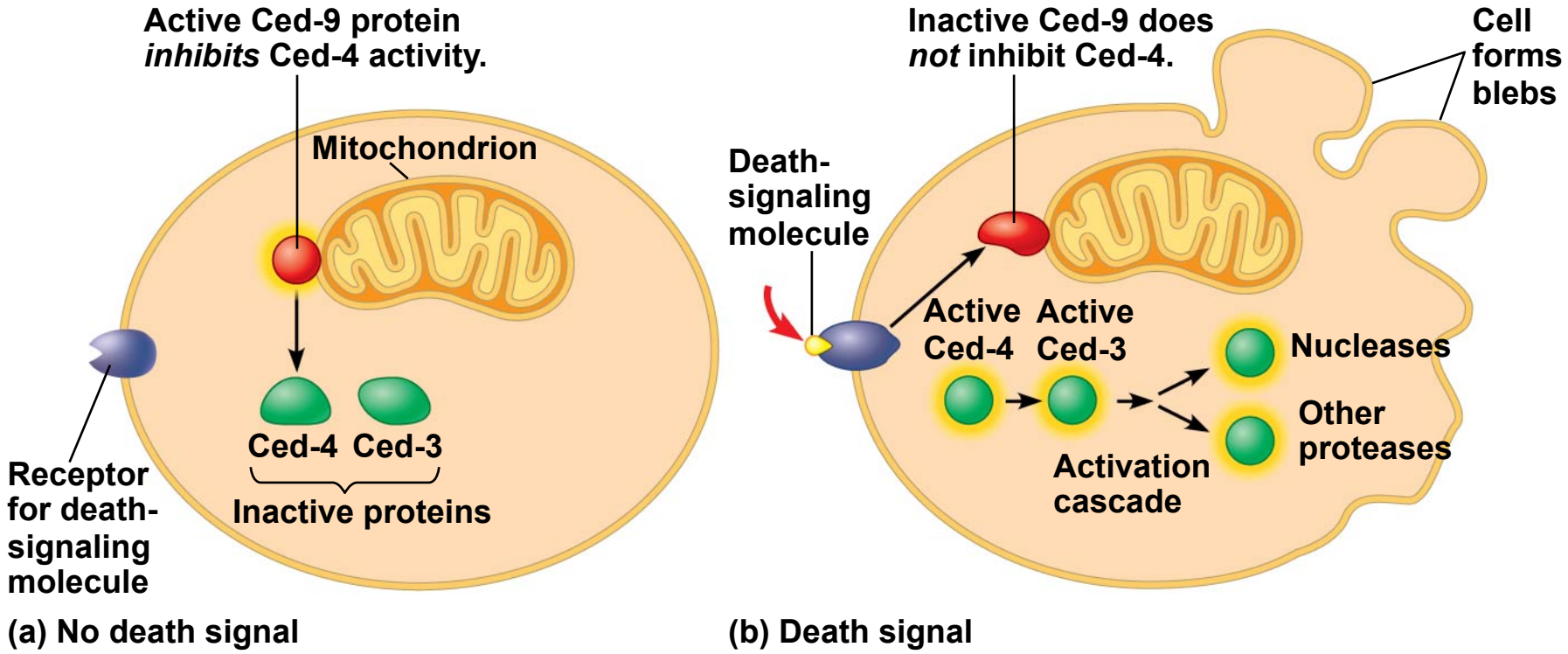


Figure 9.20a

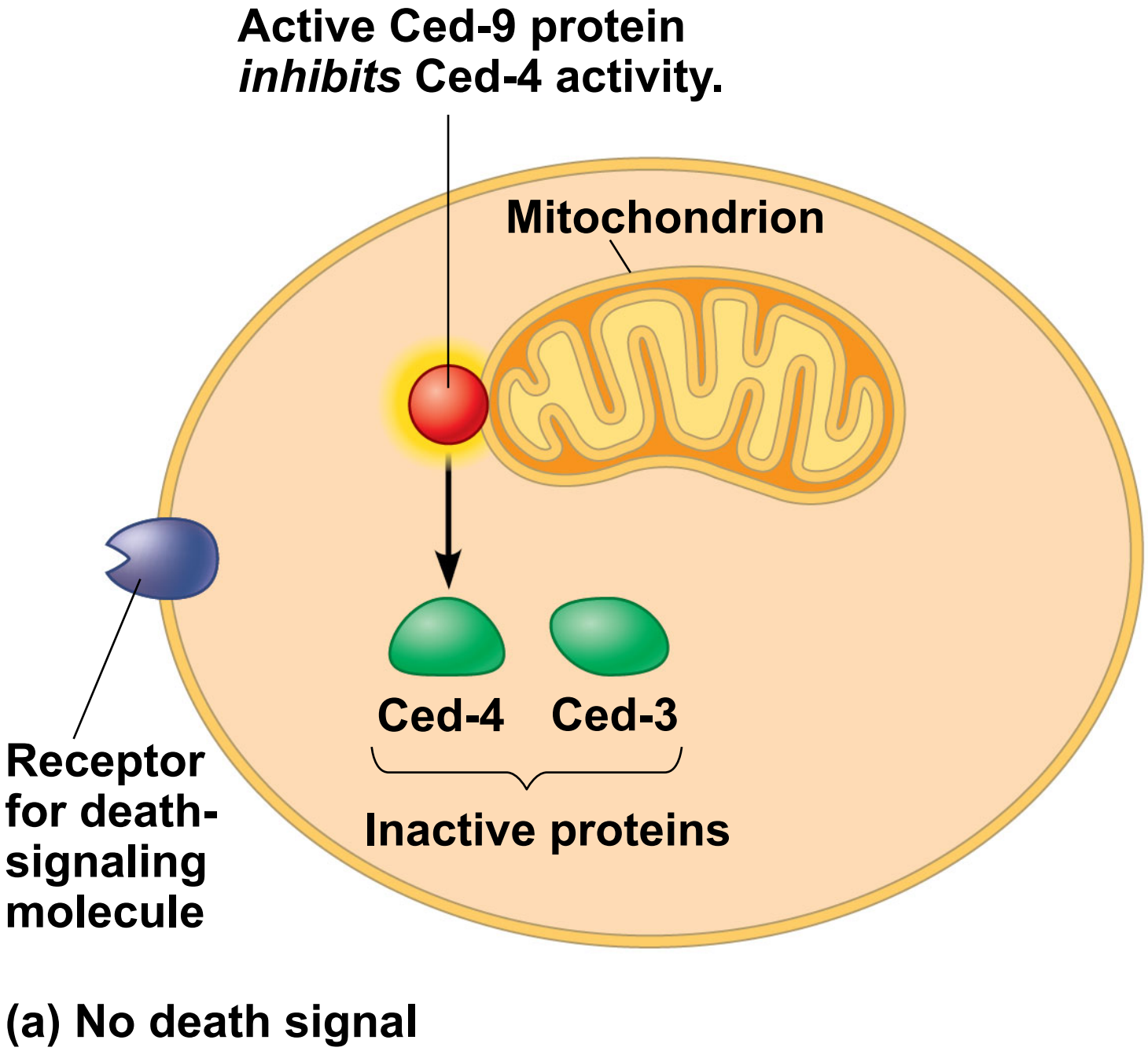
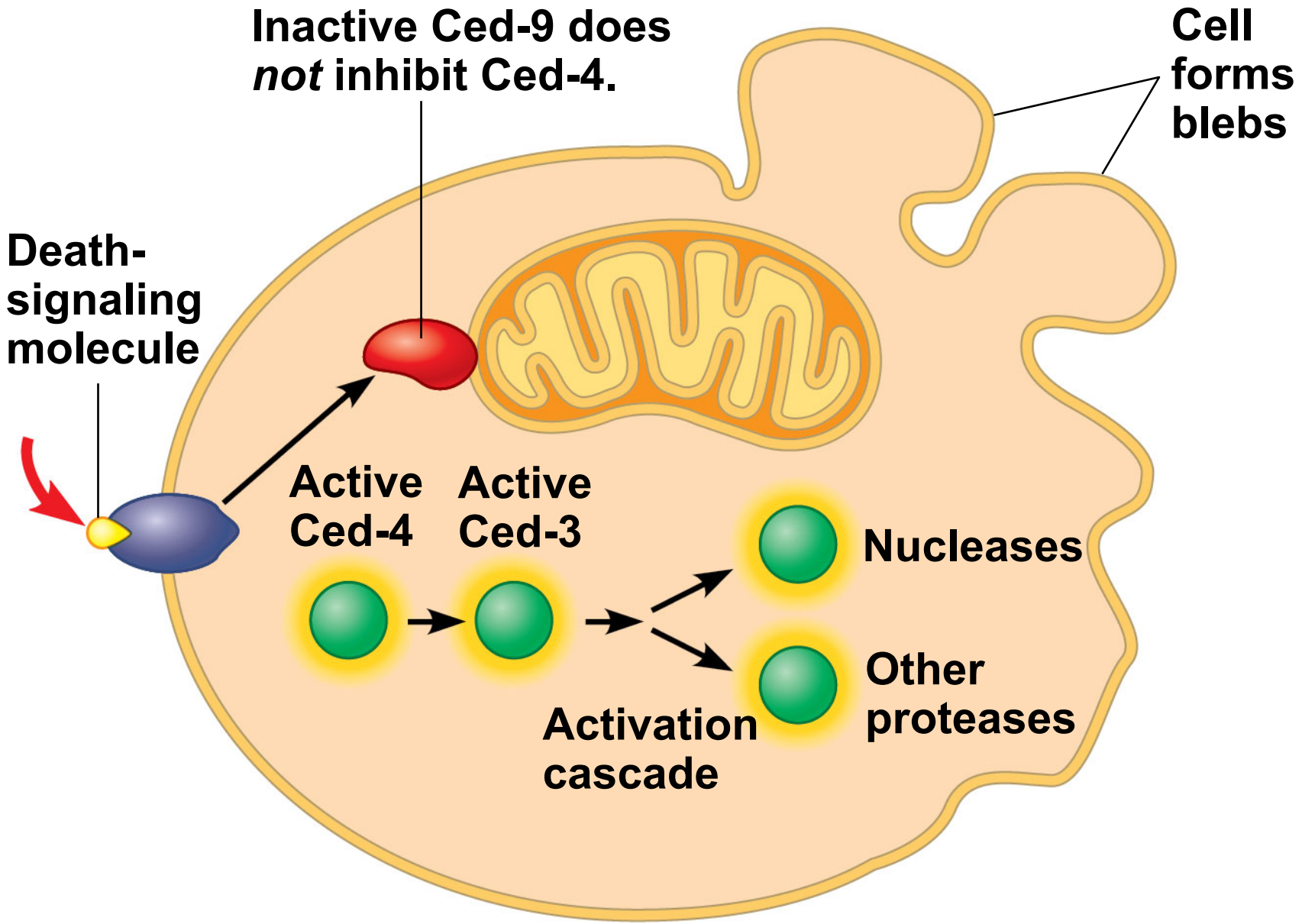


Figure 9.20b



(b) Death signal

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

- 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

Figure 9.21

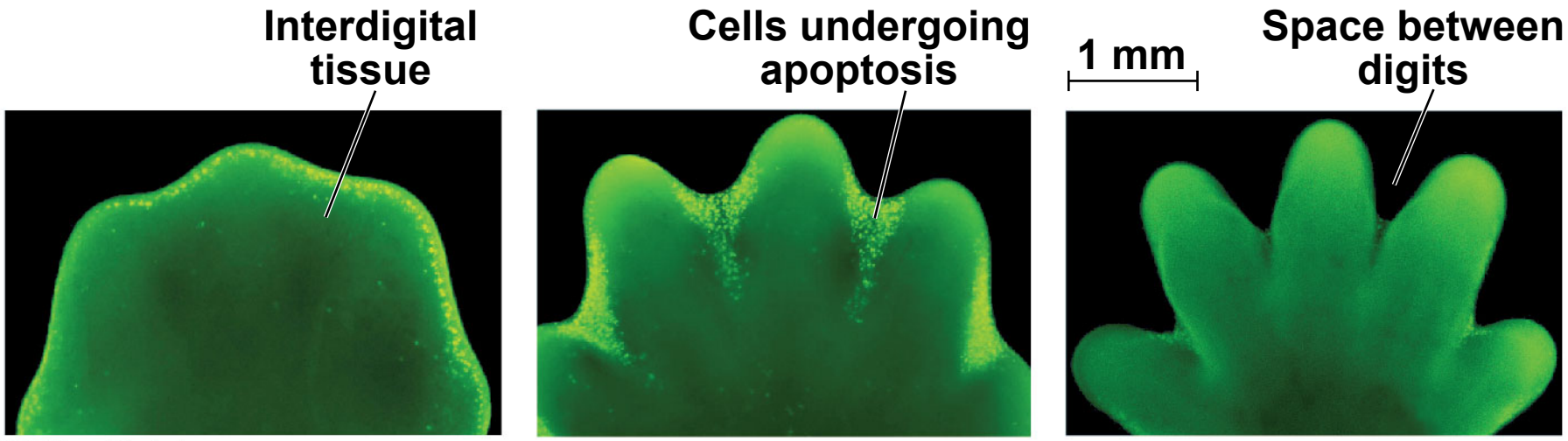


Figure 9.21a

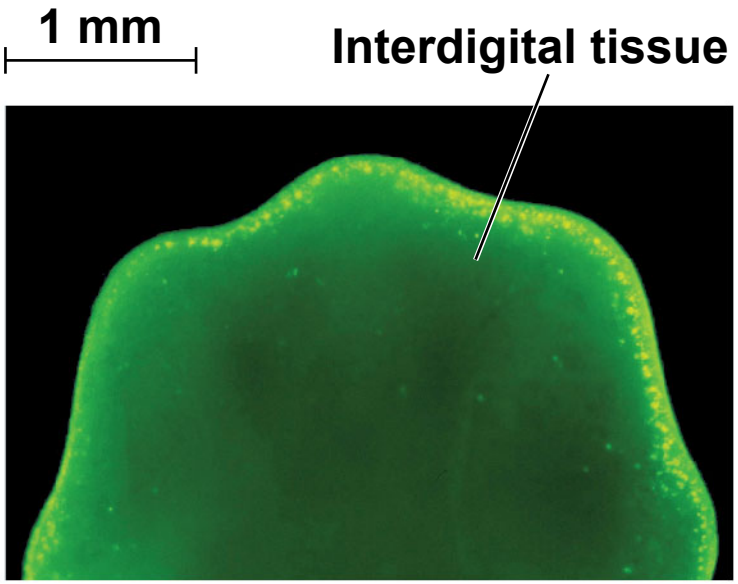


Figure 9.21b

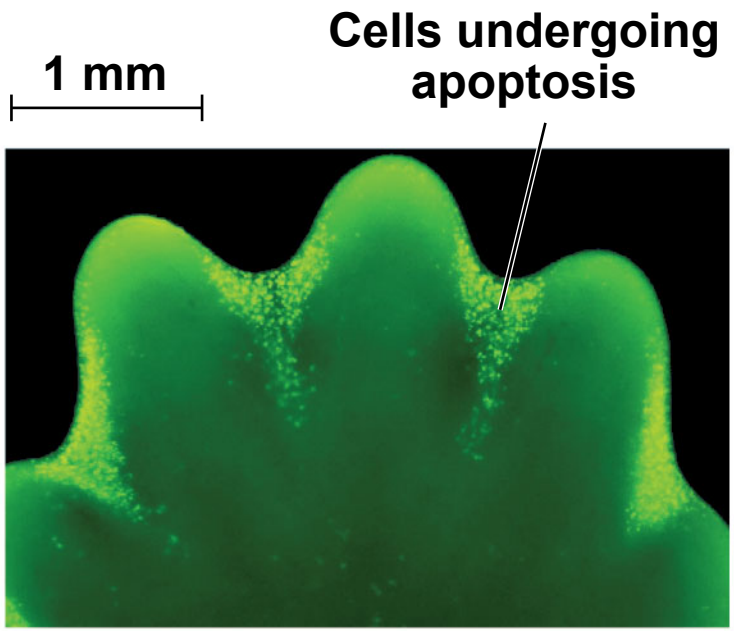


Figure 9.21c

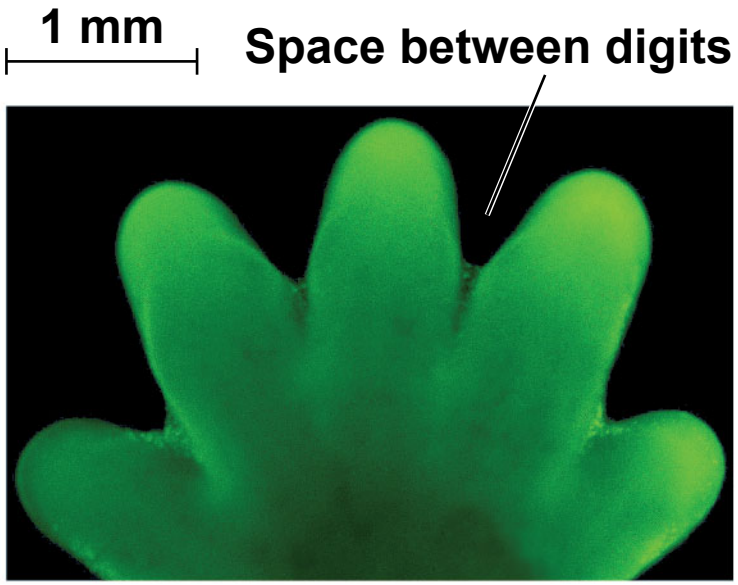


Figure 9.8d_1

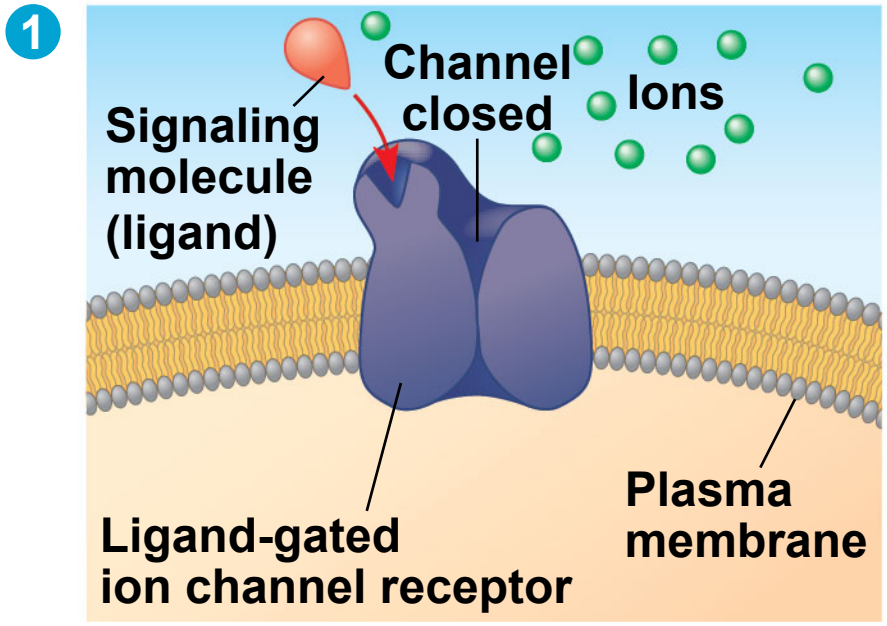


Figure 9.8d_2

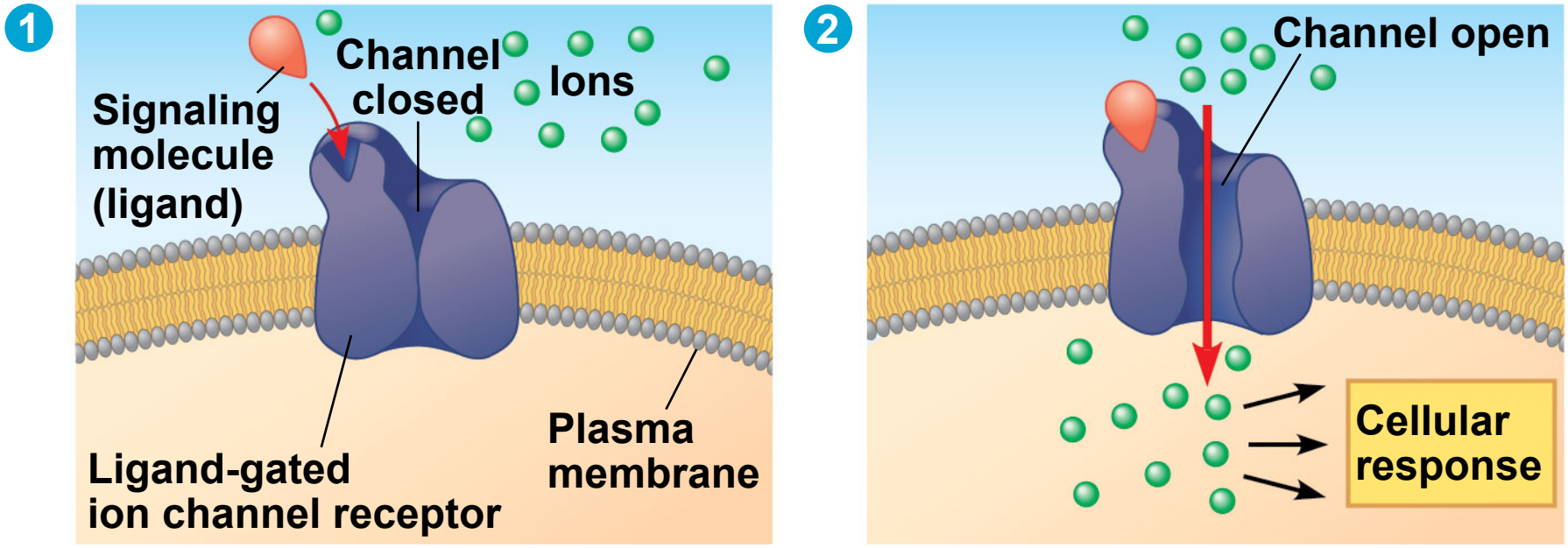


Figure 9.8d_3

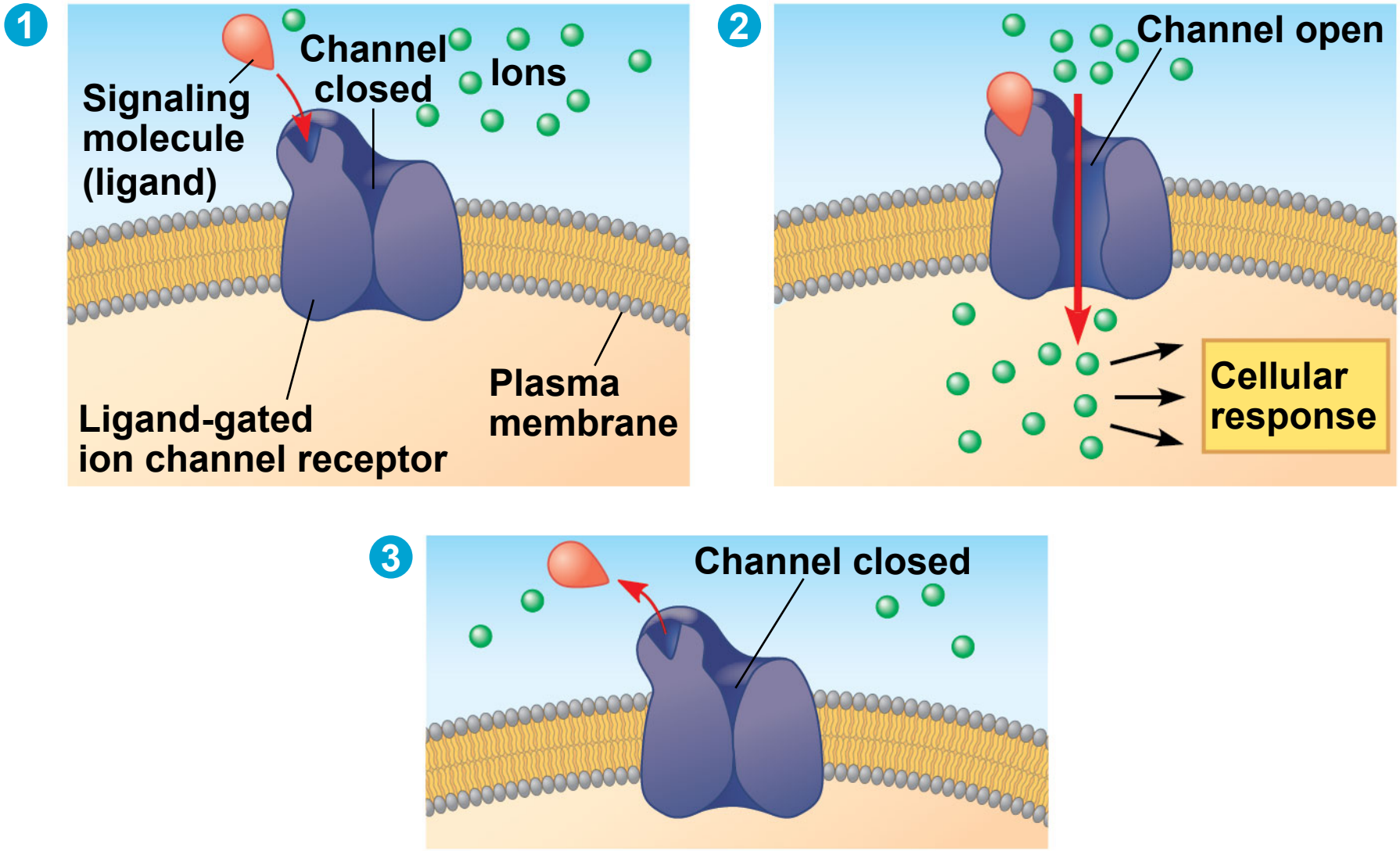
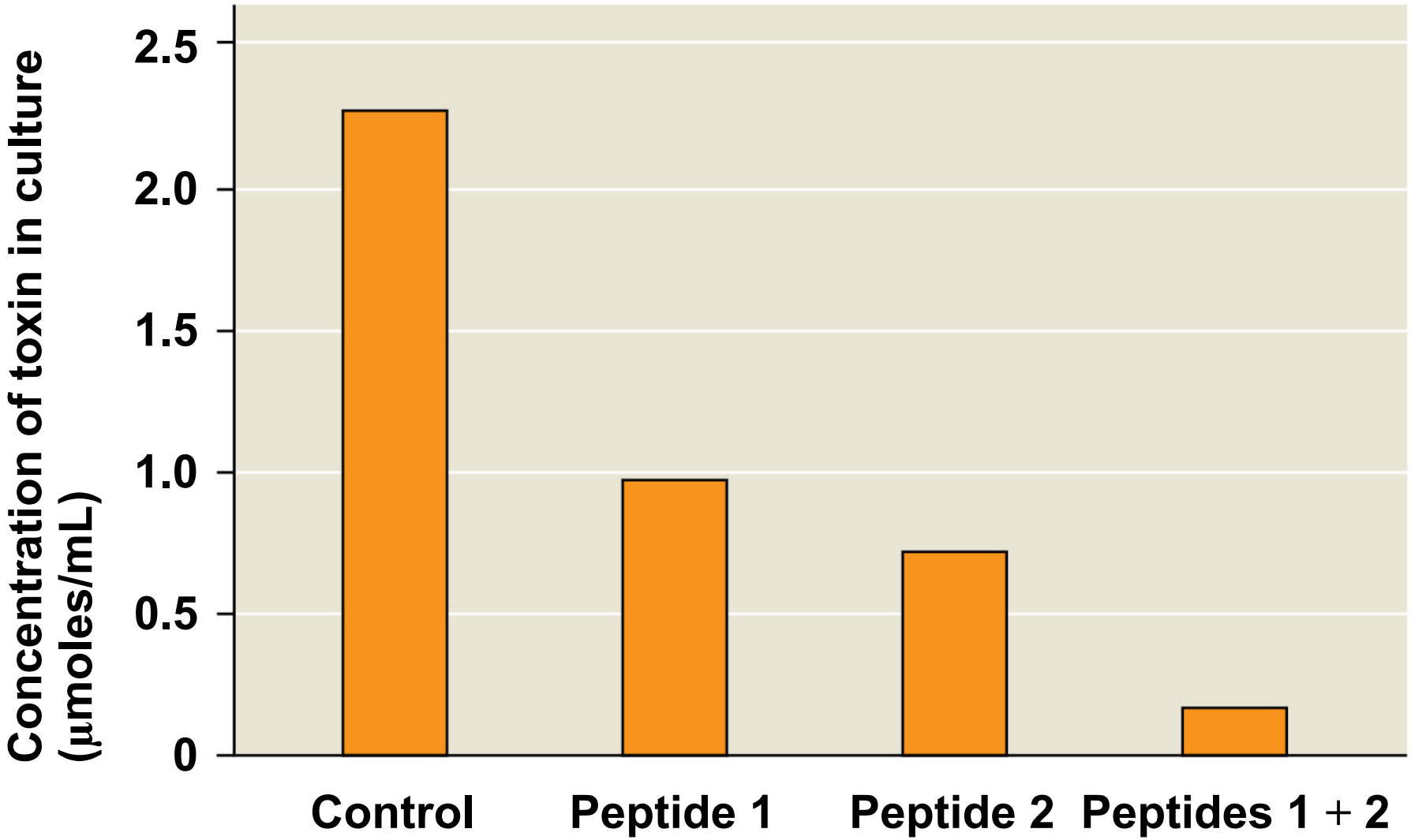


Figure 9.UN01a

Figure 9.UN01b



Data from N. Balaban et al., Treatment of *Staphylococcus aureus* biofilm infection by the quorum-sensing inhibitor RIP, *Antimicrobial Agents and Chemotherapy* 51(6):2226–2229 (2007).

Figure 9.UN02

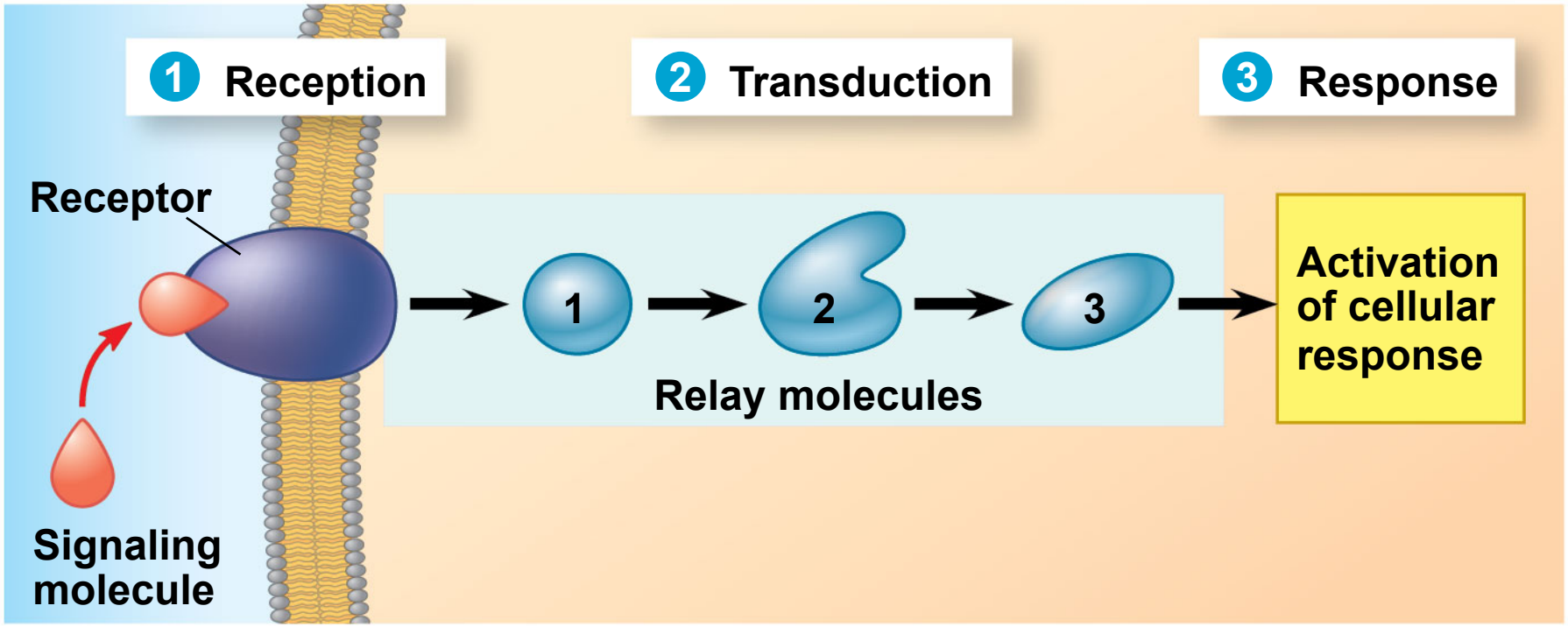


Figure 9.UN03