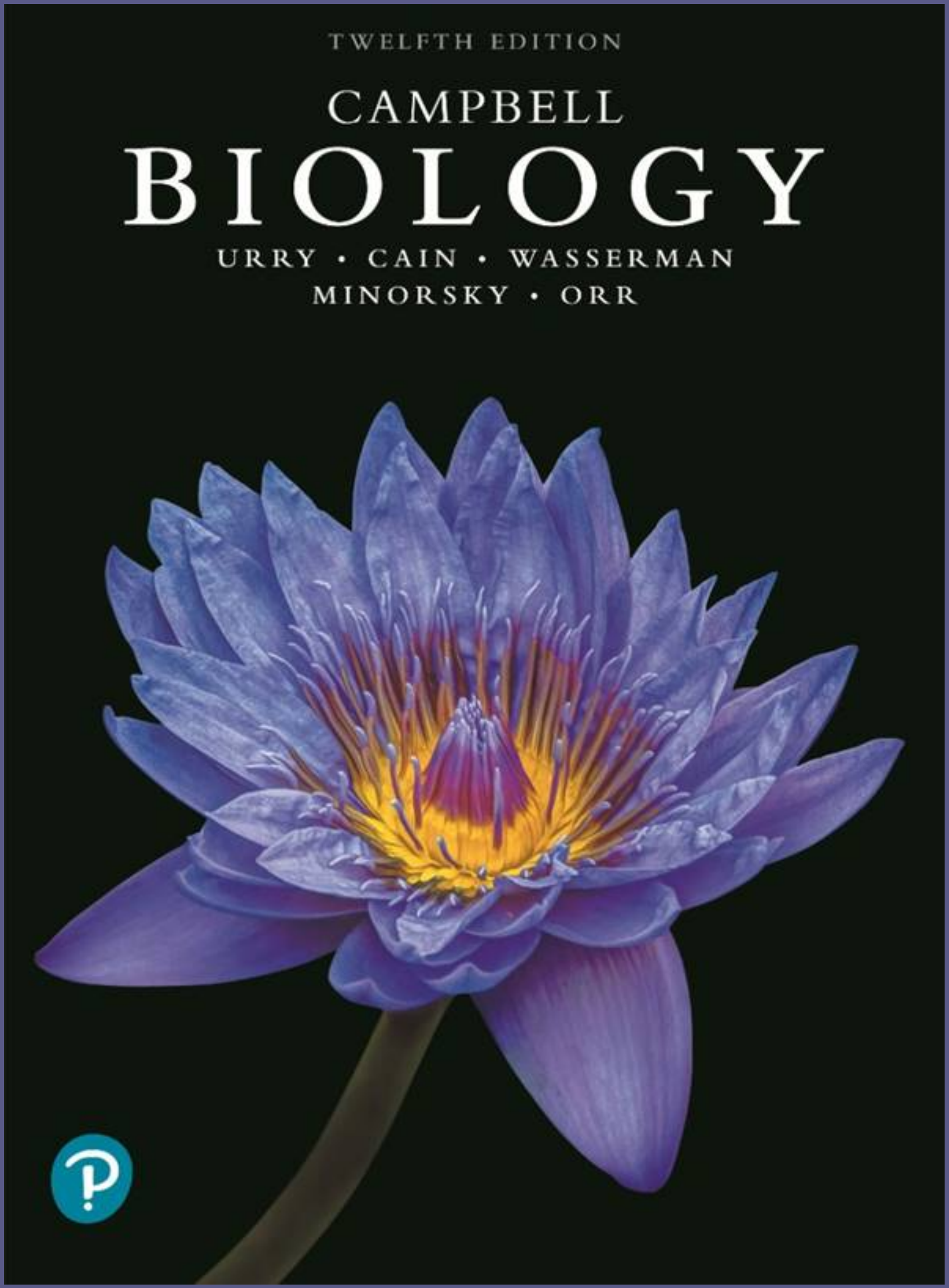


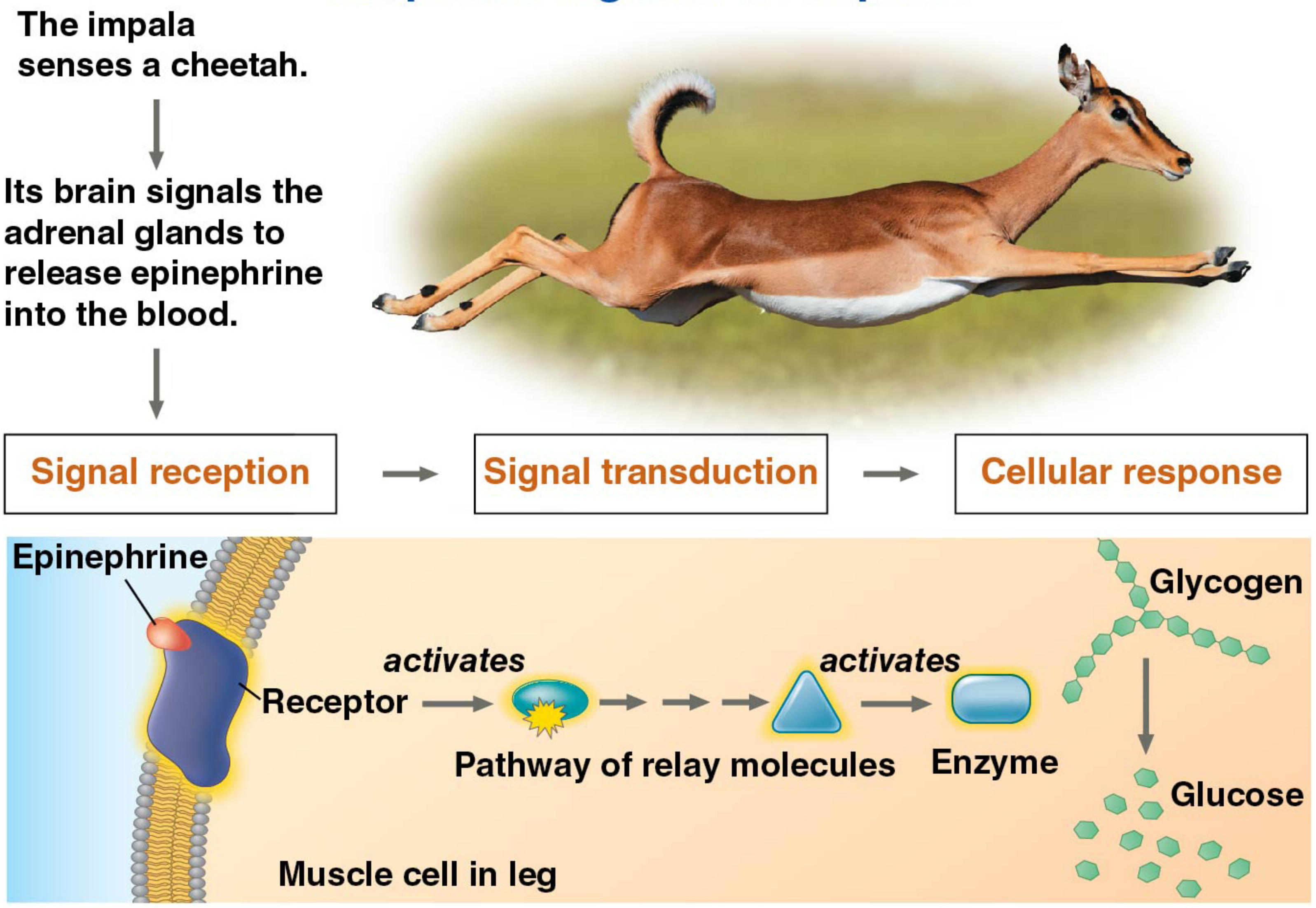
Chapter 11

Cell Communication

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

Figure 11.1a

How does cell signaling fuel the desperate flight of an impala?



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

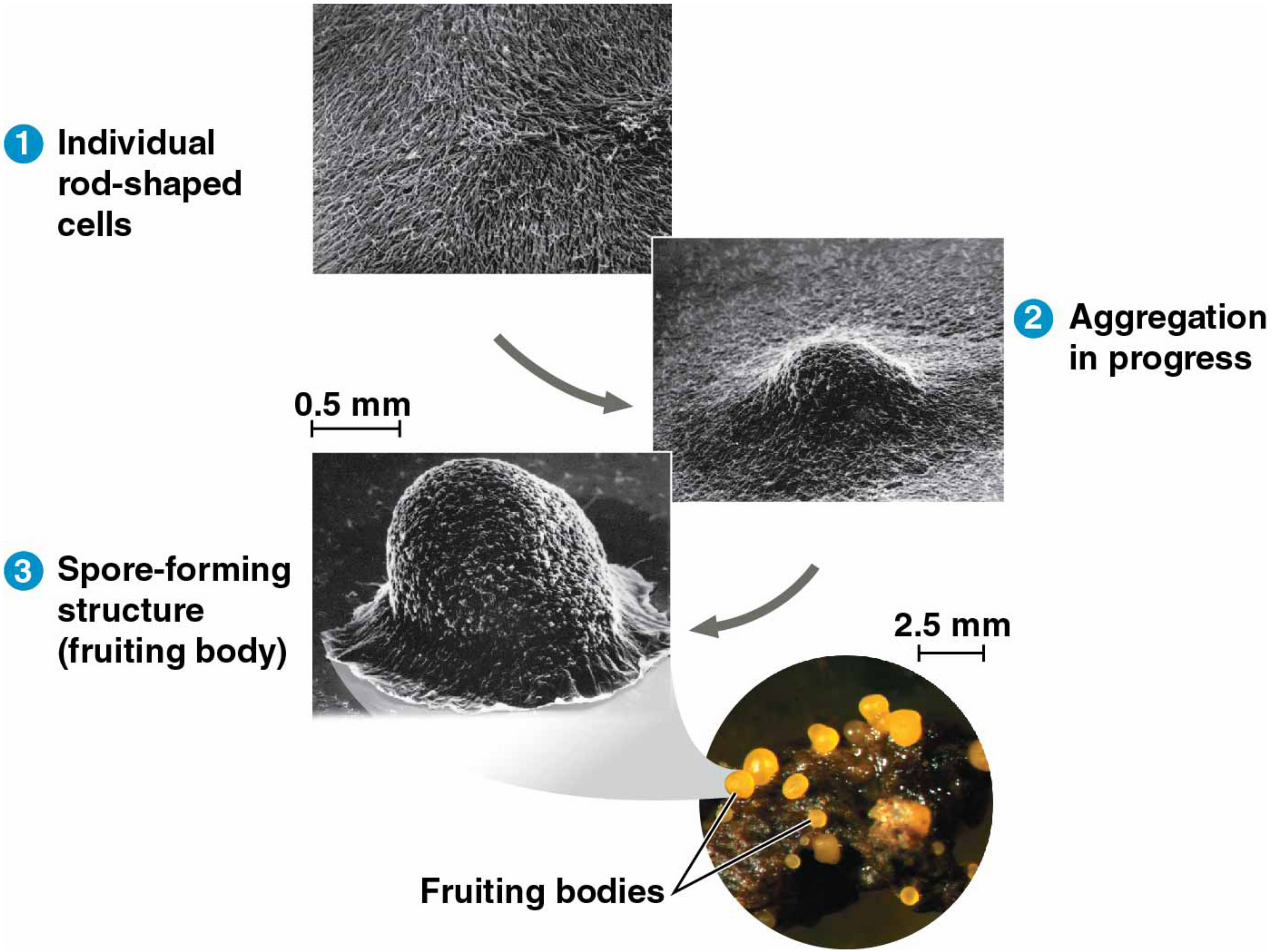
- Ancestral signaling molecules likely evolved in prokaryotes and single-celled eukaryotes and were adopted for use in their multicellular descendants

Evolution of Cell Signaling

- Research in the 1970s suggested that bacterial cells were capable of signaling to each other
- Cell signaling is critical among prokaryotes
- A concentration of signaling molecules allows bacteria to sense local population density in a process called *quorum sensing*

- 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

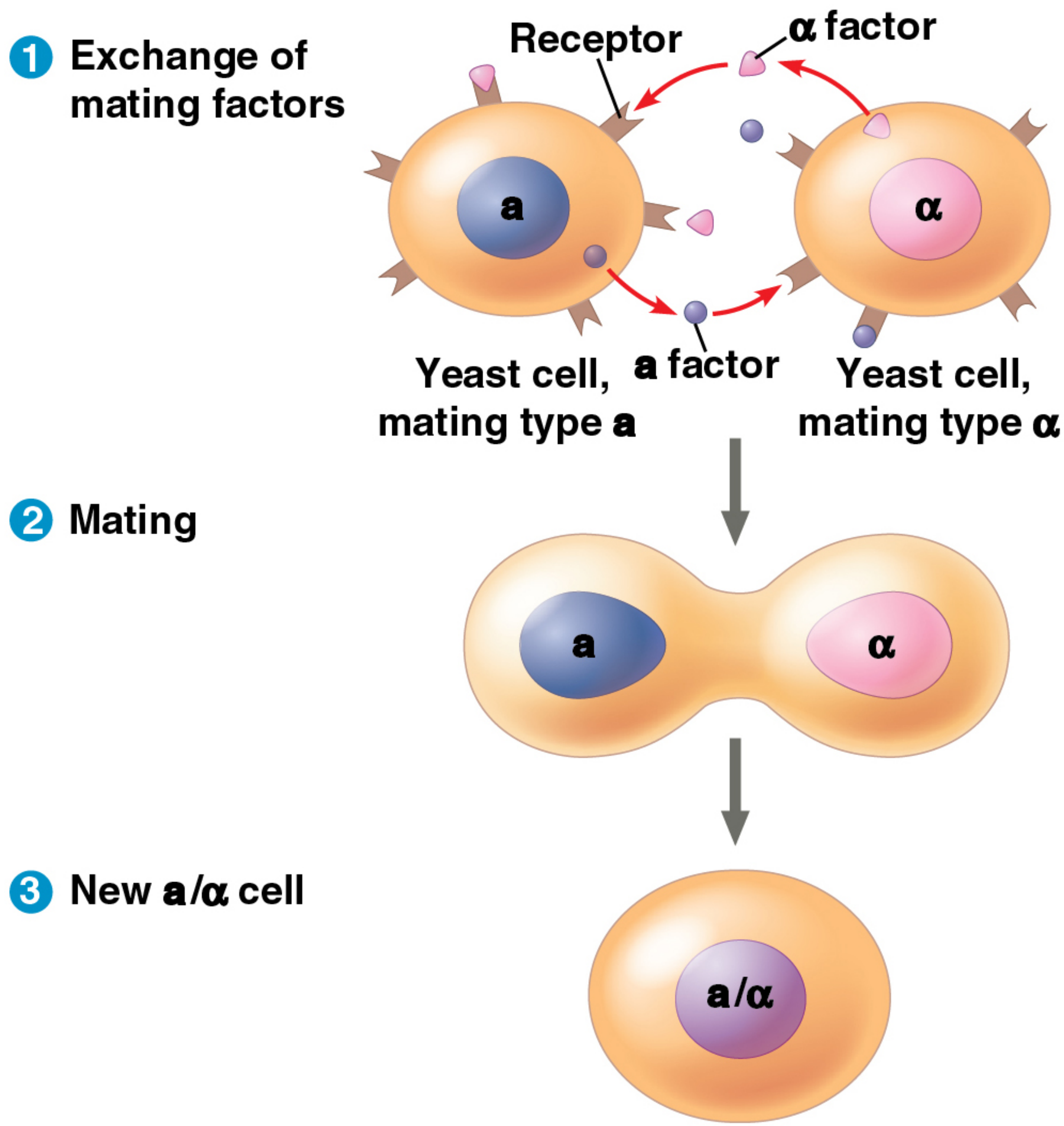
Figure 11.2



1 Individual rod-shaped cells
2 Aggregation in progress
0.5 mm
3 Spore-forming structure (fruiting body)
2.5 mm
Fruiting bodies

- 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 11.3



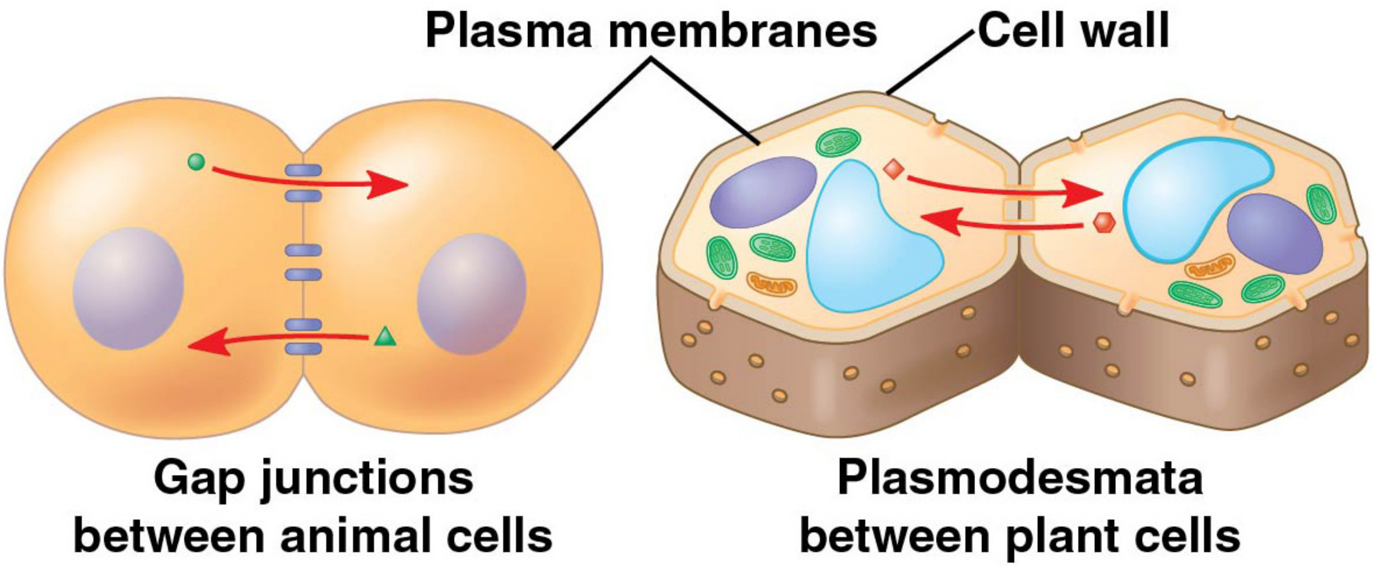
1 Exchange of mating factors
Receptor
α factor
a
α
Yeast cell, mating type a
a factor
Yeast cell, mating type α
2 Mating
a
α
3 New a/α cell
a/α

Local and Long-Distance Signaling

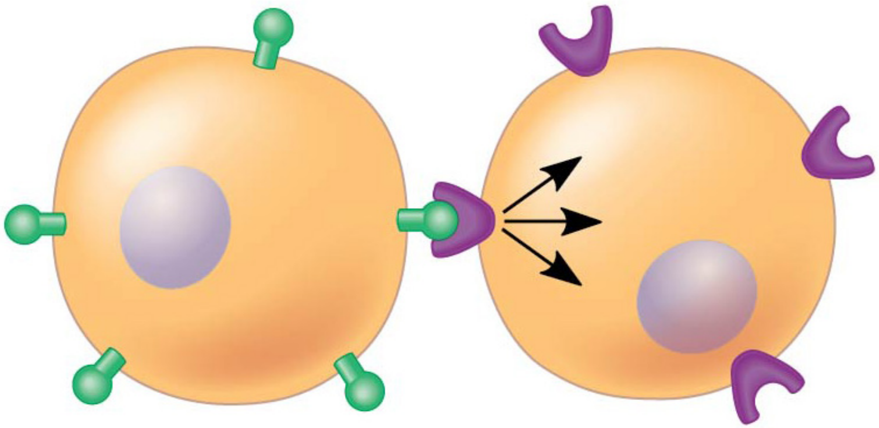
- Cells in a multicellular organism communicate via signaling molecules
- In local signaling, animal cells may communicate by direct contact
- Animal and plant cells have cell junctions that directly connect the cytoplasm of adjacent cells
- Signaling substances in the cytosol can pass between adjacent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

- Animal cells may also communicate by direct contact between cell-surface molecules
- Local signaling is especially important in embryonic development, immune response, and maintaining adult stem cell populations

Figure 11.4



(a) Cell junctions



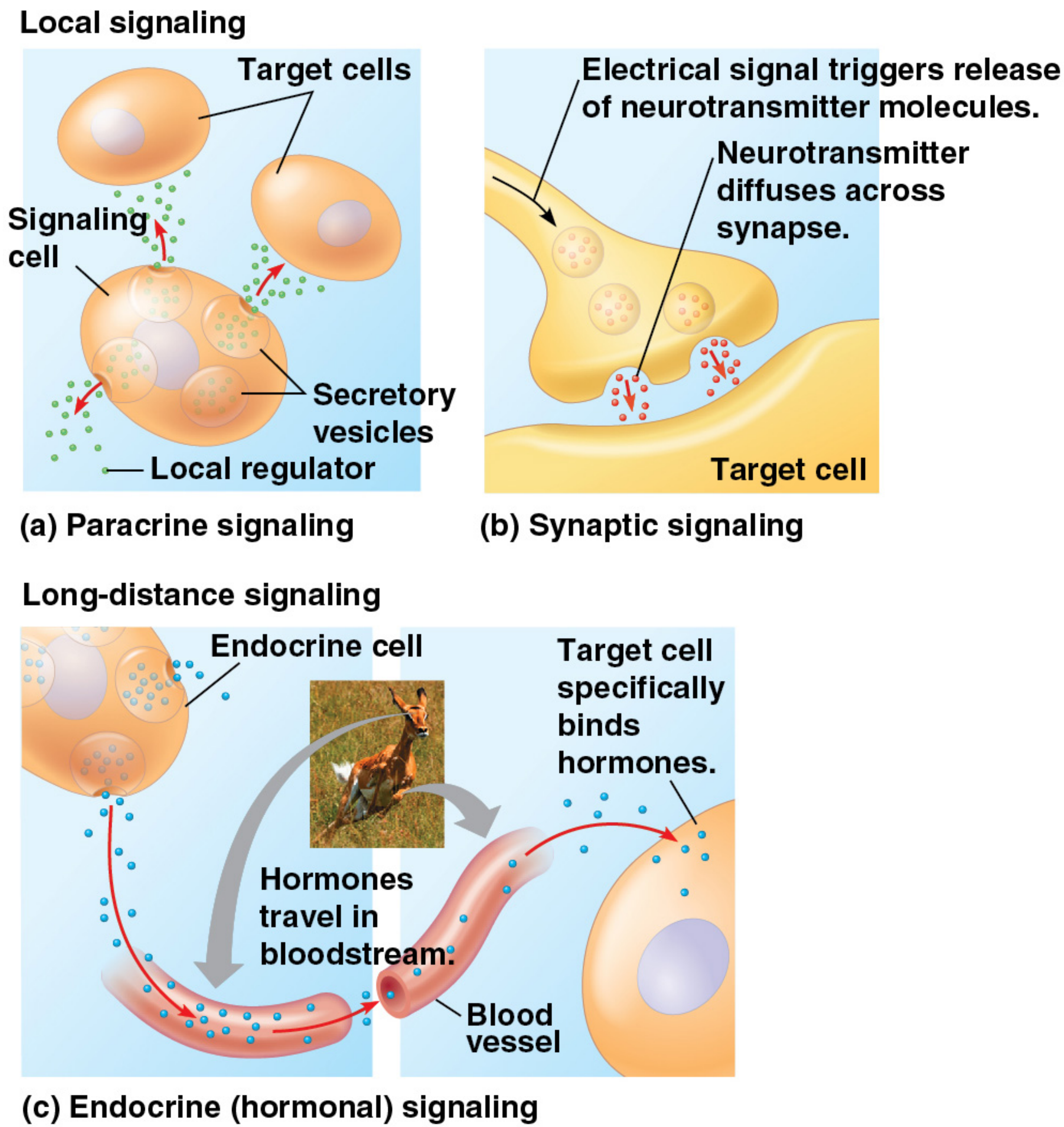
(b) Cell-surface molecules

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

- *Synaptic signaling* occurs in the animal nervous system when a neurotransmitter is released in response to an electric signal
- Drugs used to treat depression, anxiety, and post-traumatic stress disorder (PTSD) affect this signaling process

- In long-distance signaling, plants and animals use molecules called **hormones**
- In hormonal (or endocrine) signaling in animals 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 11.5

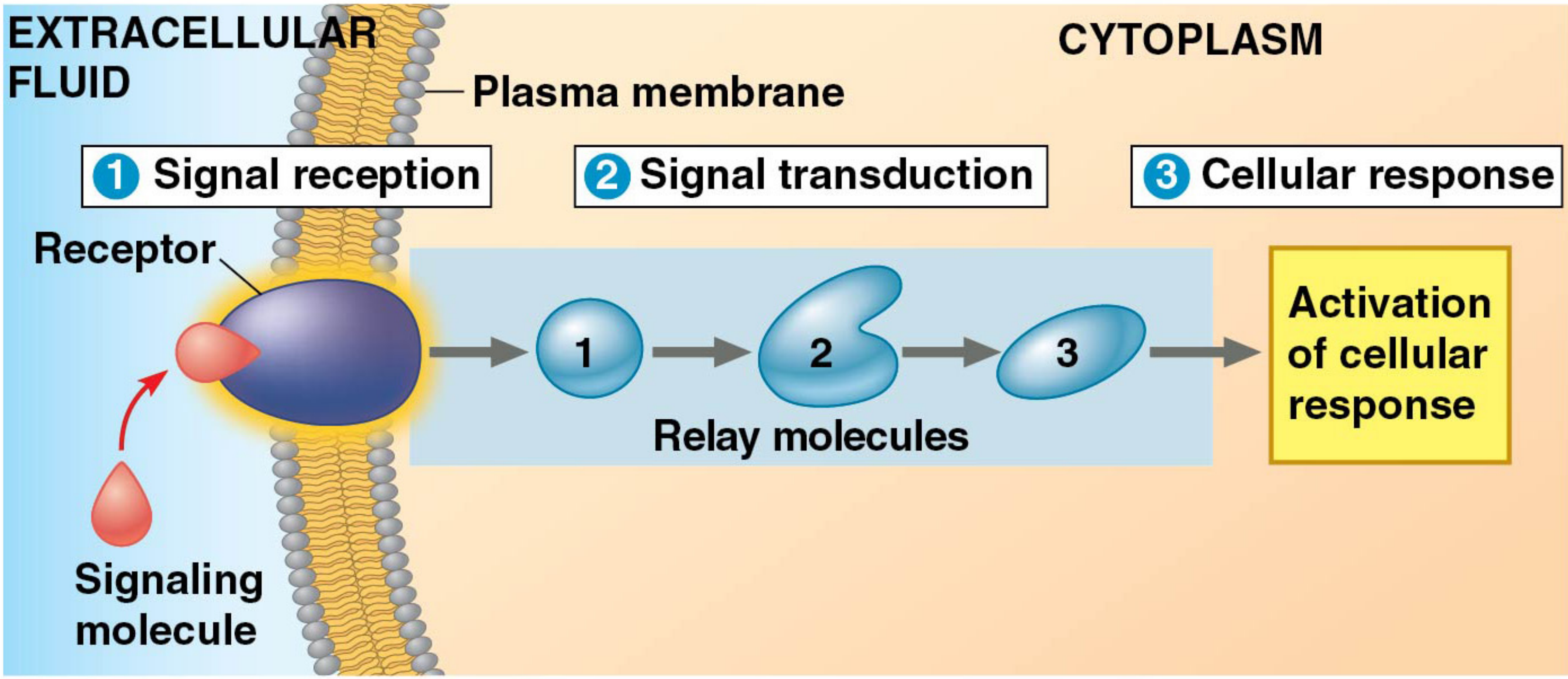

Local signaling
Target cells
Signaling cell
Secretory vesicles
Local regulator
Electrical signal triggers release of neurotransmitter molecules.
Neurotransmitter diffuses across synapse.
Target cell
(a) Paracrine signaling
(b) Synaptic signaling
Long-distance signaling
Endocrine cell
Target cell specifically binds hormones.
Hormones travel in bloodstream.
Blood vessel
(c) Endocrine (hormonal) signaling

The Three Stages of Cell Signaling: *A Preview*

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

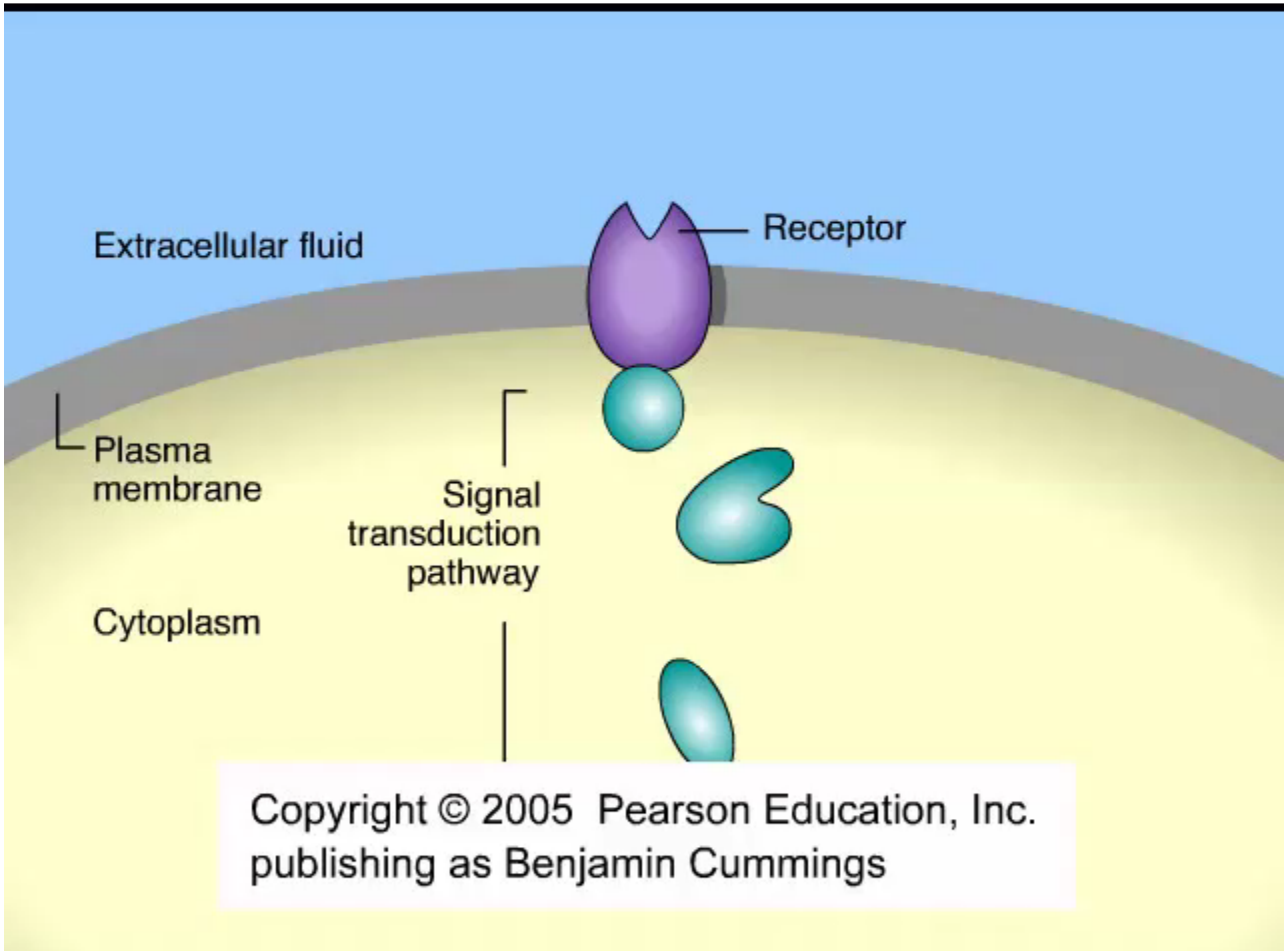
- In reception, the target cell detects a signaling molecule that binds to a receptor protein on the cell surface
- In transduction, the binding of the signaling molecule alters the receptor and initiates a **signal transduction pathway**; transduction often occurs in a series of steps
- In response,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

Figure 11.6



EXTRACELLULAR FLUID
CYTOPLASM
Plasma membrane
1 Signal reception
2 Signal transduction
3 Cellular response
Receptor
1
2
3
Relay molecules
Activation of cellular response
Signaling molecule

Animation: Overview of Cell Signaling



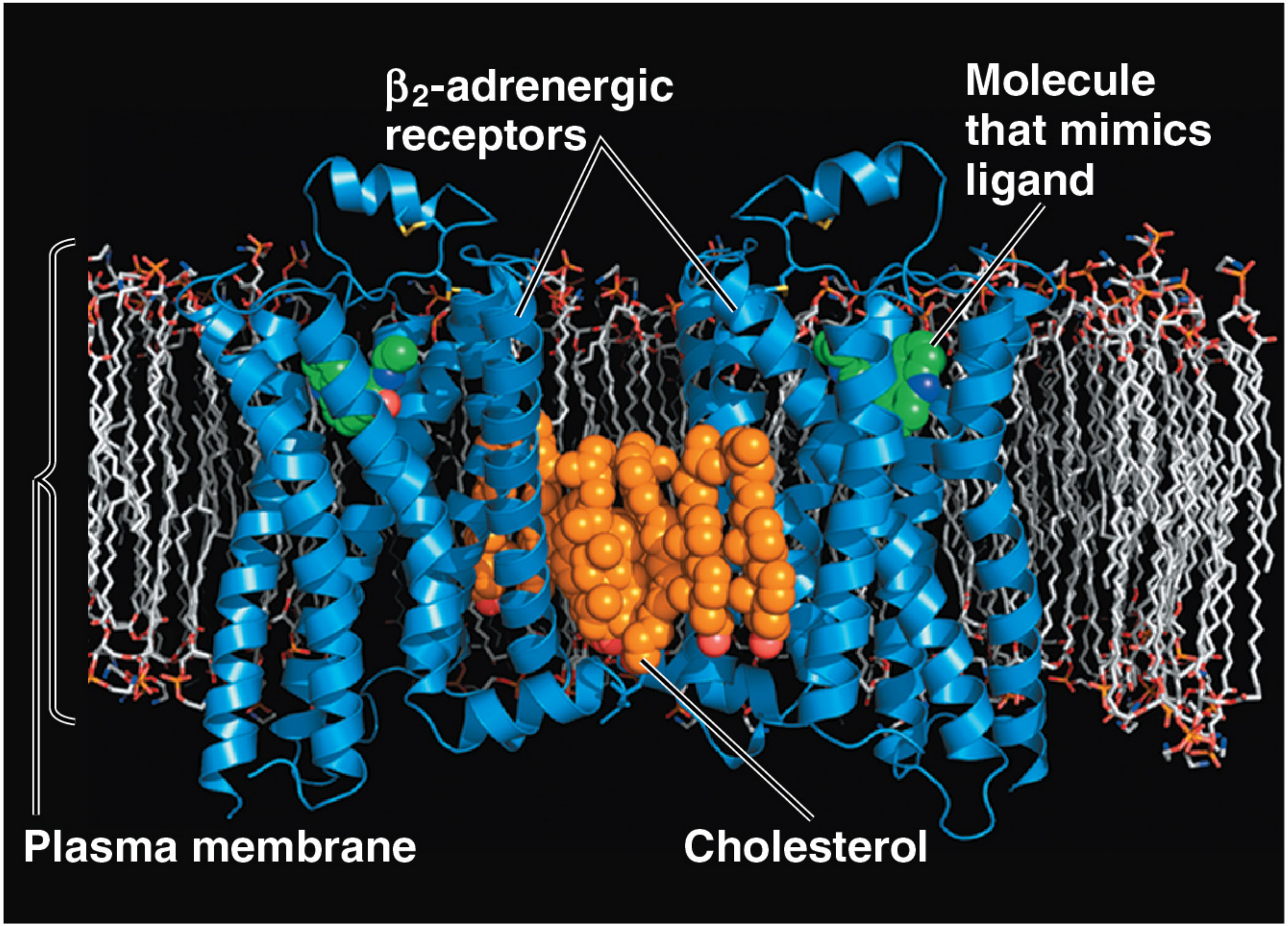
CONCEPT 11.2: Reception: A signaling molecule binds to a receptor protein, causing it to change shape

- The binding between a signal molecule (**ligand**) and receptor is highly specific
- A shape change in a receptor is generally the initial transduction of the signal
- Most signal receptors are plasma membrane proteins, but others are located inside the cell

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 transmit information from the extracellular environment to the inside of the cell

Figure 11.7

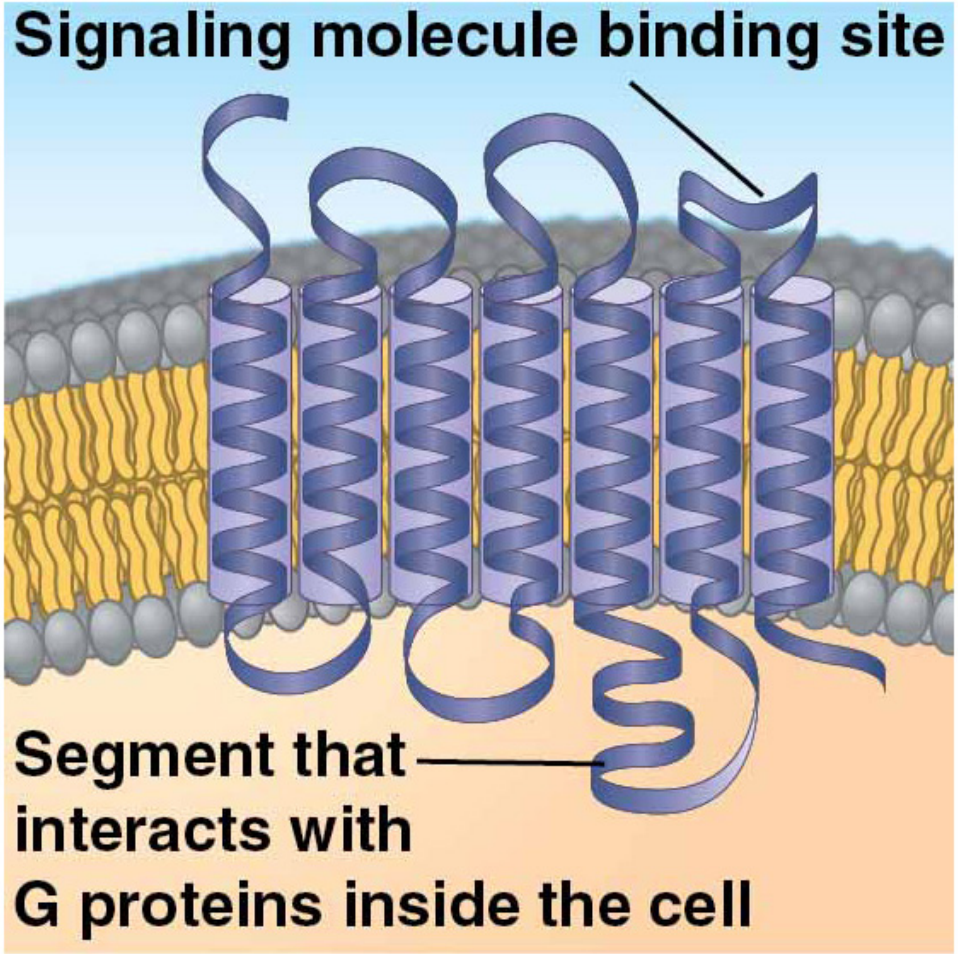


β2-adrenergic receptors
Molecule that mimics ligand
Plasma membrane
Cholesterol

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

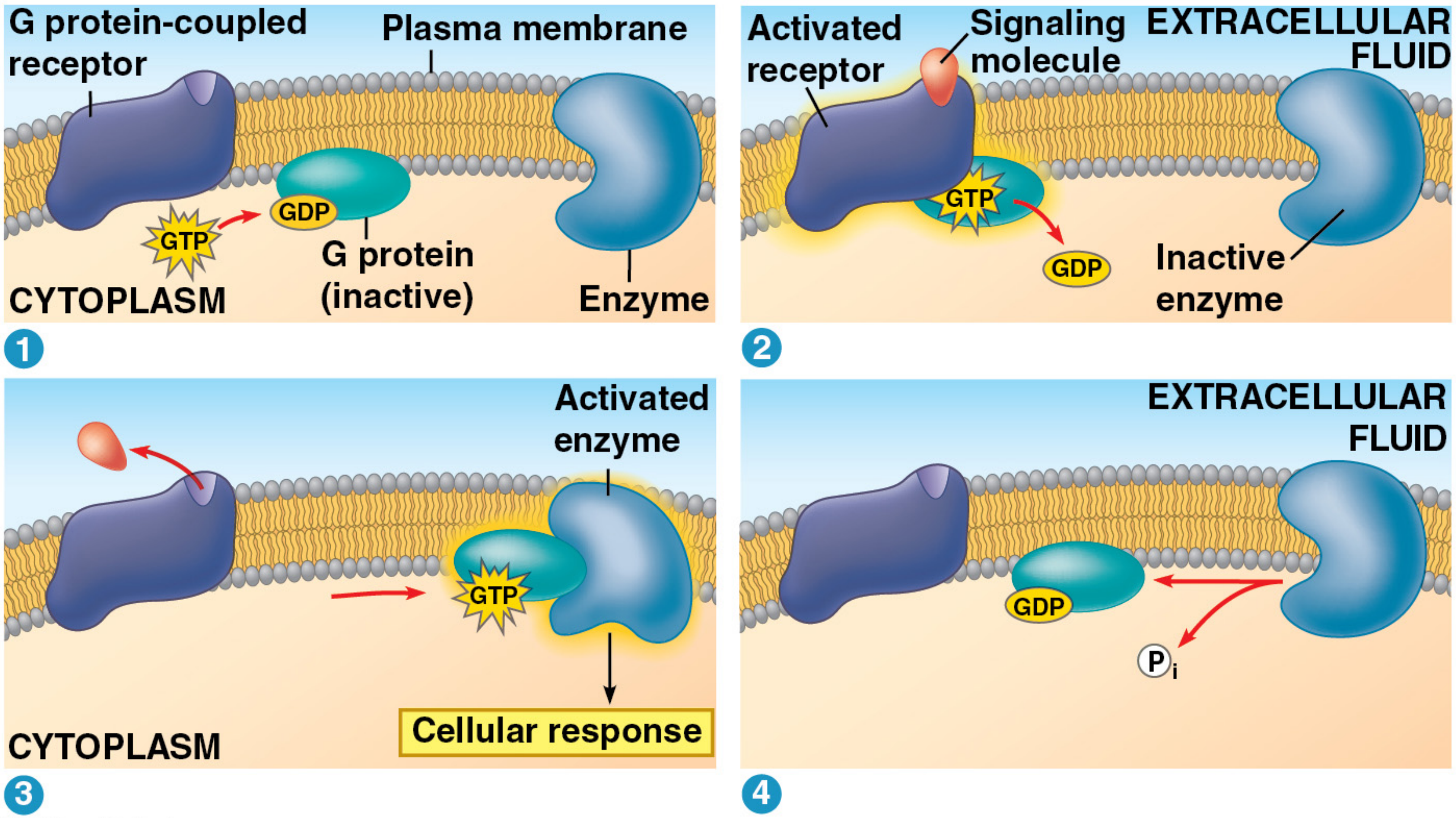
- **G protein-coupled receptors** (GPCRs) are cell-surface transmembrane receptors that work with the help of a **G protein**
- G proteins bind the energy-rich GTP
- G proteins are all very similar in structure
- GPCR systems are extremely widespread and diverse in their functions

Figure 11.8a



G protein-coupled receptor

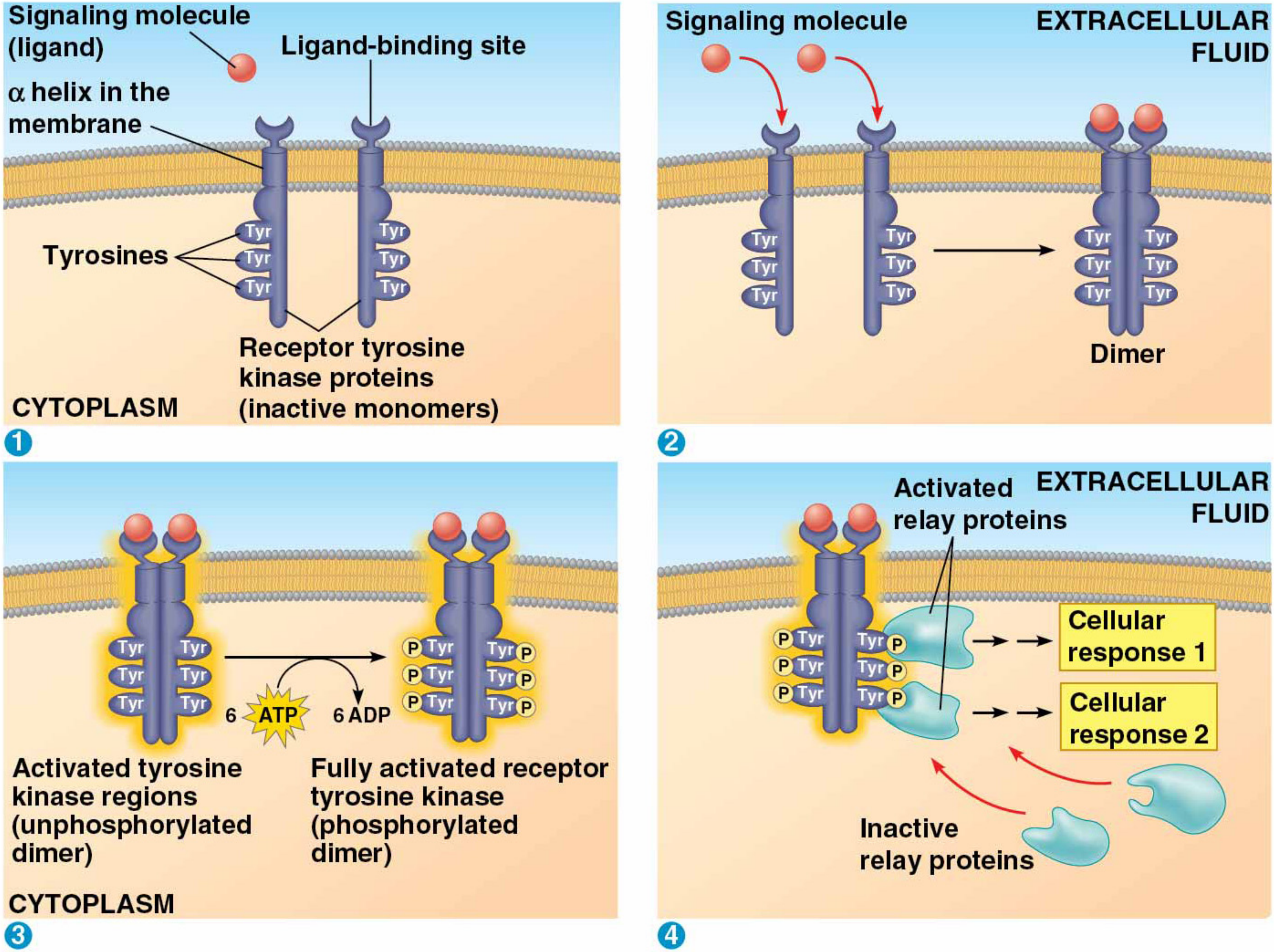
Figure 11.8b



G protein-coupled receptor
Plasma membrane
GTP
GDP
G protein (inactive)
CYTOPLASM
Enzyme
1
Activated receptor
Signaling molecule
EXTRACELLULAR FLUID
GTP
GDP
Inactive enzyme
2
Activated enzyme
GTP
Cellular response
CYTOPLASM
3
EXTRACELLULAR FLUID
GDP
P_i
4

- **Receptor tyrosine kinases (RTKs)** are membrane receptors that catalyze the transfer of 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

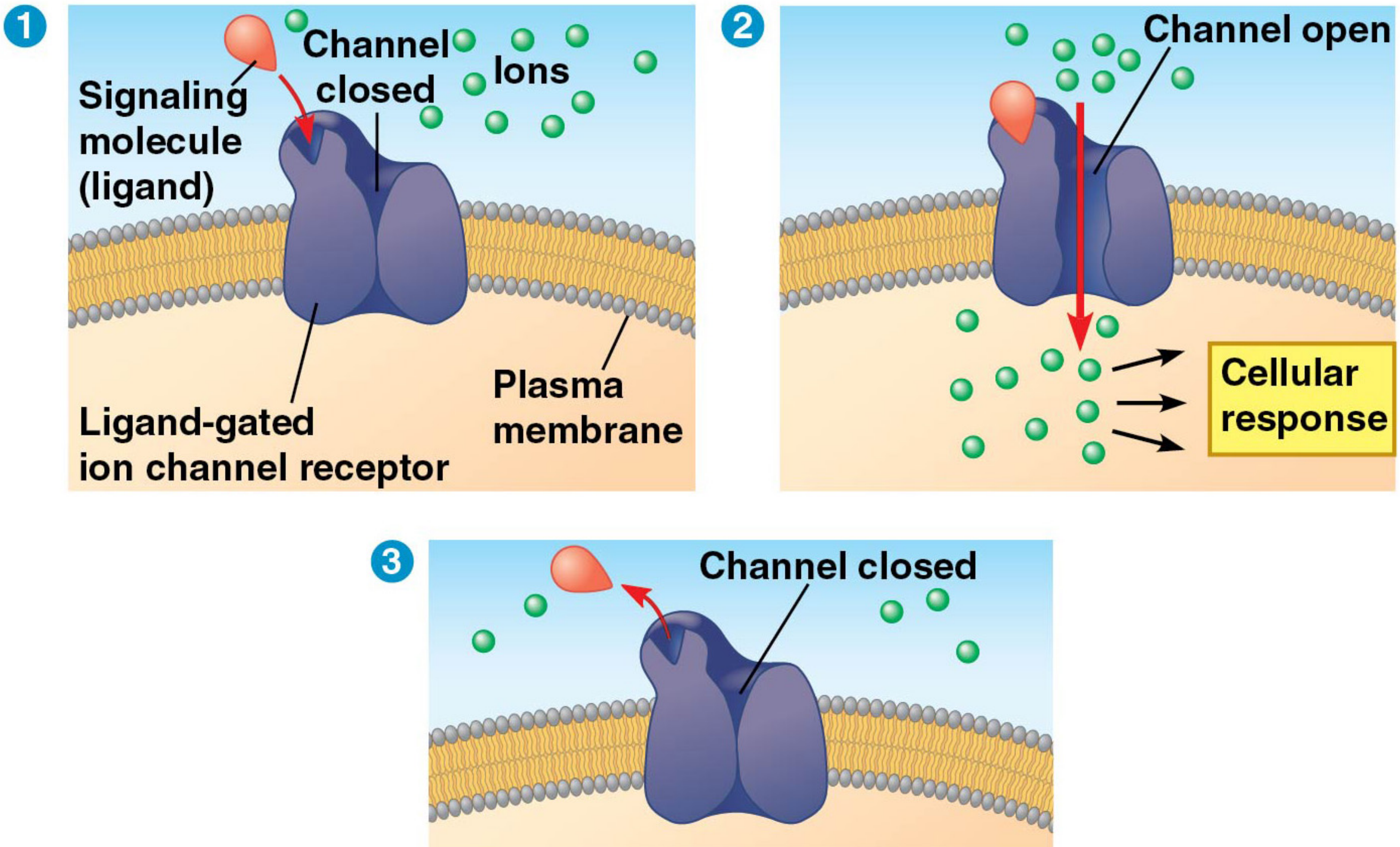
Figure 11.8c



Signaling molecule (ligand)
Ligand-binding site
α helix in the membrane
Tyrosines
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Receptor tyrosine kinase proteins (inactive monomers)
CYTOPLASM
1
Signaling molecule
EXTRACELLULAR FLUID
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
Dimer
2
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
6 ATP
6 ADP
P Tyr
P Tyr
P Tyr
Tyr P
Tyr P
Tyr P
Activated tyrosine kinase regions (unphosphorylated dimer)
Fully activated receptor tyrosine kinase (phosphorylated dimer)
CYTOPLASM
3
Activated relay proteins
EXTRACELLULAR FLUID
P Tyr
P Tyr
P Tyr
Tyr P
Tyr P
Tyr P
Cellular response 1
Cellular response 2
Inactive relay proteins
4

- 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

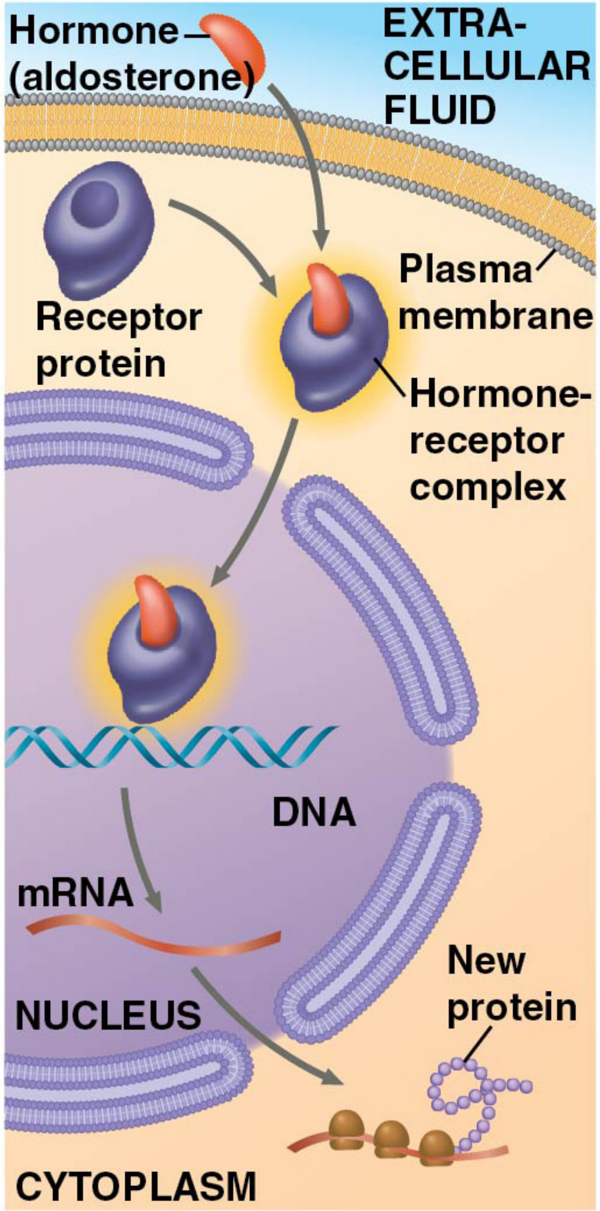
Figure 11.8d


1
Signaling molecule (ligand)
Channel closed
Ions
Ligand-gated ion channel receptor
Plasma membrane
2
Channel open
Cellular response
3
Channel closed

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 11.9



Hormone
(aldosterone)
EXTRA-
CELLULAR
FLUID
Plasma
membrane
Receptor
protein
Hormone-
receptor
complex
DNA
mRNA
NUCLEUS
New
protein
CYTOPLASM

CONCEPT 11.3: Transduction: Cascades of molecular interactions transmit signals from receptors to relay 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

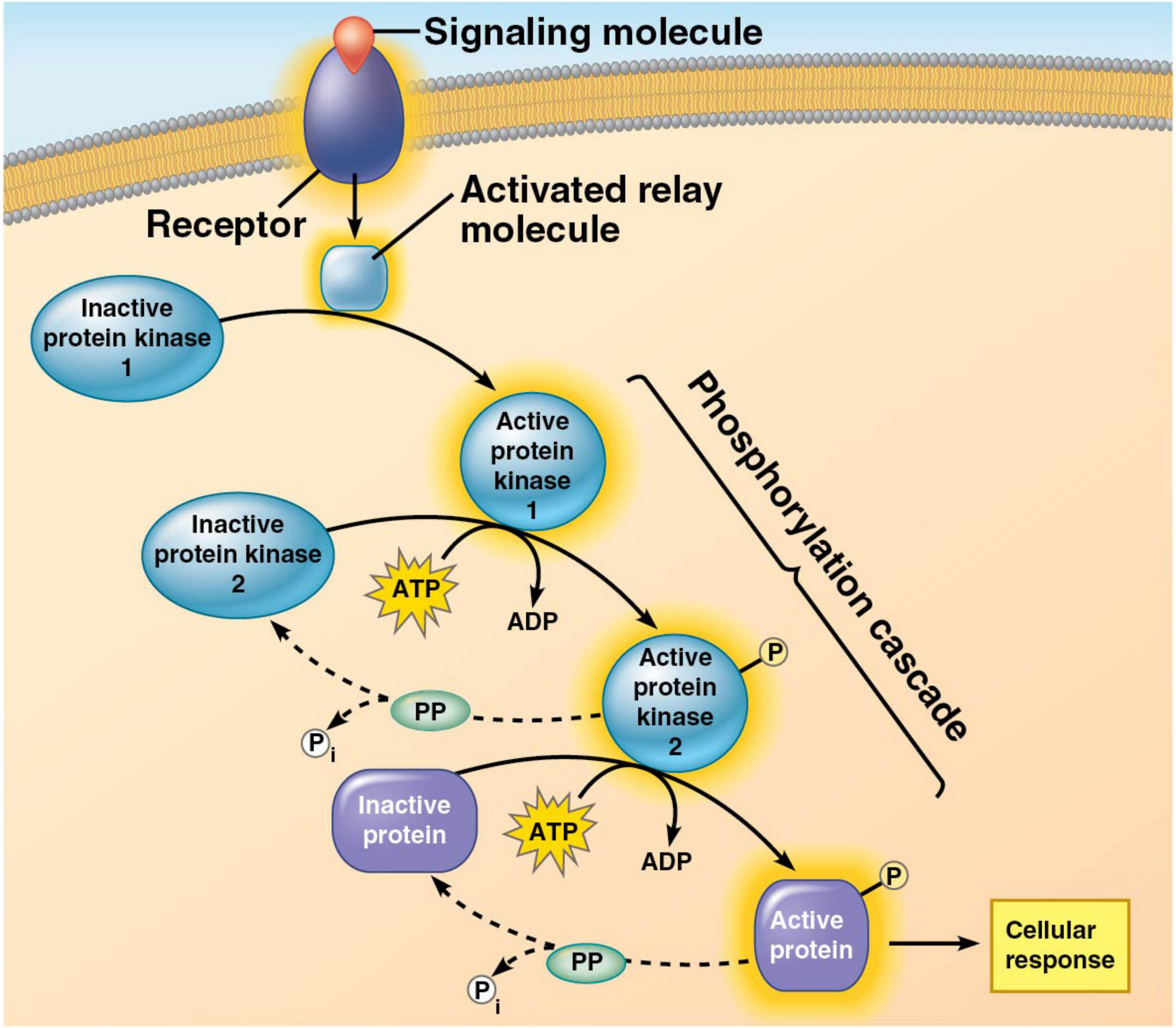
Signal Transduction Pathways

- The binding of a signaling molecule to a receptor triggers the first step in a chain of molecular interactions
- The activated 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, commonly a shape change in a protein

Protein Phosphorylation and Dephosphorylation

- Phosphorylation and dephosphorylation of proteins are commonly used in cells to regulate 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 11.10


Signaling molecule
Receptor
Activated relay molecule
Inactive protein kinase 1
Active protein kinase 1
Inactive protein kinase 2
ATP
ADP
Active protein kinase 2
P
PP
Pi
Inactive protein
ATP
ADP
Active protein
P
PP
Pi
Cellular response
Phosphorylation cascade

- **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

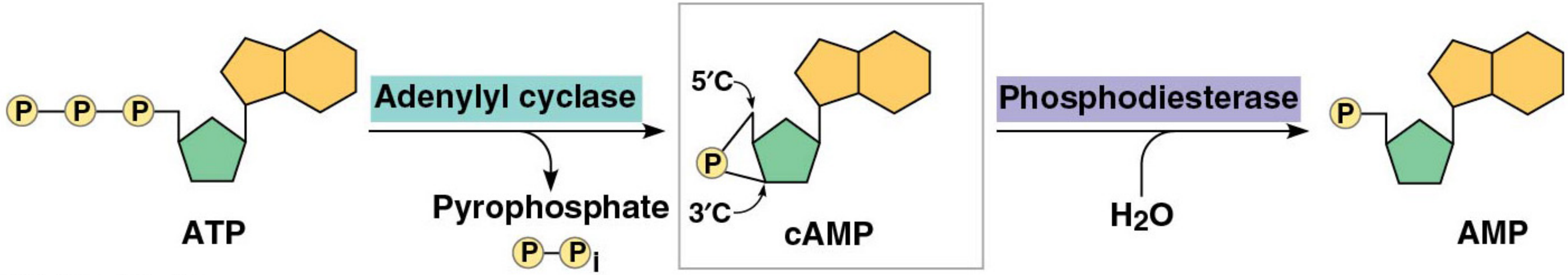
Small Molecules and Ions as Second Messengers

- 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)**, a small molecule produced from ATP, 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

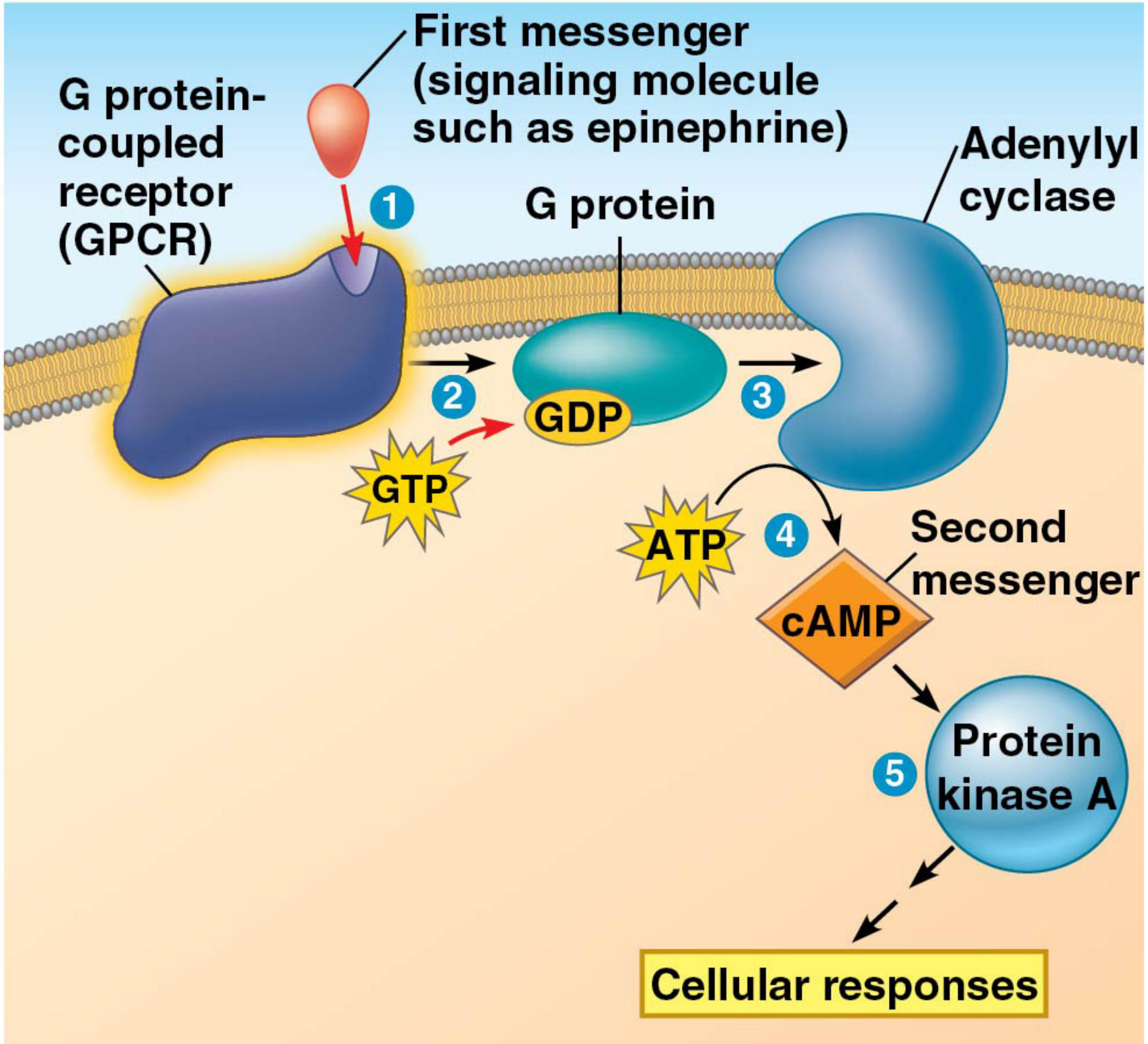
Figure 11.11



P
P
P
ATP
Adenylyl cyclase
Pyrophosphate
P
P
i
5′C
P
3′C
cAMP
Phosphodiesterase
H_2O
P
AMP

- 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 11.12

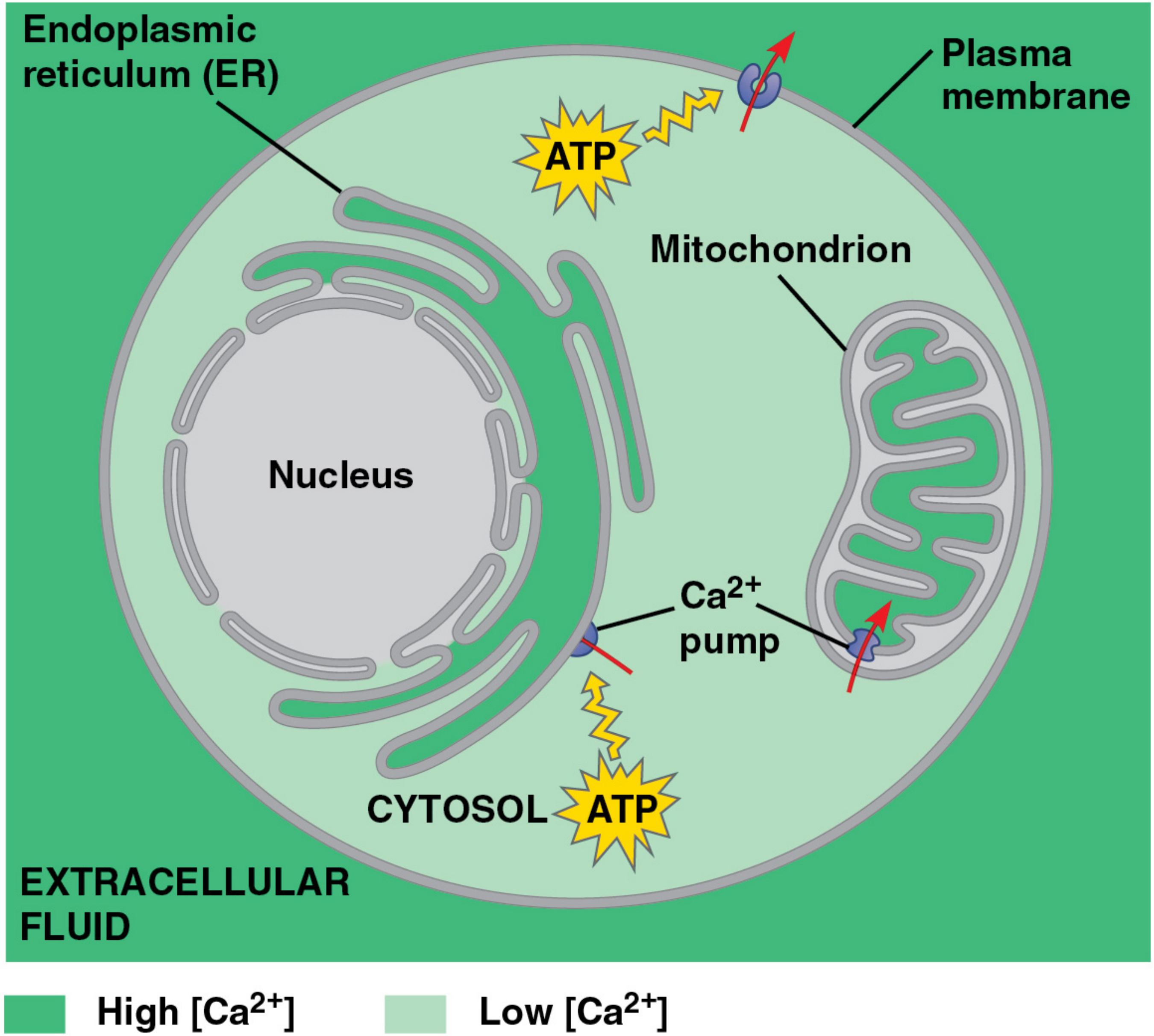

First messenger (signaling molecule such as epinephrine)
G protein-coupled receptor (GPCR)
G protein
Adenylyl cyclase
1
2
3
4
5
GDP
GTP
ATP
cAMP
Second messenger
Protein kinase A
Cellular responses

- 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; even more so than cAMP
- 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

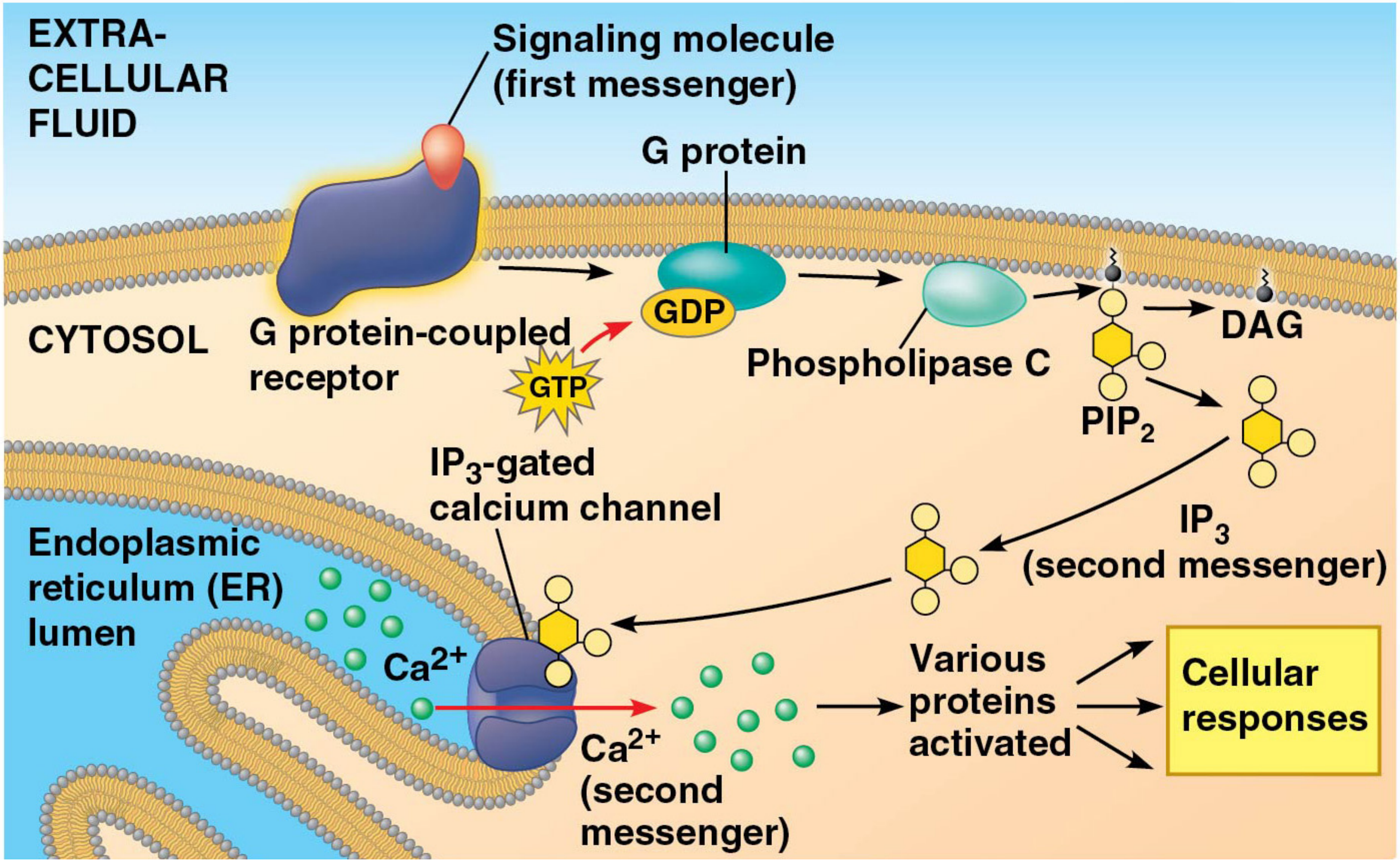
Figure 11.13



Endoplasmic reticulum (ER)
ATP
Plasma membrane
Mitochondrion
Nucleus
Ca2+ pump
CYTOSOL
ATP
EXTRACELLULAR FLUID
High [Ca2+]
Low [Ca2+]

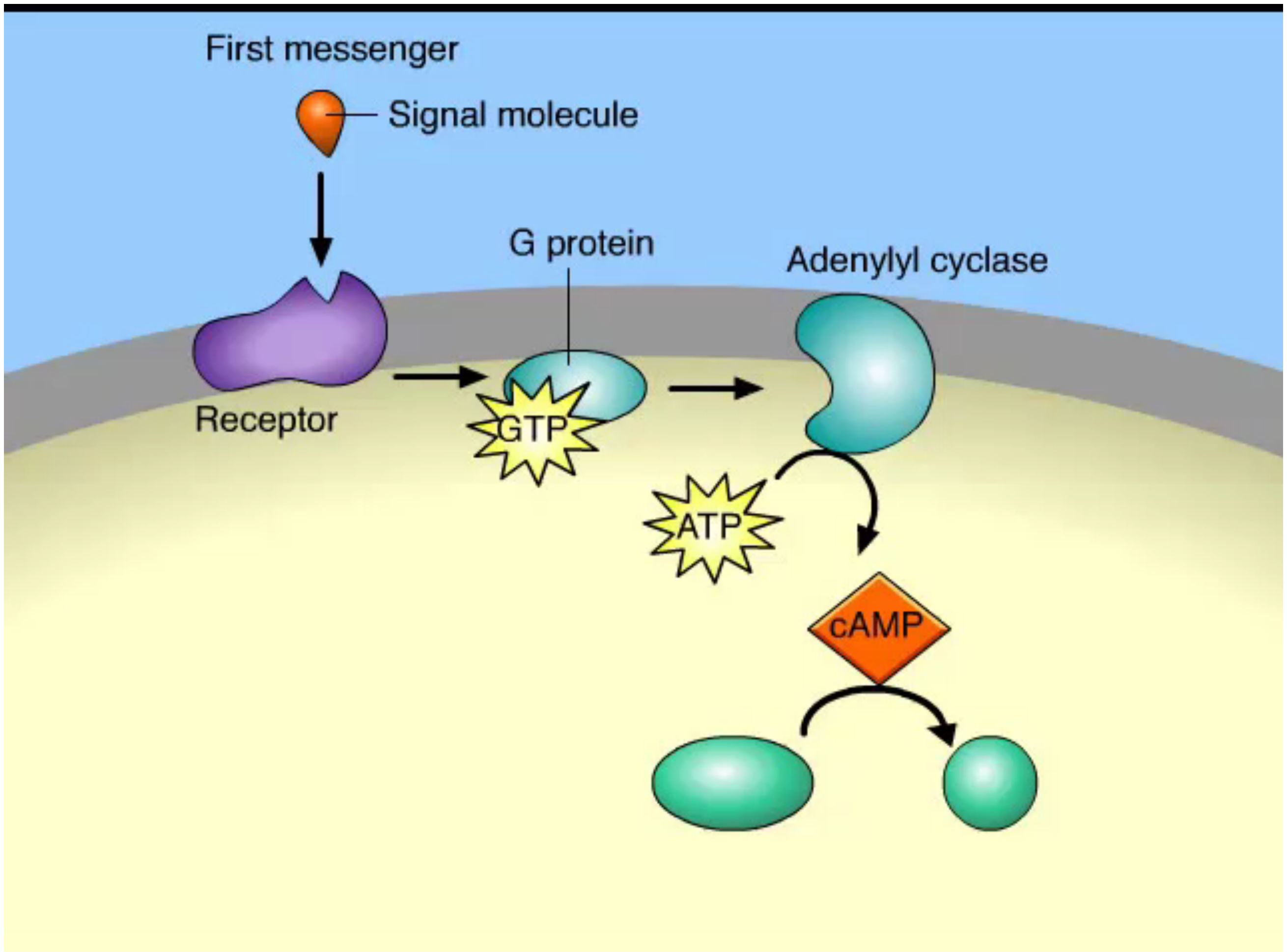
- A signal relayed by a signal transduction pathway may trigger an increase in calcium in the cytosol
- Pathways leading to the release of calcium involve **inositol triphosphate (IP_3)** and **diacylglycerol (DAG)** as additional second messengers
- These two are produced by cleavage of a certain kind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

Figure 11.14



EXTRA-
CELLULAR
FLUID
Signaling molecule
(first messenger)
G protein
CYTOSOL
G protein-coupled
receptor
GDP
GTP
Phospholipase C
DAG
PIP2
IP3-gated
calcium channel
IP3
(second messenger)
Endoplasmic
reticulum (ER)
lumen
Ca2+
Ca2+
(second
messenger)
Various
proteins
activated
Cellular
responses

Animation: Signal Transduction Pathways



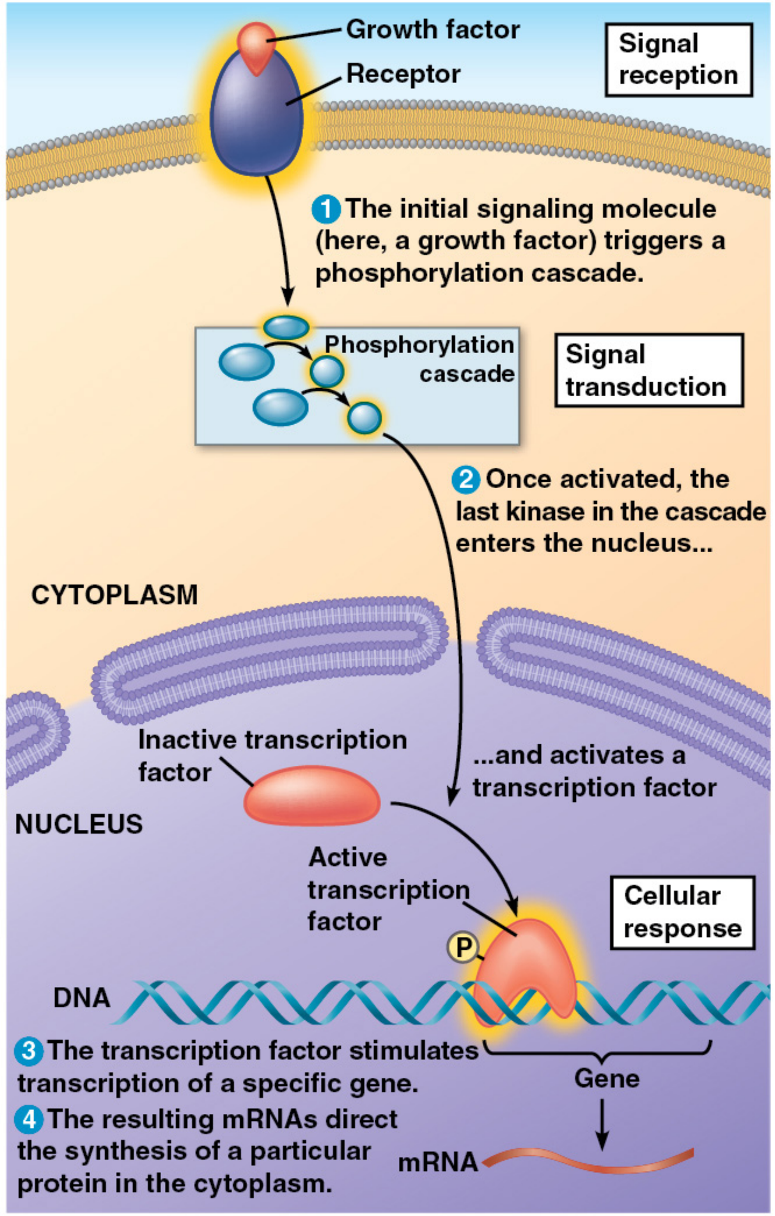
CONCEPT 11.4: Cellular response: Cell signaling leads to regulation of transcription or cytoplasmic activities

- 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

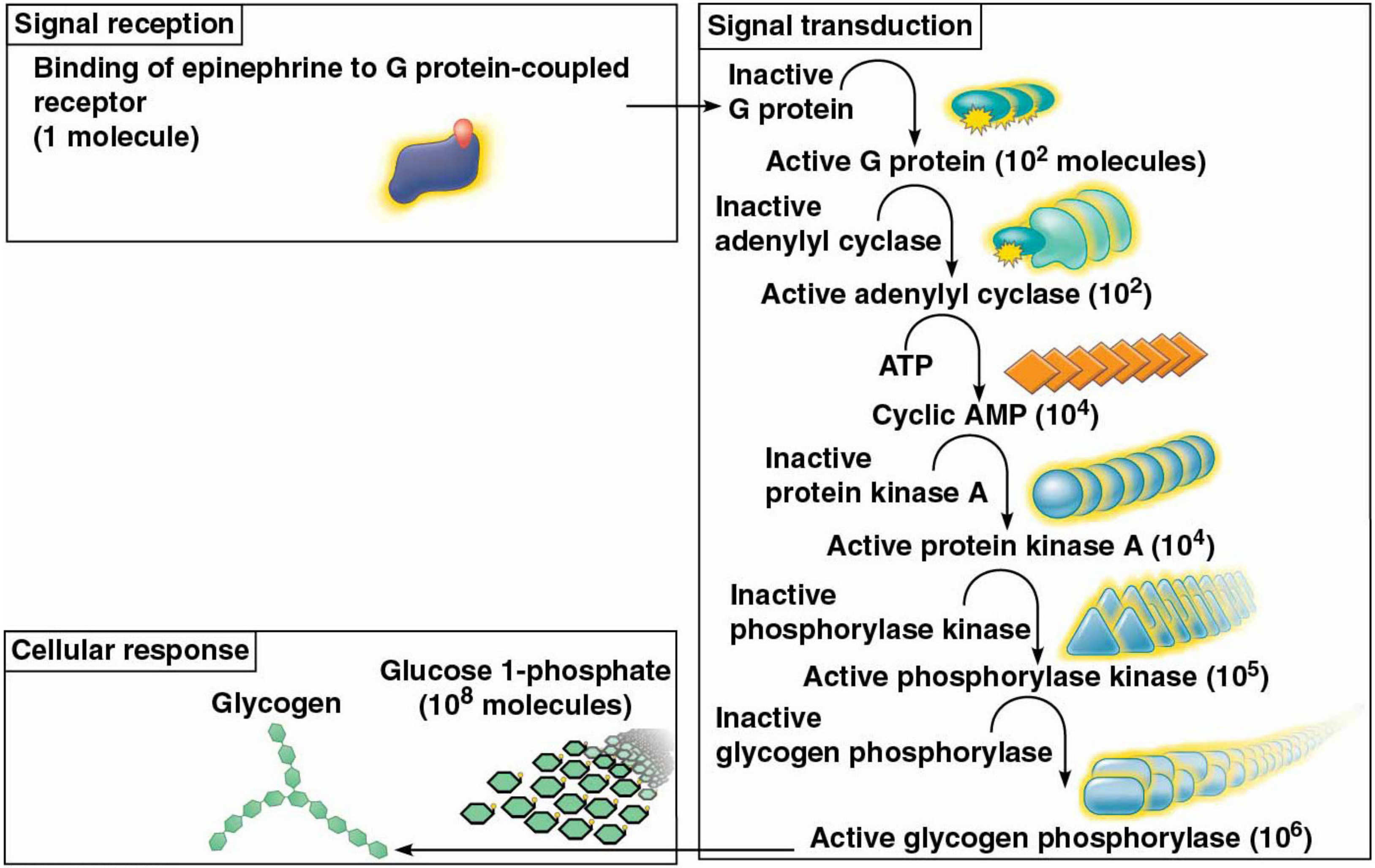
Figure 11.15



Growth factor
Receptor
Signal reception
1 The initial signaling molecule (here, a growth factor) triggers a phosphorylation cascade.
Phosphorylation cascade
Signal transduction
2 Once activated, the last kinase in the cascade enters the nucleus...
CYTOPLASM
Inactive transcription factor
...and activates a transcription factor
NUCLEUS
Active transcription factor
Cellular response
P
DNA
3 The transcription factor stimulates transcription of a specific gene.
Gene
4 The resulting mRNAs direct the synthesis of a particular protein in the cytoplasm.
mRNA

- Other pathways may regulate the activity of proteins 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 the activity of a metabolic enzyme

Figure 11.16


Signal reception
Binding of epinephrine to G protein-coupled receptor (1 molecule)
Signal transduction
Inactive G protein
Active G protein (10^2 molecules)
Inactive adenylyl cyclase
Active adenylyl cyclase (10^2)
ATP
Cyclic AMP (10^4)
Inactive protein kinase A
Active protein kinase A (10^4)
Inactive phosphorylase kinase
Active phosphorylase kinase (10^5)
Inactive glycogen phosphorylase
Active glycogen phosphorylase (10^6)
Cellular response
Glycogen
Glucose 1-phosphate (10^8 molecules)

- Signal receptors, relay molecules, and second messengers participate in a variety of pathways, leading to nuclear and cytoplasmic responses, including 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

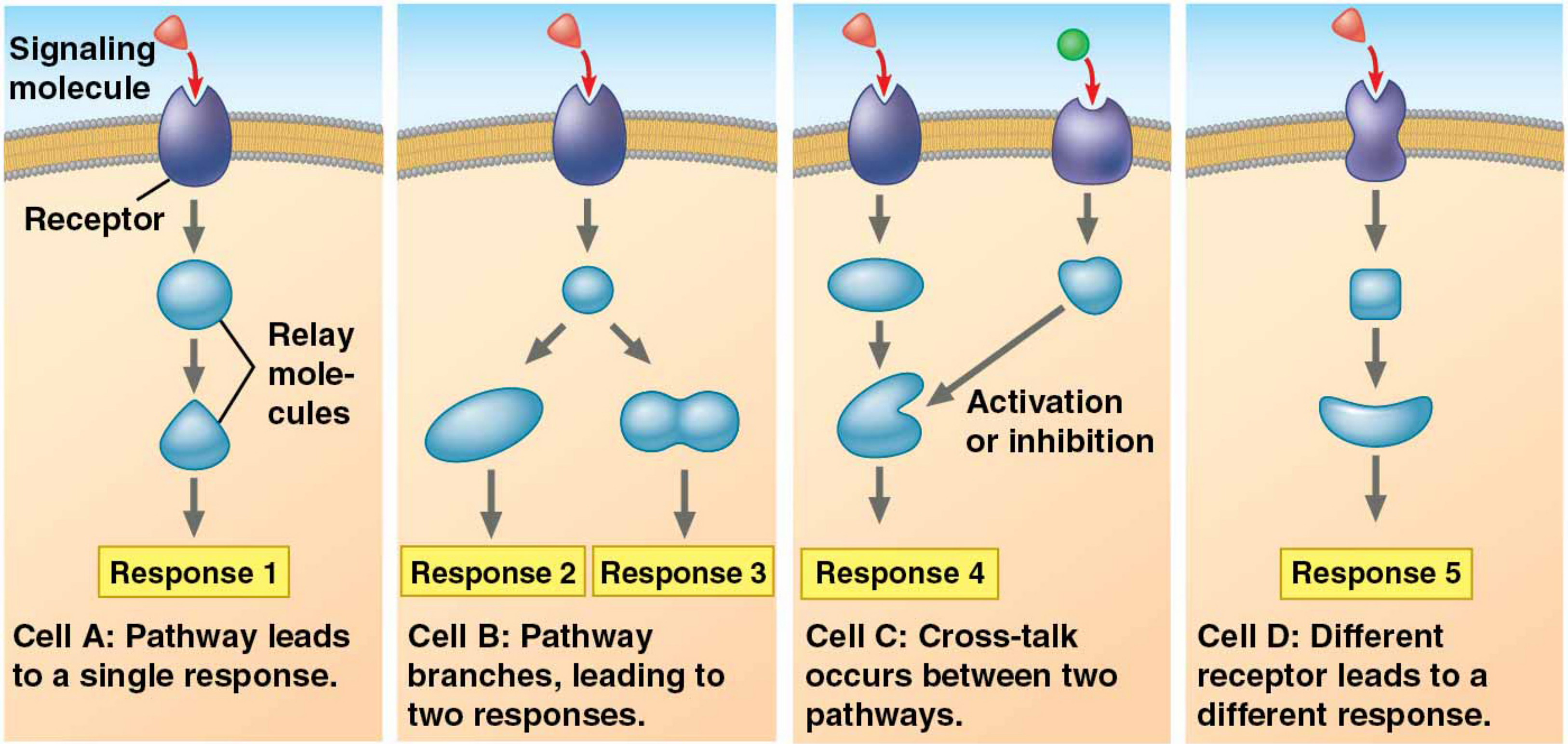
Signal Amplification

- 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 11.17

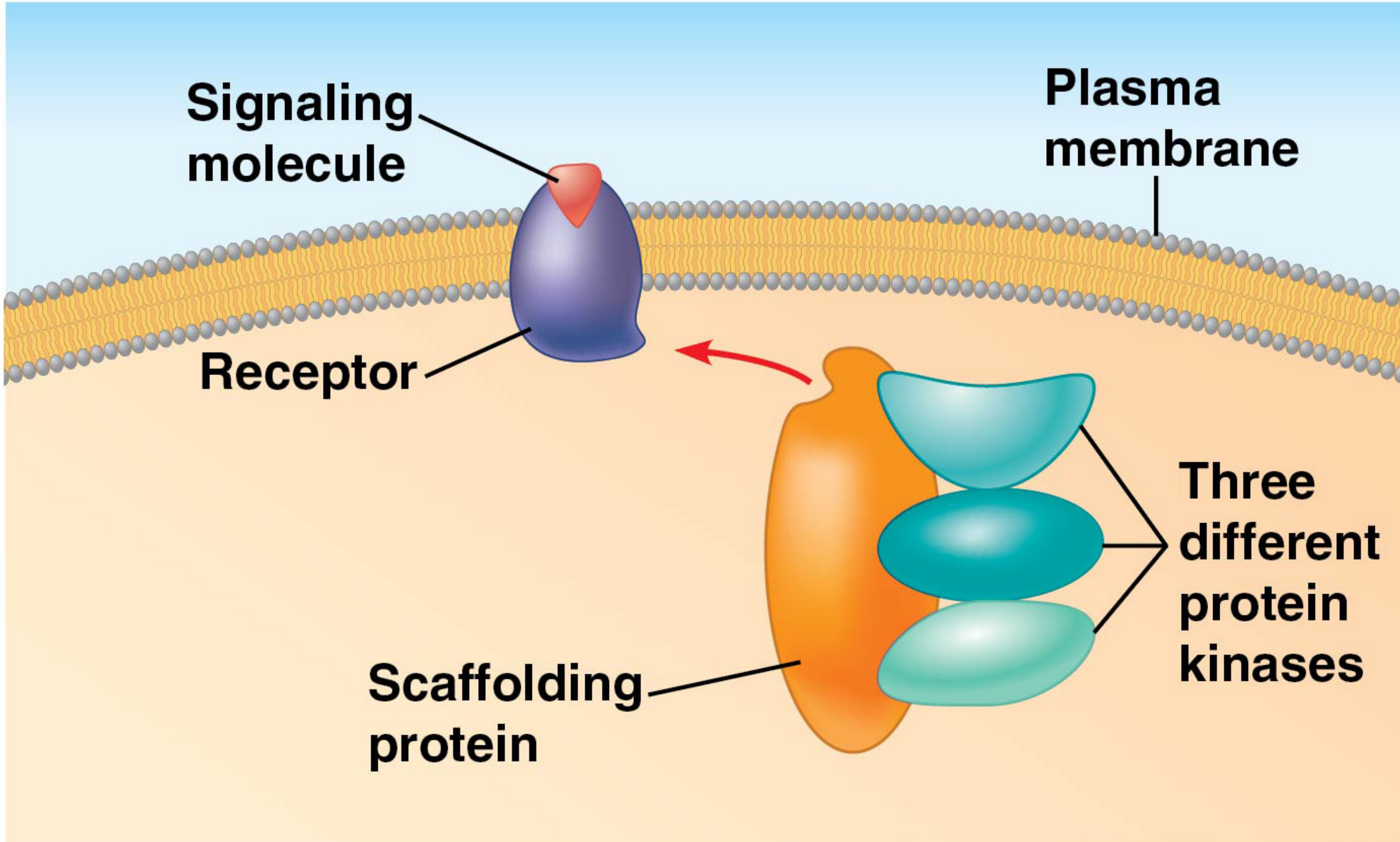


Signaling molecule
Receptor
Relay mole-cules
Response 1
Cell A: Pathway leads to a single response.
Response 2
Response 3
Cell B: Pathway branches, leading to two responses.
Activation or inhibition
Response 4
Cell C: Cross-talk occurs between two pathways.
Response 5
Cell D: Different receptor leads to a different response.

Signaling Efficiency: Scaffolding Proteins and Signaling Complexes

- **Scaffolding proteins** are large relay proteins to which several 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 11.18



Signaling molecule
Plasma membrane
Receptor
Three different protein kinases
Scaffolding protein

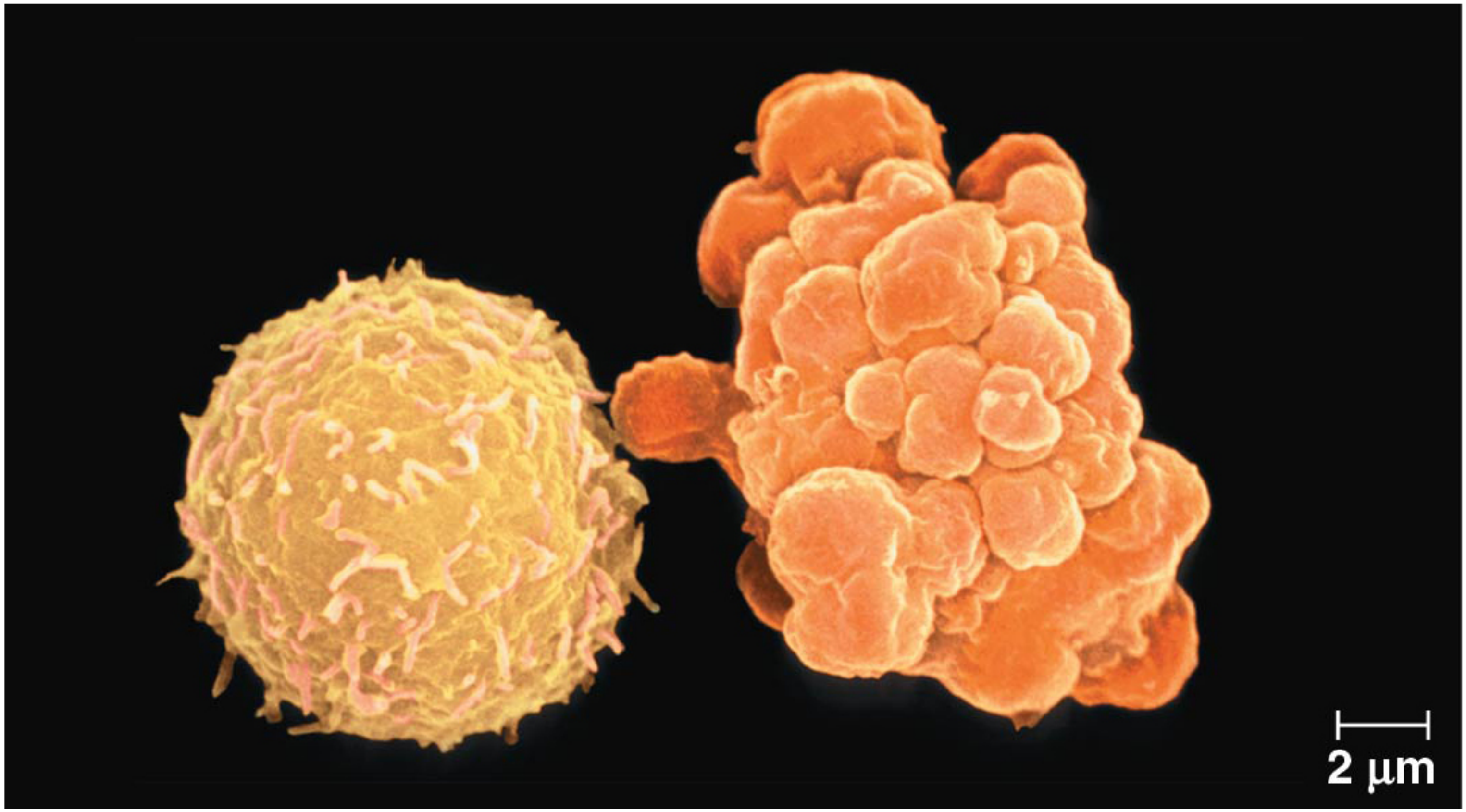
Termination of the Signal

- *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 11.5: Apoptosis requires integration of 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 11.19

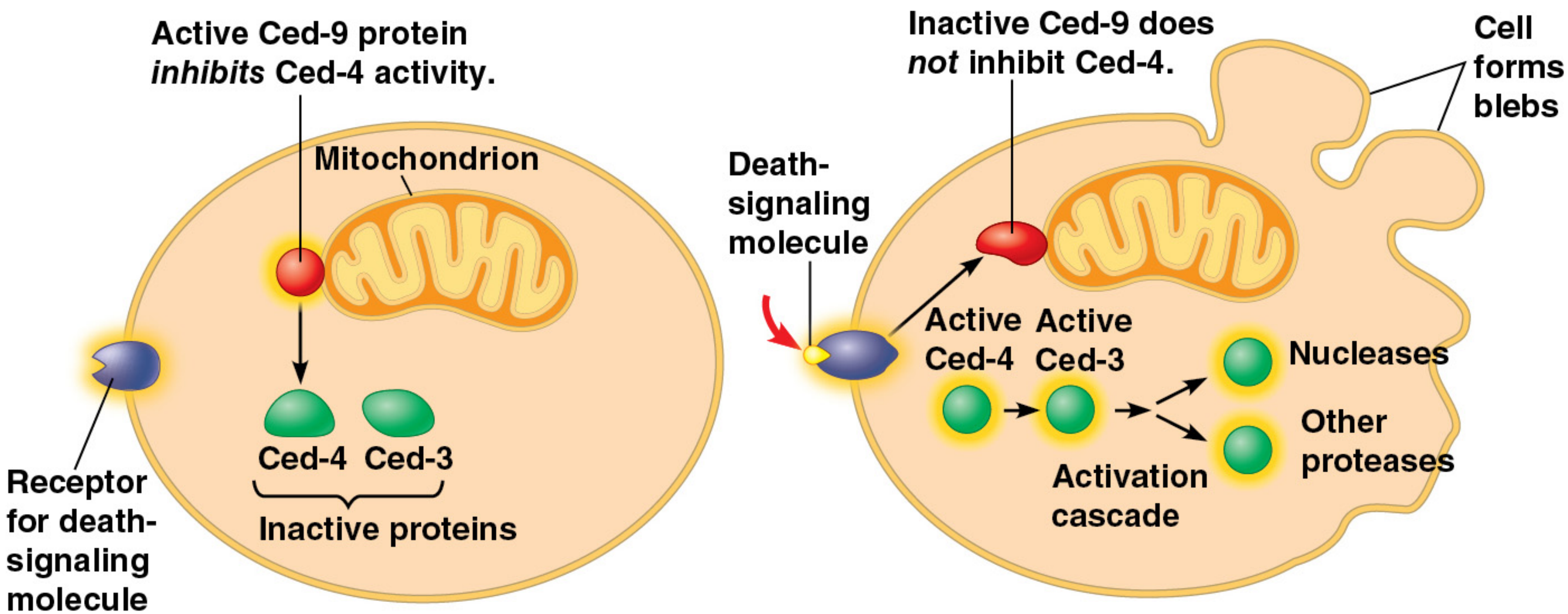


Apoptosis in the Soil Worm Caenorhabditis elegans

- In worms and other organisms, apoptosis is triggered by signals that activate a cascade of "suicide" proteins in the cells destined to die
- In *C. elegans*, a protein called Ced-9,in the outer mitochondrial membrane serves as a master regulator of apoptosis
- Ced-9 acts as a brake in the absence of a signal promoting apoptosis

- When the death signal is received, an apoptosis-inhibiting protein (Ced-9) is inactivated, which disables the “brake”
- The apoptotic pathway activates proteases and nucleases, that cut up proteins and DNA of the cell
- The chief caspase in the nematode is called Ced-3

Figure 11.20



(a) No death signal

(b) Death signal

Apoptotic Pathways and the Signals That Trigger Them

- In humans and other mammals, several different pathways, involving 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 11.21

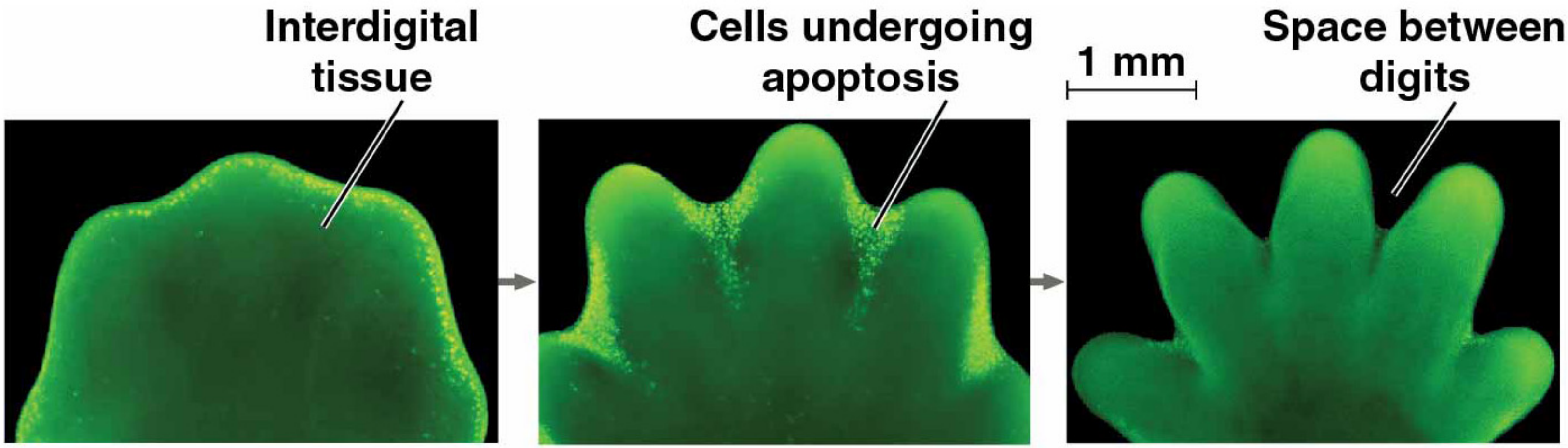

Interdigital tissue
Cells undergoing apoptosis
1 mm
Space between digits

Figure 11.UN01

Figure 11.UN02

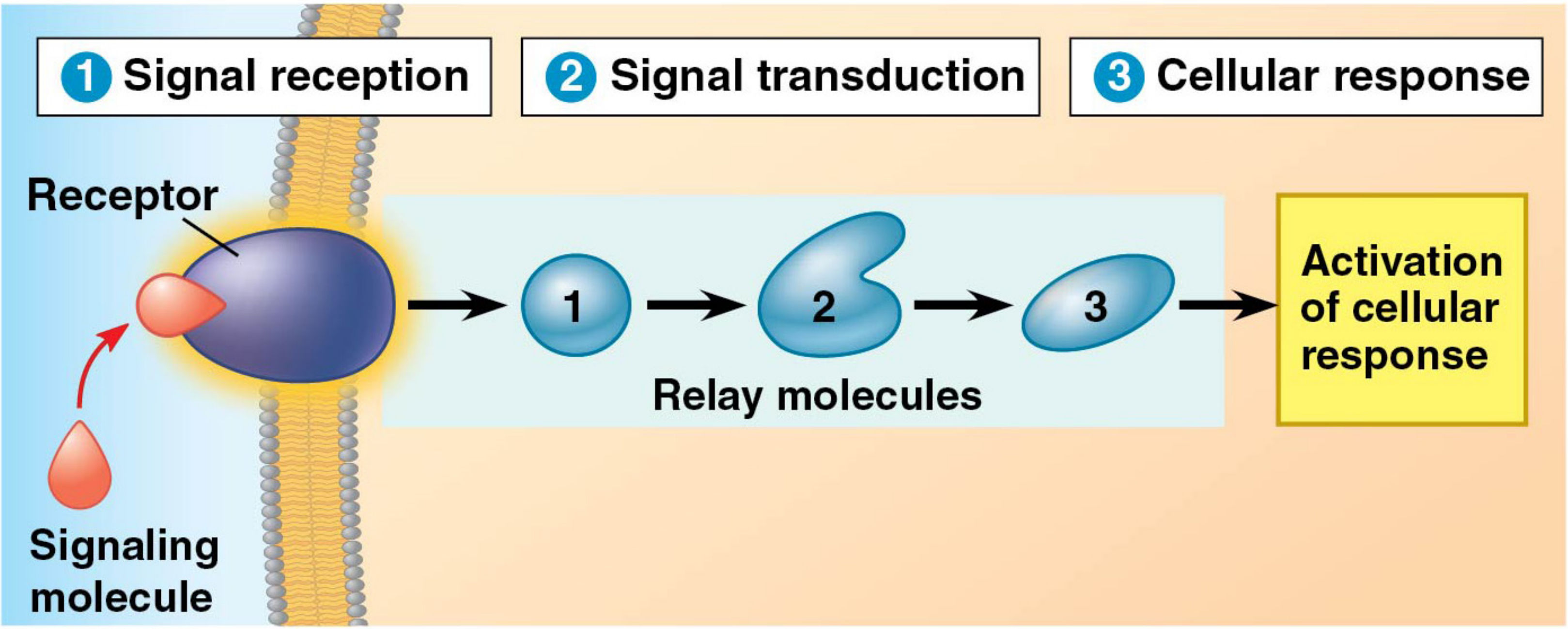


Figure 11.UN03