CAMPBELL BIOLOGY IN FOCUS

URRY • CAIN • WASSERMAN • MINORSKY • REECE

5

Membrane Transport and Cell Signaling

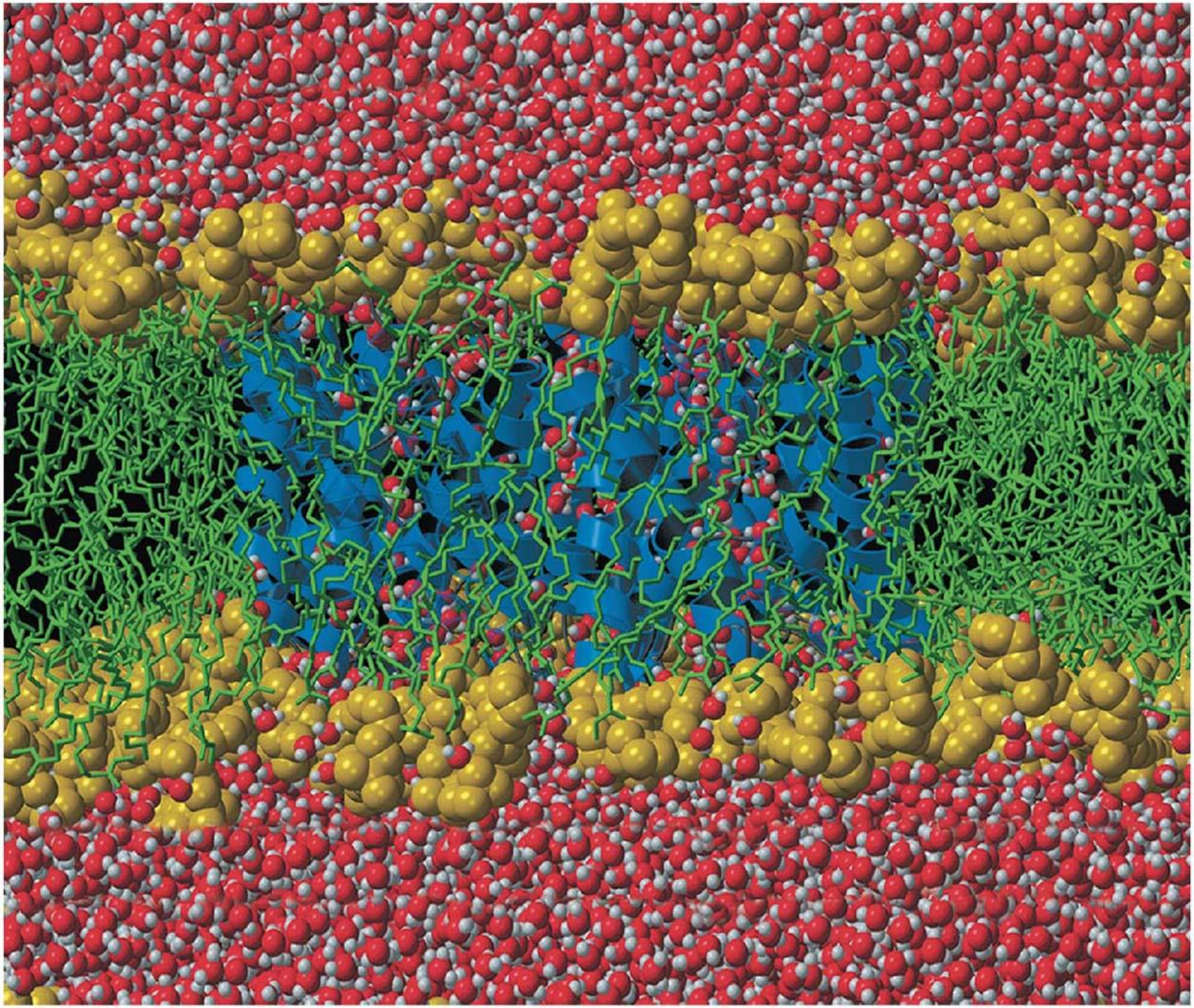
Lecture Presentations by
Kathleen Fitzpatrick and
Nicole Tunbridge,
Simon Fraser University

SECOND EDITION

Overview: Life at the Edge

- The plasma membrane separates the living cell from its surroundings
- The plasma membrane exhibits **selective permeability**, allowing some substances to cross it more easily than others

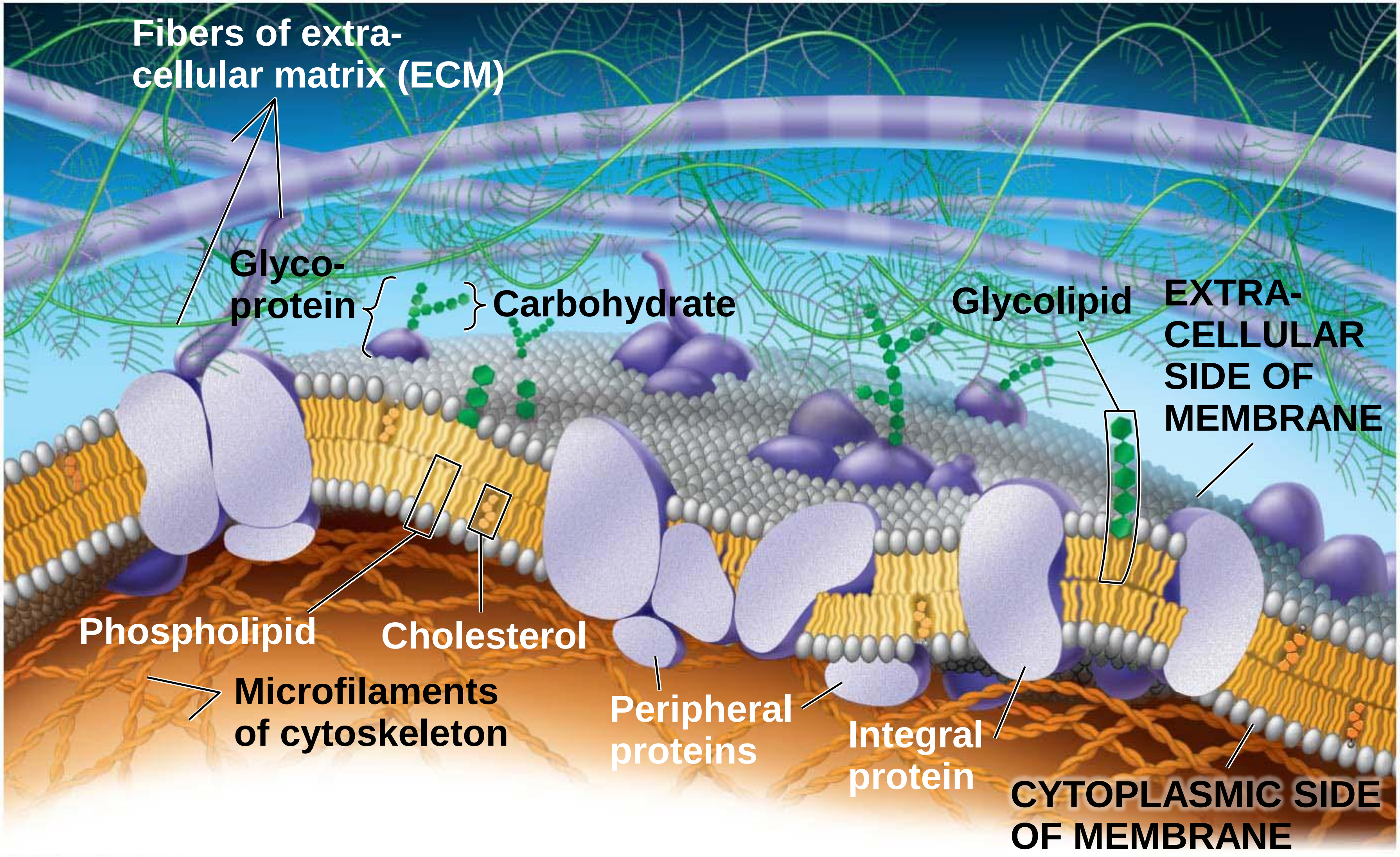
Figure 5.1



Concept 5.1: Cellular membranes are fluid mosaics of lipids and proteins

- Phospholipids are the most abundant lipid in most membranes
- Phospholipids are **amphipathic** molecules, containing hydrophobic and hydrophilic regions
- A phospholipid bilayer can exist as a stable boundary between two aqueous compartments

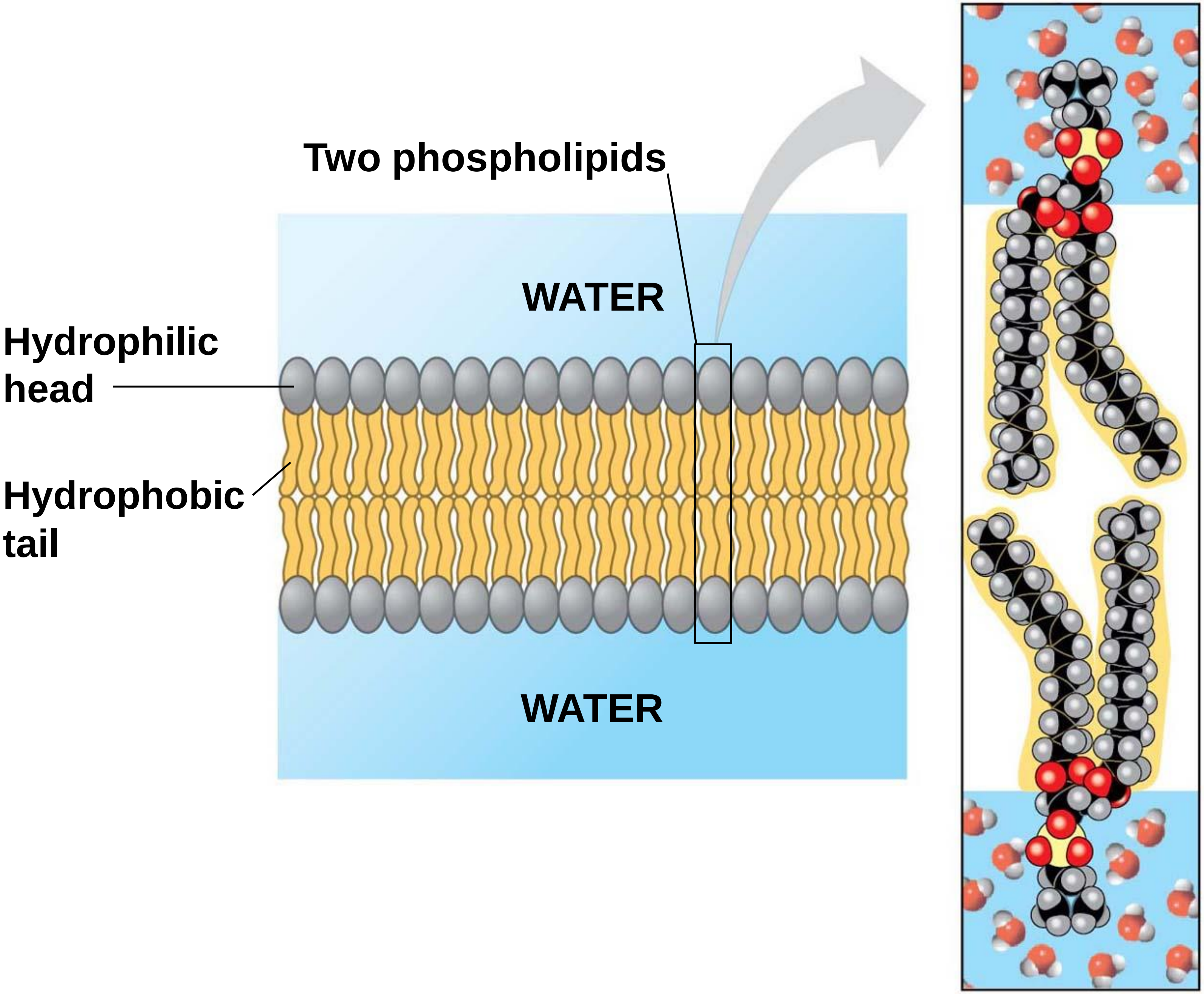
Figure 5.2



Fibers of extra-cellular matrix (ECM)
Glyco-protein
Carbohydrate
Glycolipid
EXTRA-CELLULAR SIDE OF MEMBRANE
Phospholipid
Cholesterol
Microfilaments of cytoskeleton
Peripheral proteins
Integral protein
CYTOPLASMIC SIDE OF MEMBRANE

- Most membrane proteins are also amphipathic and reside in the bilayer with their hydrophilic portions protruding
- The **fluid mosaic model** states that the membrane is a mosaic of protein molecules bobbing in a fluid bilayer of phospholipids
- Groups of certain proteins or certain lipids may associate in long-lasting, specialized patches

Figure 5.3


Two phospholipids
WATER
Hydrophilic head
Hydrophobic tail
WATER

The Fluidity of Membranes

- Most of the lipids and some proteins in a membrane can shift about laterally
- The lateral movement of phospholipids is rapid; proteins move more slowly
- Some proteins move in a directed manner; others seem to be anchored in place

Figure 5.4-s1

Results

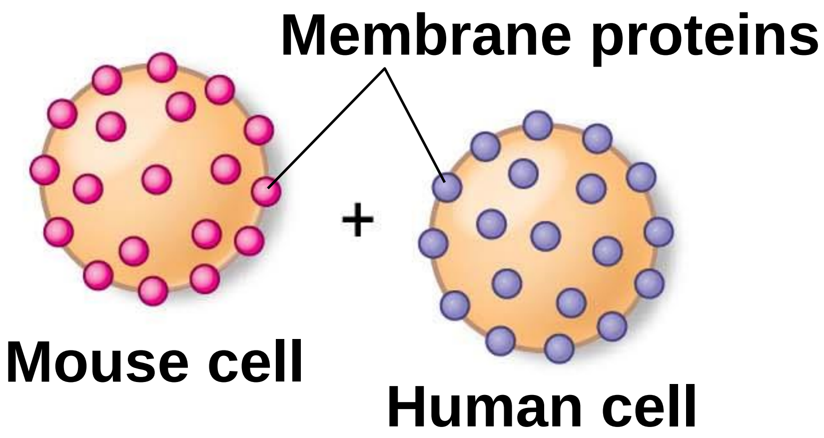


Figure 5.4-s2

Results

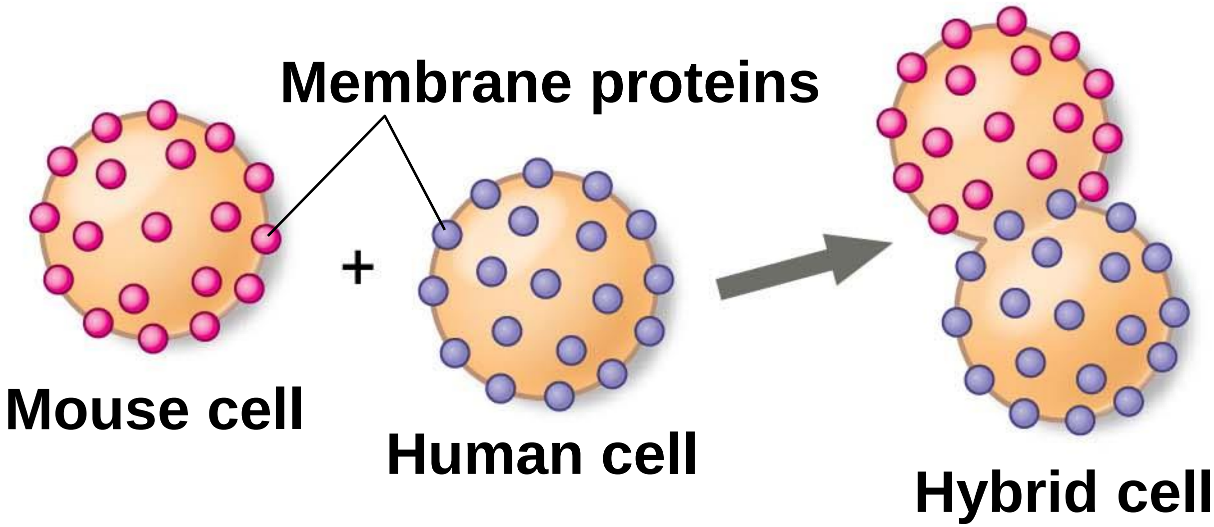
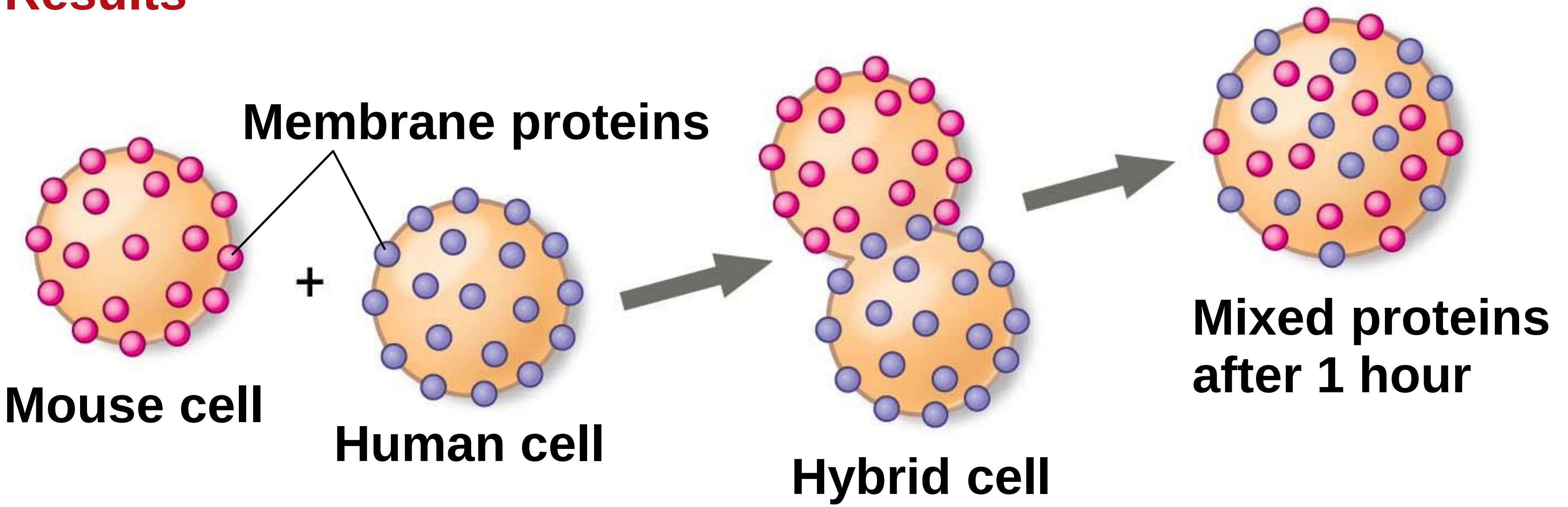


Figure 5.4-s3

Results

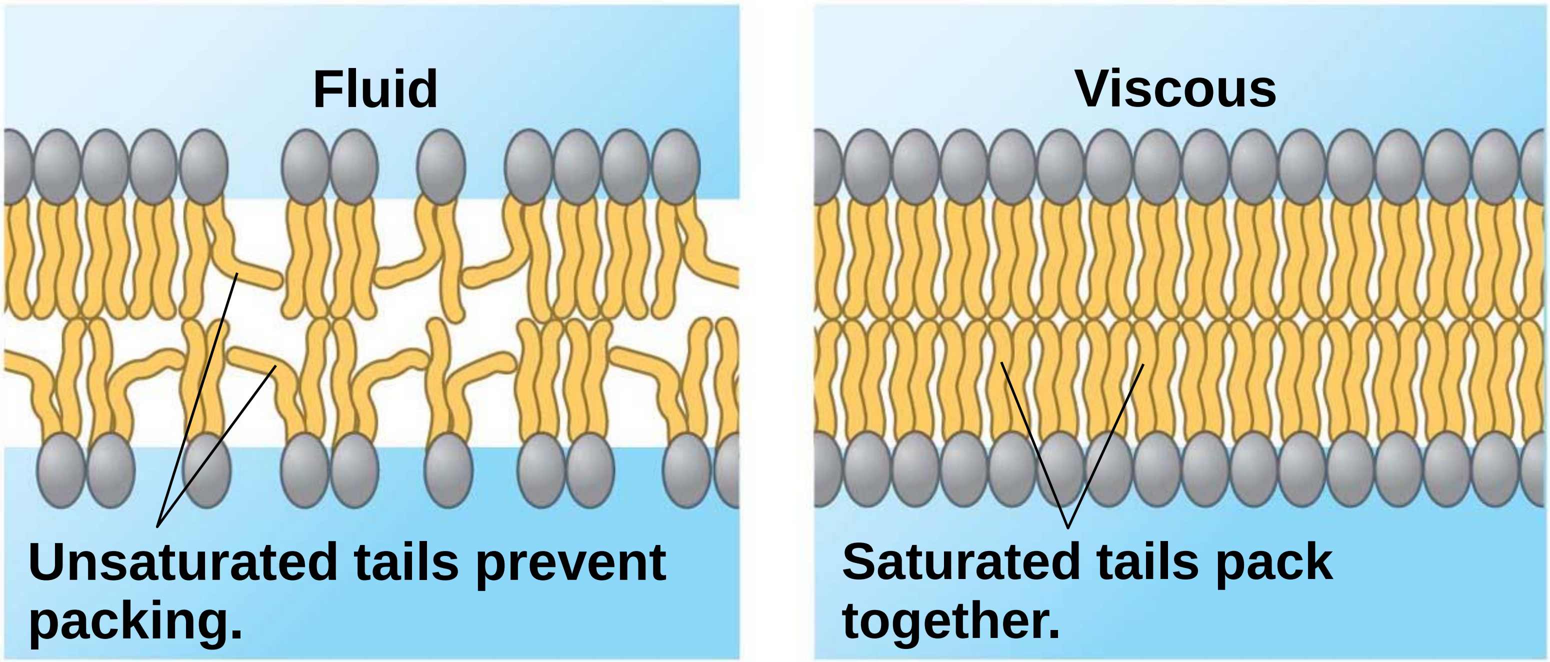


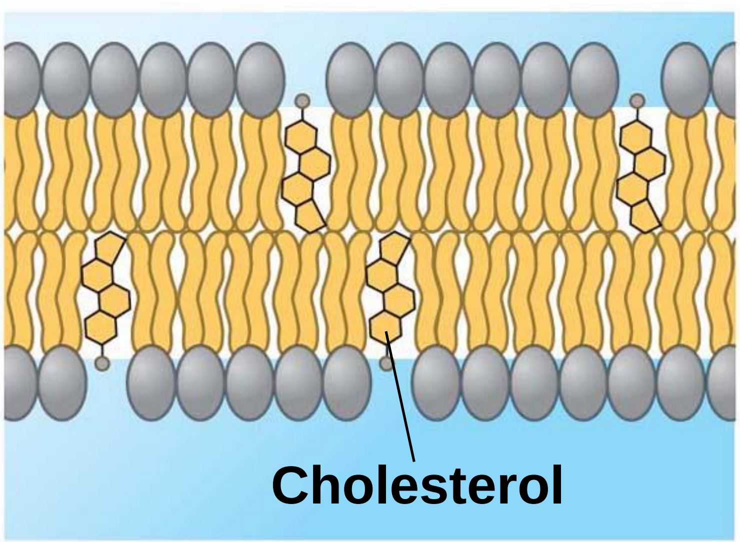
- As temperatures cool, membranes switch from a fluid state to a solid state
- The temperature at which a membrane solidifies depends on the types of lipids
- A membrane remains fluid to a lower temperature if it is rich in phospholipids with unsaturated hydrocarbon tails
- Membranes must be fluid to work properly; they are usually about as fluid as salad oil

- The steroid cholesterol has different effects on membrane fluidity at different temperatures
- At warm temperatures (such as 37°C), cholesterol restrains movement of phospholipids
- At cool temperatures, it maintains fluidity by preventing tight packing

Figure 5.5

(a) Unsaturated versus saturated hydrocarbon tails.





(b) Cholesterol reduces membrane fluidity at moderate temperatures, but at low temperatures hinders solidification.

Evolution of Differences in Membrane Lipid Composition

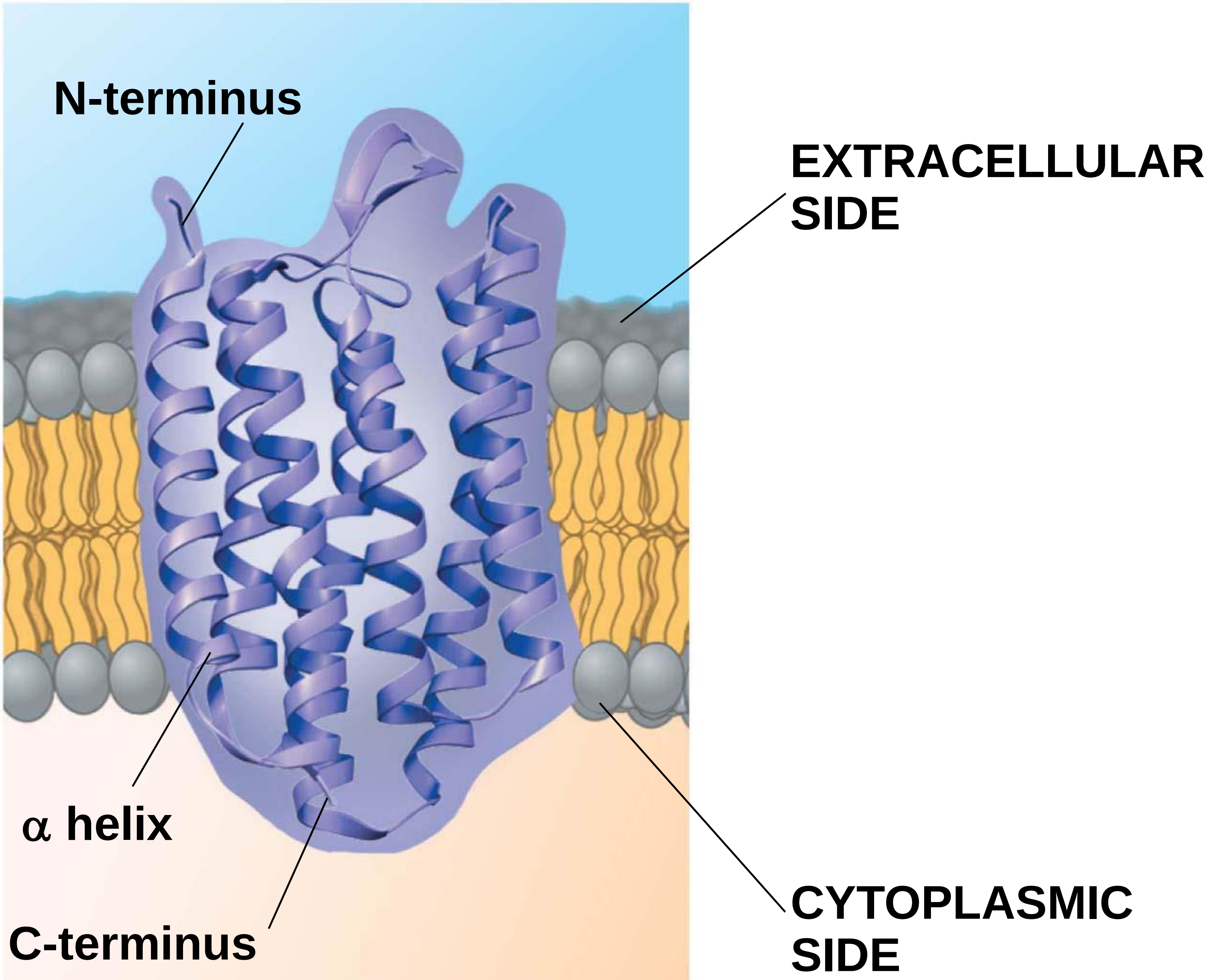
- Variations in lipid composition of cell membranes of many species appear to be adaptations to specific environmental conditions
- Ability to change the lipid compositions in response to temperature changes has evolved in organisms that live where temperatures vary

Membrane Proteins and Their Functions

- A membrane is a collage of different proteins embedded in the fluid matrix of the lipid bilayer
- Proteins determine most of the membrane's specific functions

- **Integral proteins** penetrate the hydrophobic interior of the lipid bilayer
- Integral proteins that span the membrane are called transmembrane proteins
- The hydrophobic regions of an integral protein consist of one or more stretches of nonpolar amino acids, often coiled into α helices
- **Peripheral proteins** are loosely bound to the surface of the membrane

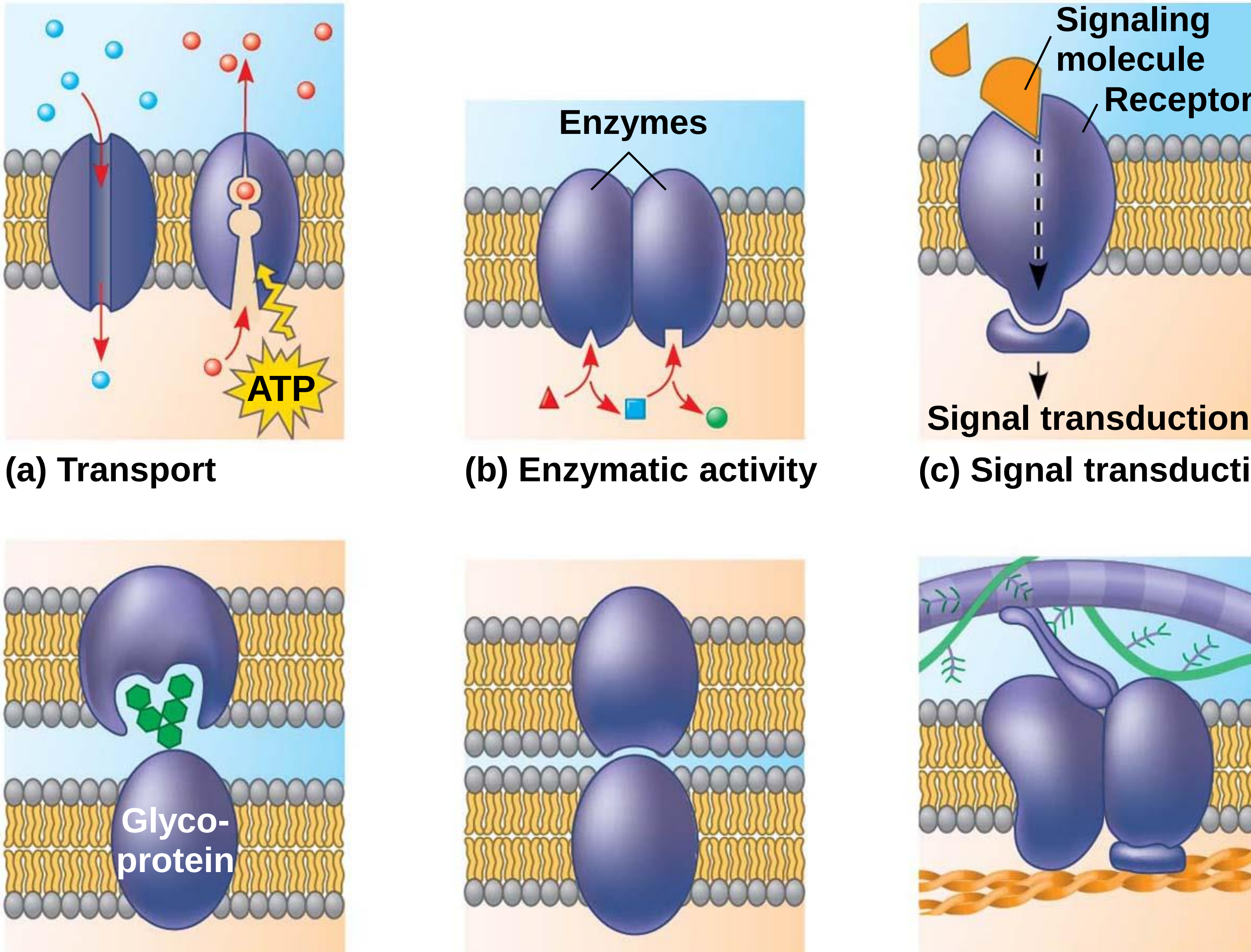
Figure 5.6



N-terminus
EXTRACELLULAR SIDE
α helix
C-terminus
CYTOPLASMIC SIDE

- Six major functions of membrane proteins
  - Transport
  - Enzymatic activity
  - Signal transduction
  - Cell-cell recognition
  - Intercellular joining
  - Attachment to the cytoskeleton and extracellular matrix (ECM)

Figure 5.7



(a) Transport

(b) Enzymatic activity

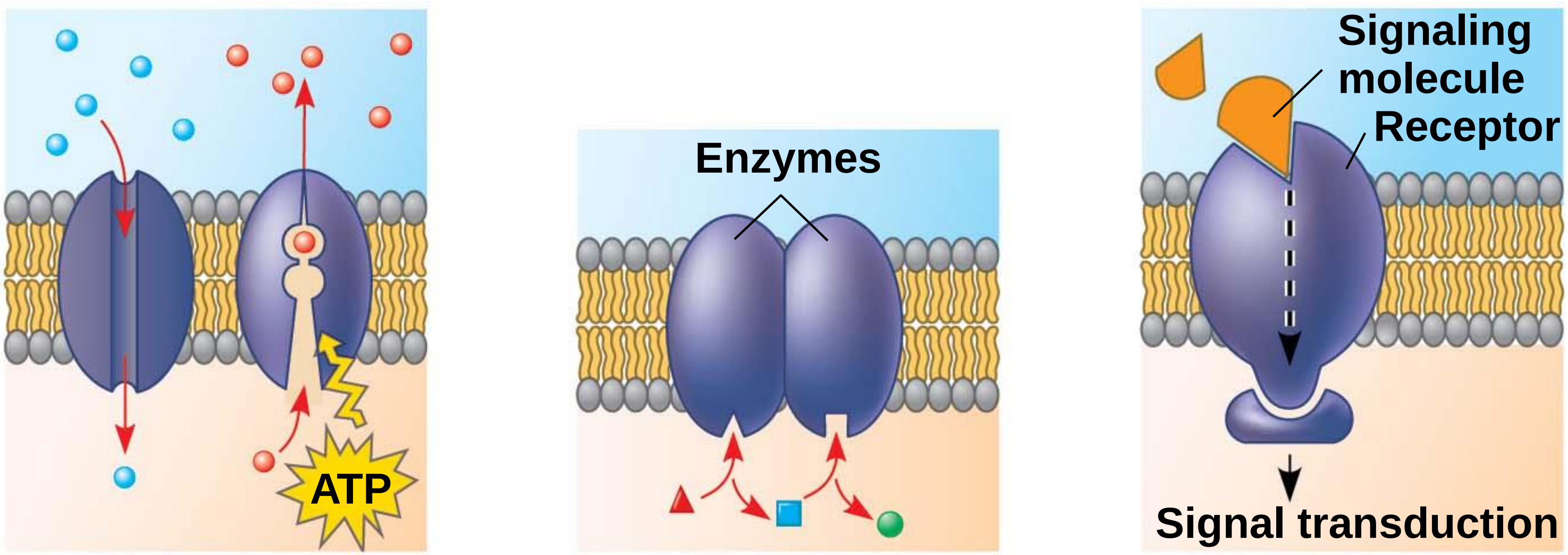
(c) Signal transduction

(d) Cell-cell recognition

(e) Intercellular joining

(f) Attachment to the cytoskeleton and extra-cellular matrix (ECM)

Figure 5.7-1

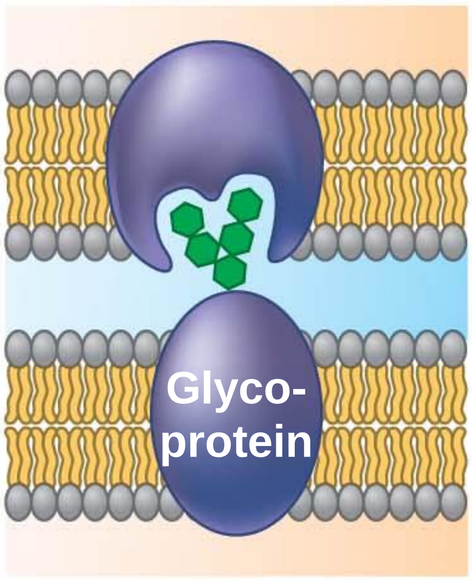


(a) Transport

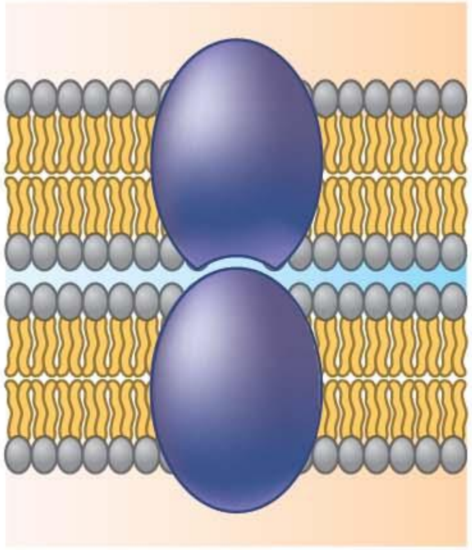
(b) Enzymatic activity

(c) Signal transduction

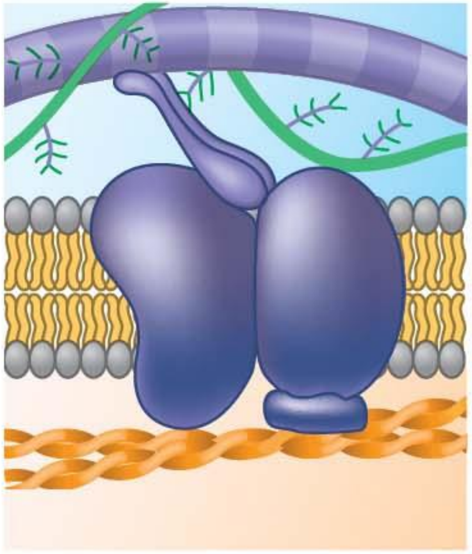
Figure 5.7-2



(d) Cell-cell recognition



(e) Intercellular joining



(f) Attachment to the cytoskeleton and extra-cellular matrix (ECM)

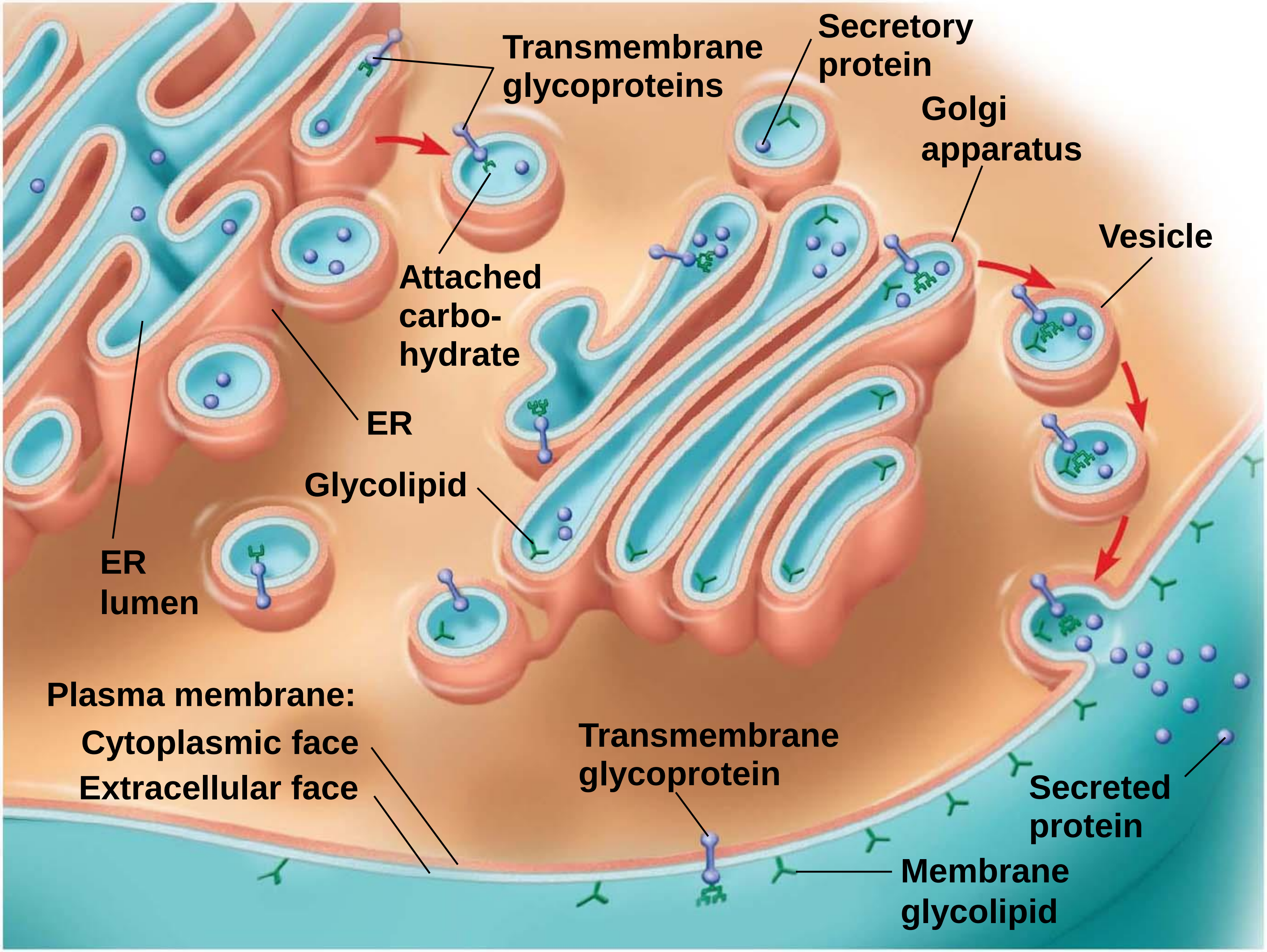
The Role of Membrane Carbohydrates in Cell-Cell Recognition

- Cells recognize each other by binding to surface molecules, often containing carbohydrates, on the extracellular surface of the plasma membrane
- Membrane carbohydrates may be covalently bonded to lipids (forming **glycolipids**) or, more commonly, to proteins (forming **glycoproteins**)
- Carbohydrates on the external side of the plasma membrane vary among species, individuals, and even cell types in an individual

Synthesis and Sidedness of Membranes

- Membranes have distinct inside and outside faces
- The asymmetrical arrangement of proteins, lipids, and associated carbohydrates in the plasma membrane is determined as the membrane is built by the ER and Golgi apparatus

Figure 5.8



Transmembrane glycoproteins
Secretory protein
Golgi apparatus
Vesicle
Attached carbo-hydrate
ER
Glycolipid
ER lumen
Plasma membrane:
Cytoplasmic face
Extracellular face
Transmembrane glycoprotein
Secreted protein
Membrane glycolipid

Concept 5.2: Membrane structure results in selective permeability

- A cell must regulate transport of substances across cellular boundaries
- Plasma membranes are selectively permeable, regulating the cell's molecular traffic

The Permeability of the Lipid Bilayer

- Hydrophobic (nonpolar) molecules, such as hydrocarbons, can dissolve in the lipid bilayer of the membrane and cross it easily
- Polar molecules, such as sugars, do not cross the membrane easily

Transport Proteins

- **Transport proteins** allow passage of hydrophilic substances across the membrane
- Some transport proteins, called channel proteins, have a hydrophilic channel that certain molecules or ions can use as a tunnel
- Channel proteins called **aquaporins** facilitate the passage of water

- Other transport proteins, called carrier proteins, bind to molecules and change shape to shuttle them across the membrane
- A transport protein is specific for the substance it moves

Concept 5.3: Passive transport is diffusion of a substance across a membrane with no energy investment

- **Diffusion** is the tendency for molecules to spread out evenly into the available space
- Although each molecule moves randomly, diffusion of a population of molecules may be directional
- At dynamic equilibrium, as many molecules cross the membrane in one direction as in the other

Animation: Diffusion

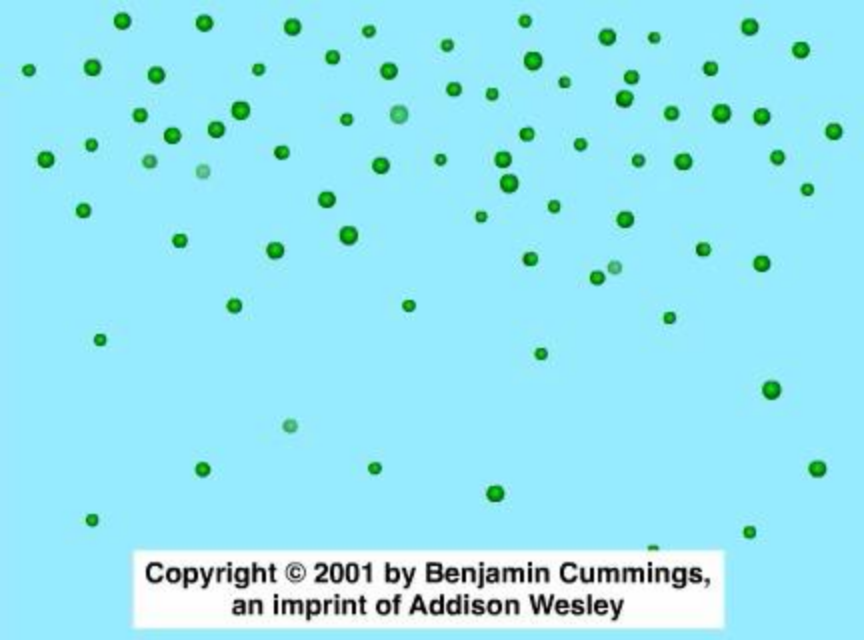
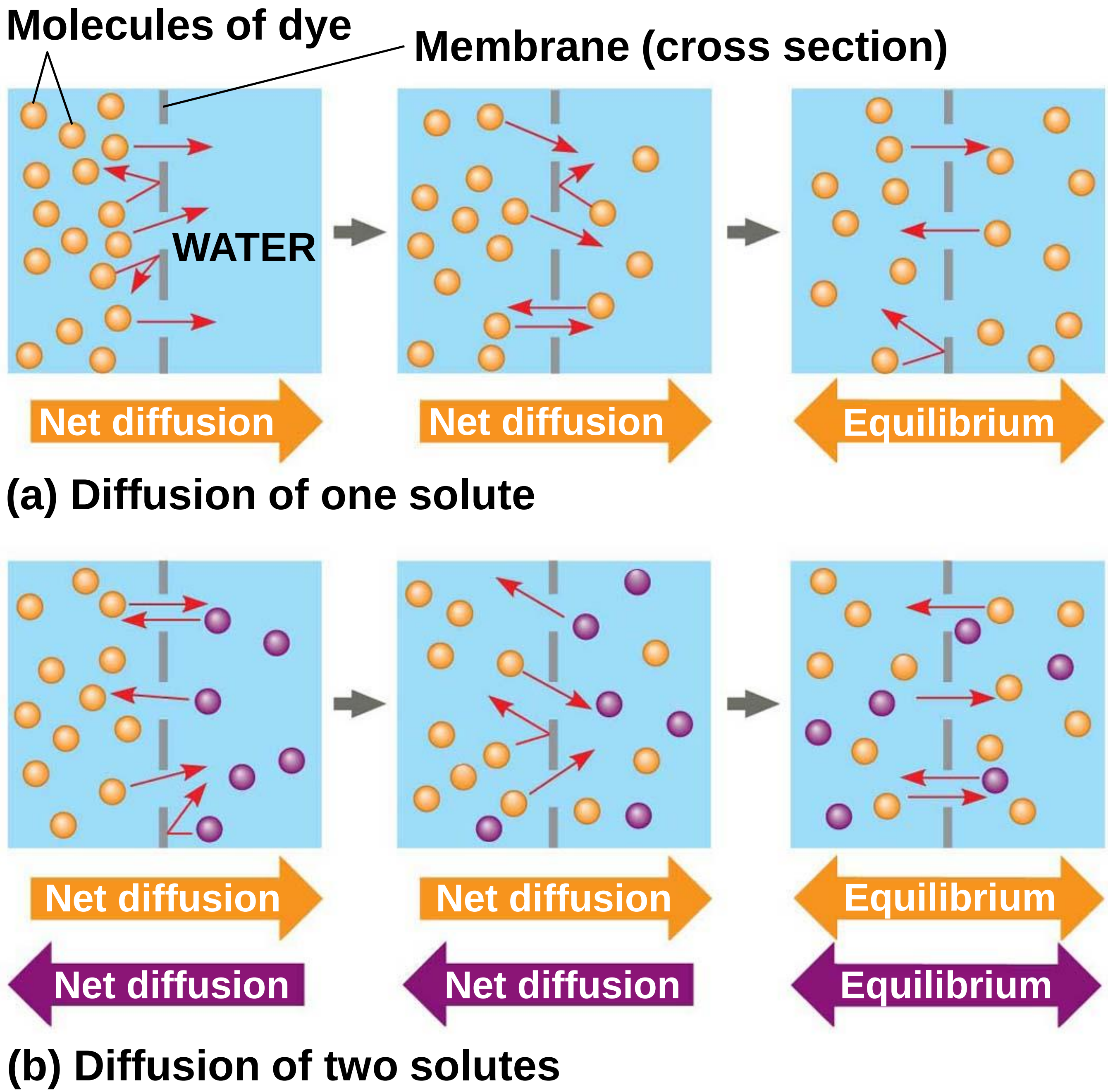


Figure 5.9


Molecules of dye
Membrane (cross section)
WATER
Net diffusion
Net diffusion
Equilibrium
(a) Diffusion of one solute
Net diffusion
Net diffusion
Equilibrium
Net diffusion
Net diffusion
Equilibrium
(b) Diffusion of two solutes

- Substances diffuse down their **concentration gradient**, from where it is more concentrated to where it is less concentrated
- No work must be done to move substances down the concentration gradient
- The diffusion of a substance across a biological membrane is **passive transport** because no energy is expended by the cell to make it happen

Effects of Osmosis on Water Balance

- **Osmosis** is the diffusion of free water across a selectively permeable membrane
- Water diffuses across a membrane from the region of lower solute concentration to the region of higher solute concentration until the solute concentration is equal on both sides

Figure 5.10

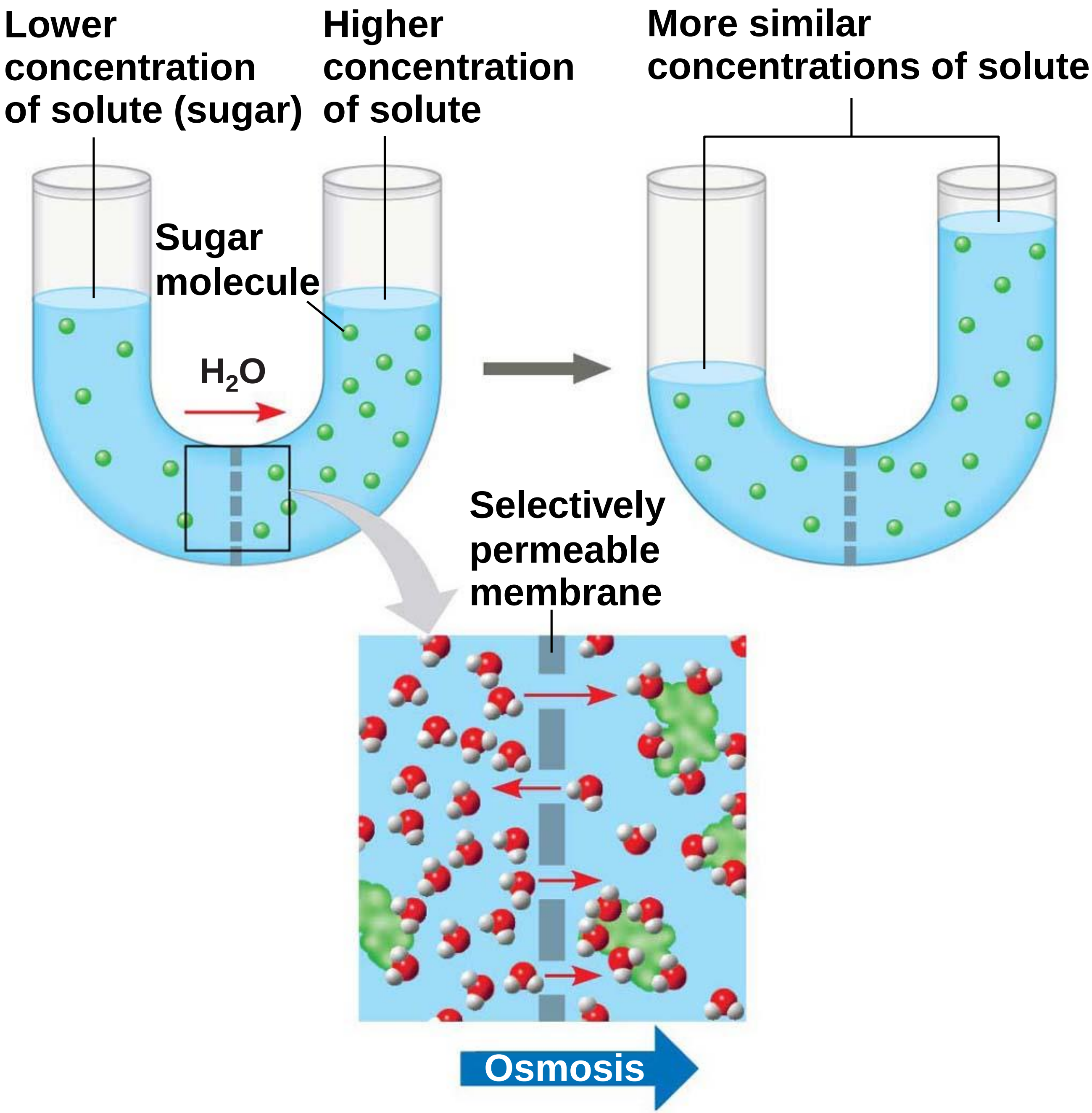

Lower concentration of solute (sugar)
Higher concentration of solute
More similar concentrations of solute
Sugar molecule
H_2O
Selectively permeable membrane
Osmosis

Figure 5.10-1

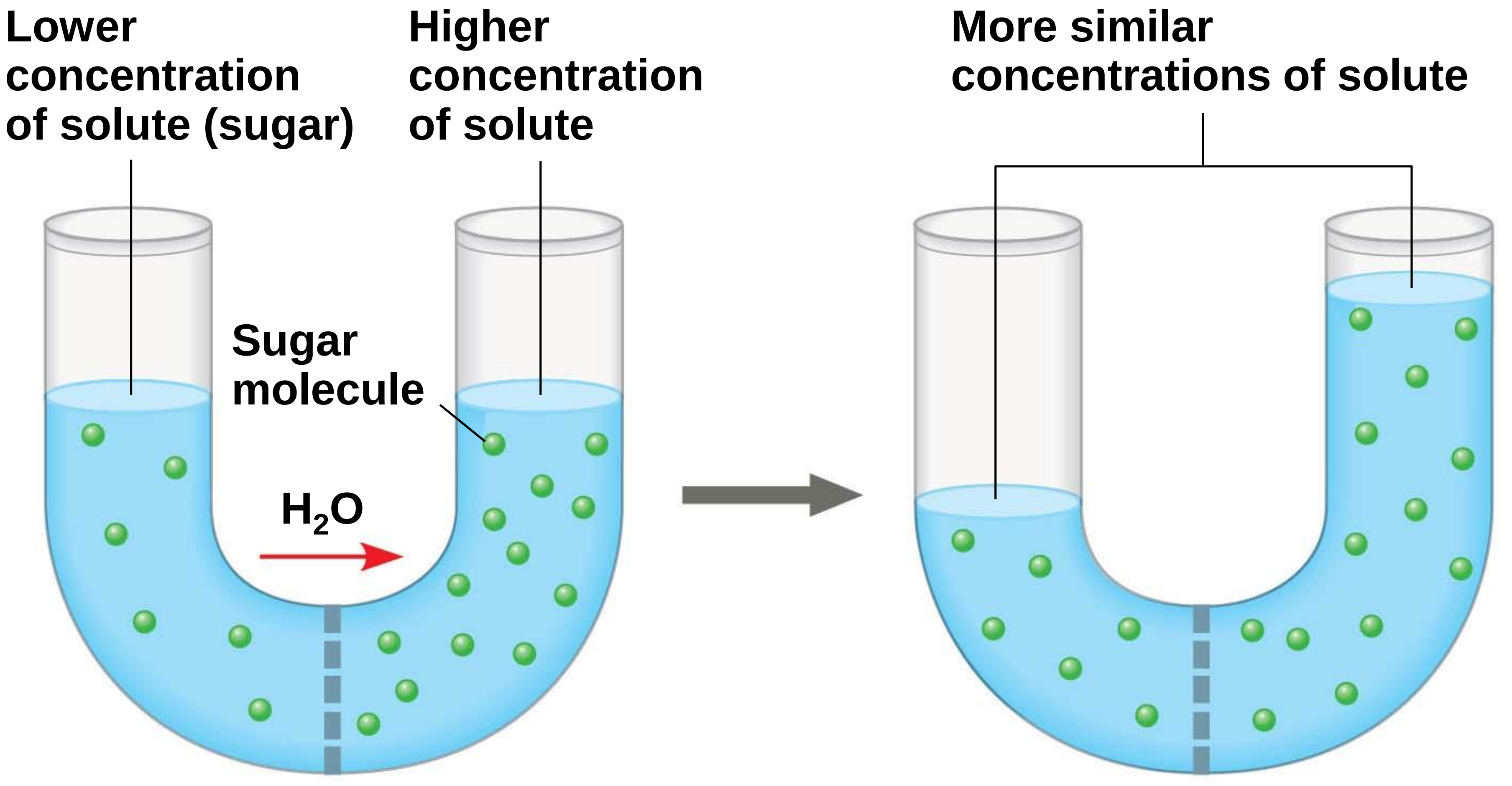
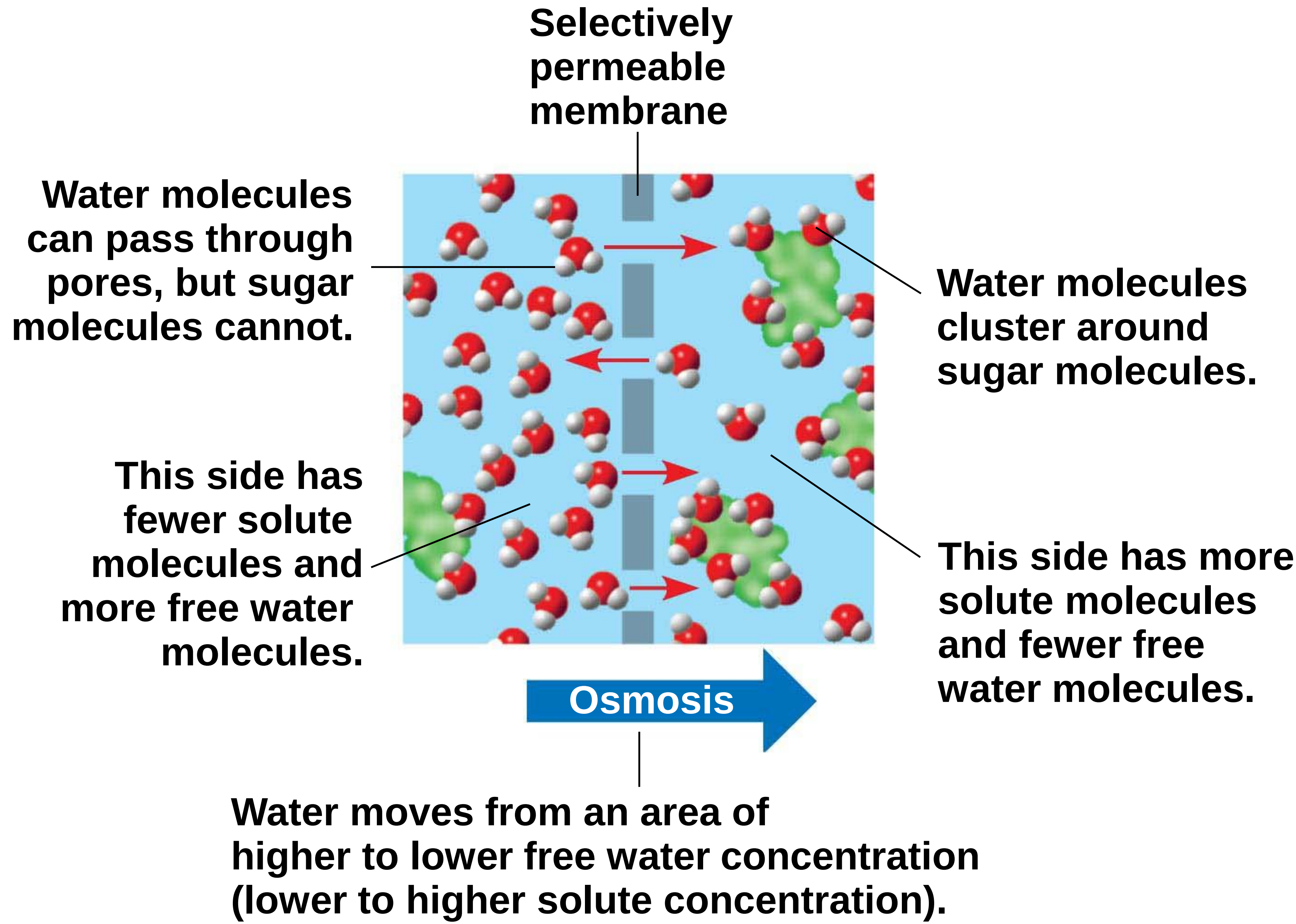

Lower concentration of solute (sugar)
Higher concentration of solute
Sugar molecule
H_2O
More similar concentrations of solute

Figure 5.10-2

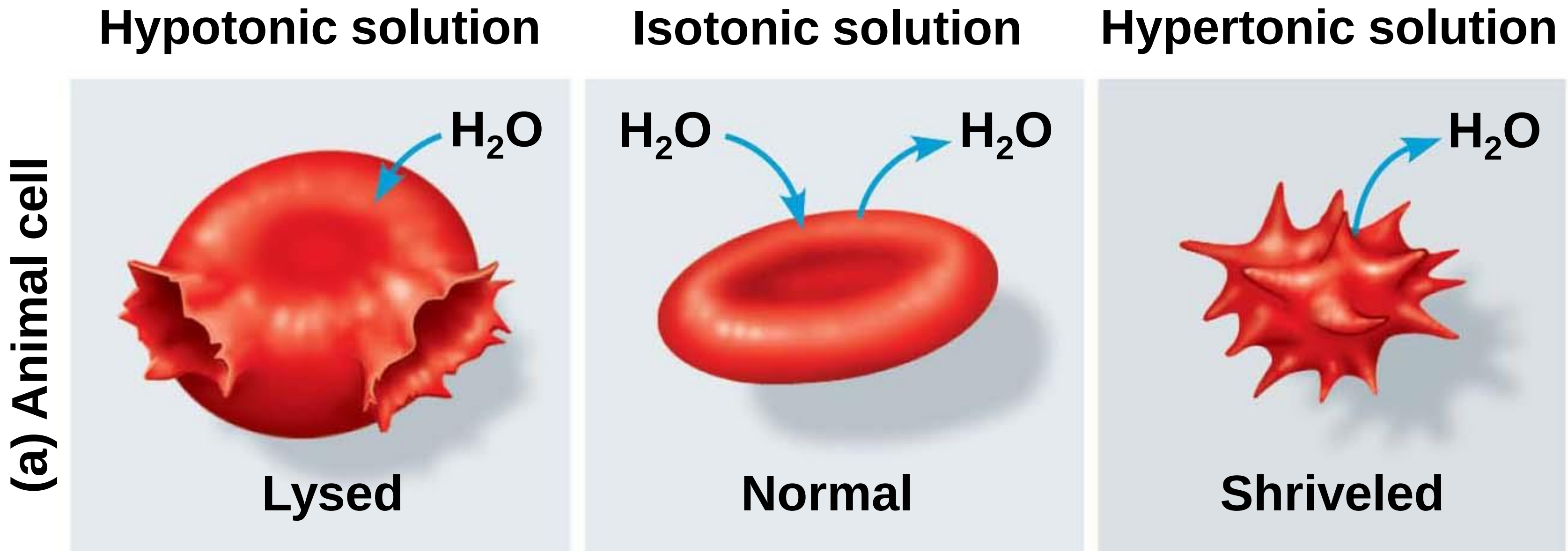


Selectively permeable membrane
Water molecules can pass through pores, but sugar molecules cannot.
Water molecules cluster around sugar molecules.
This side has fewer solute molecules and more free water molecules.
This side has more solute molecules and fewer free water molecules.
Osmosis
Water moves from an area of higher to lower free water concentration (lower to higher solute concentration).

Water Balance of Cells Without Walls

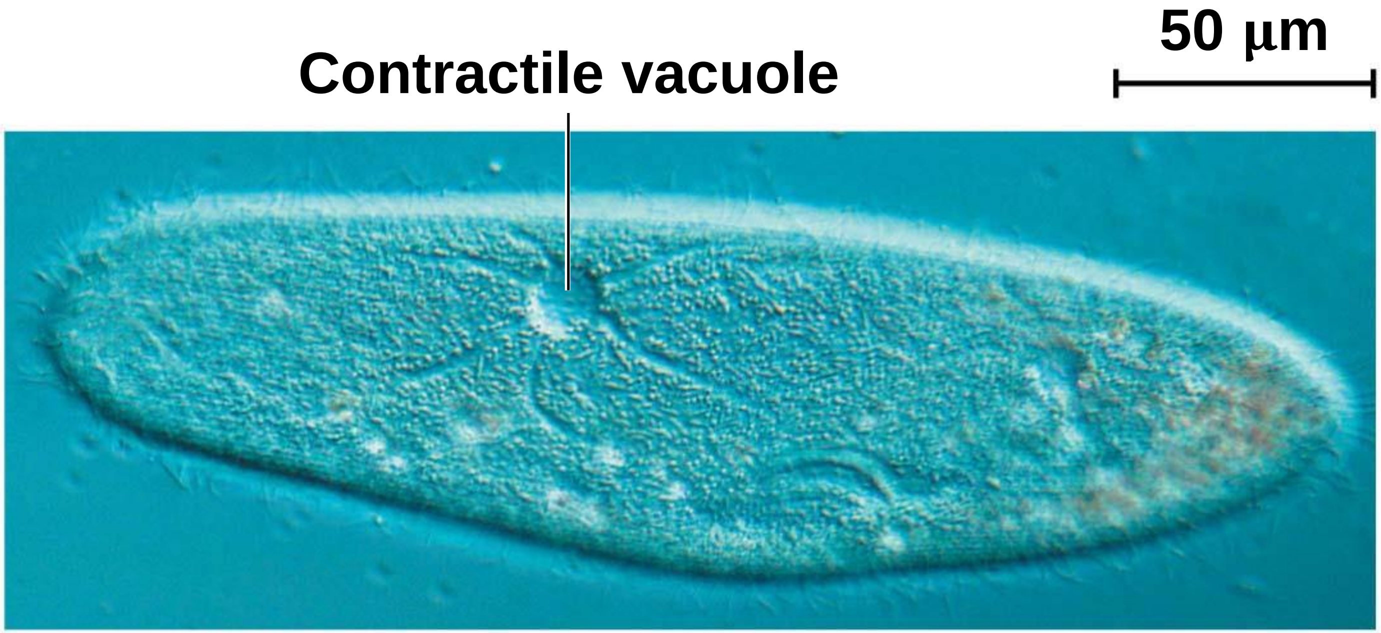
- **Tonicity** is the ability of a surrounding solution to cause a cell to gain or lose water
- **Isotonic** solution: Solute concentration is the same as inside the cell; no net water movement across the plasma membrane
- **Hypertonic** solution: Solute concentration is greater than that inside the cell; cell loses water
- **Hypotonic** solution: Solute concentration is less than that inside the cell; cell gains water

Figure 5.11a


Hypotonic solution
Isotonic solution
Hypertonic solution
(a) Animal cell
H_2O
H_2O
H_2O
H_2O
Lysed
Normal
Shriveled

- Hypertonic or hypotonic environments create osmotic problems for organisms
- **Osmoregulation**, the control of solute concentrations and water balance, is a necessary adaptation for life in such environments
- The protist *Paramecium caudatum*, which is hypertonic to its pondwater environment, has a contractile vacuole that can pump excess water out of the cell

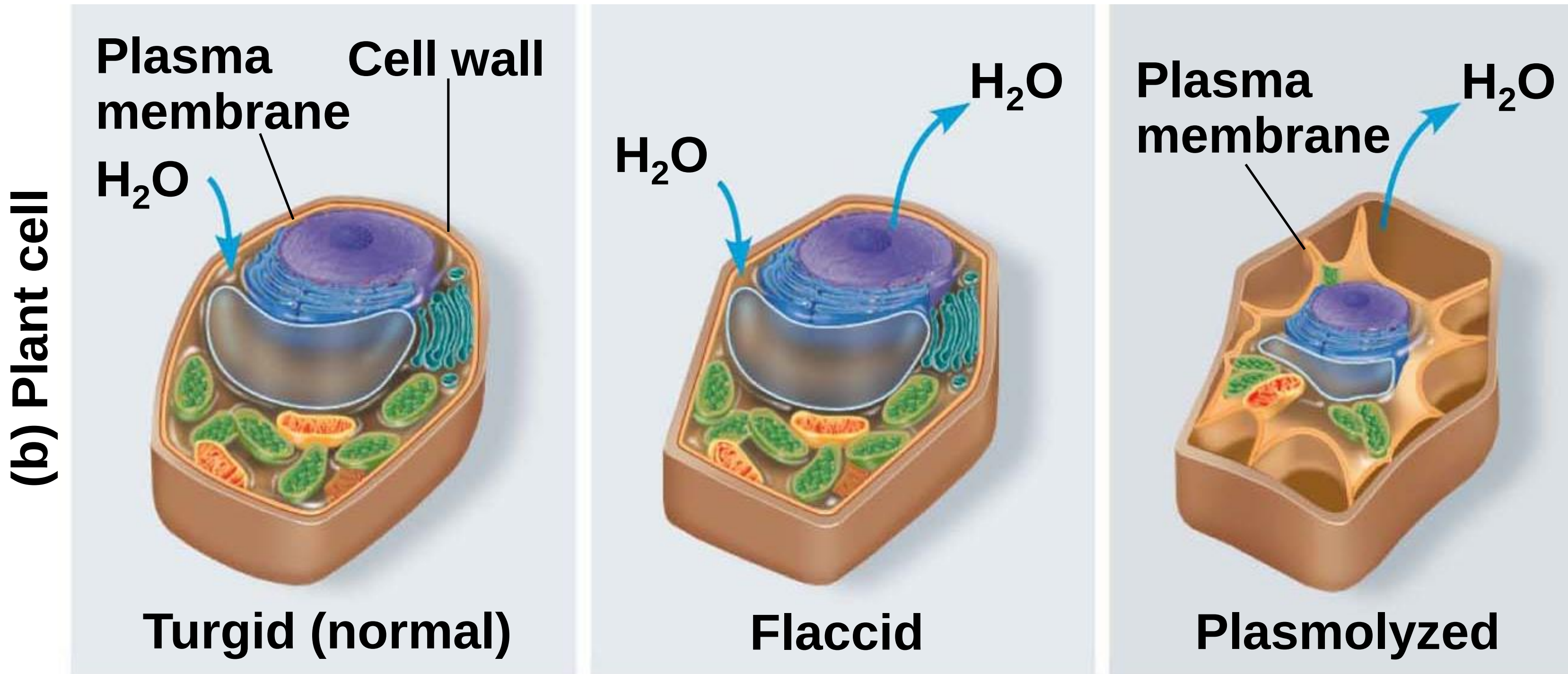
Figure 5.12



Water Balance of Cells with Walls

- Cell walls help maintain water balance
- A plant cell in a hypotonic solution swells until the wall opposes uptake; the cell is now **turgid** (very firm)
- If a plant cell and its surroundings are isotonic, there is no net movement of water into the cell; the cell becomes **flaccid** (limp), and the plant may wilt
- In a hypertonic environment, plant cells lose water; eventually, the membrane pulls away from the wall, a usually lethal effect called **plasmolysis**

Figure 5.11b



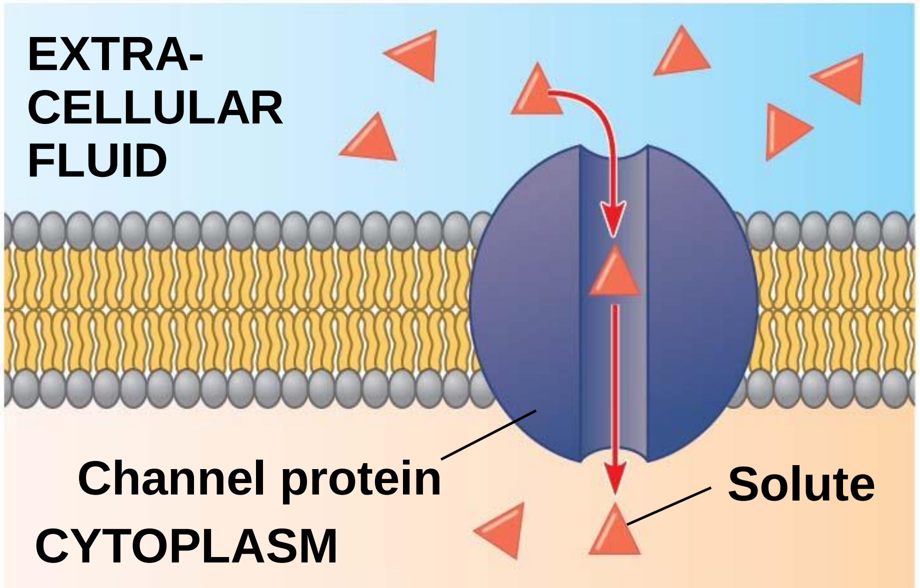
(b) Plant cell
Plasma membrane
Cell wall
H_2O
Turgid (normal)
H_2O
H_2O
Flaccid
Plasma membrane
H_2O
Plasmolyzed

Facilitated Diffusion: Passive Transport Aided by Proteins

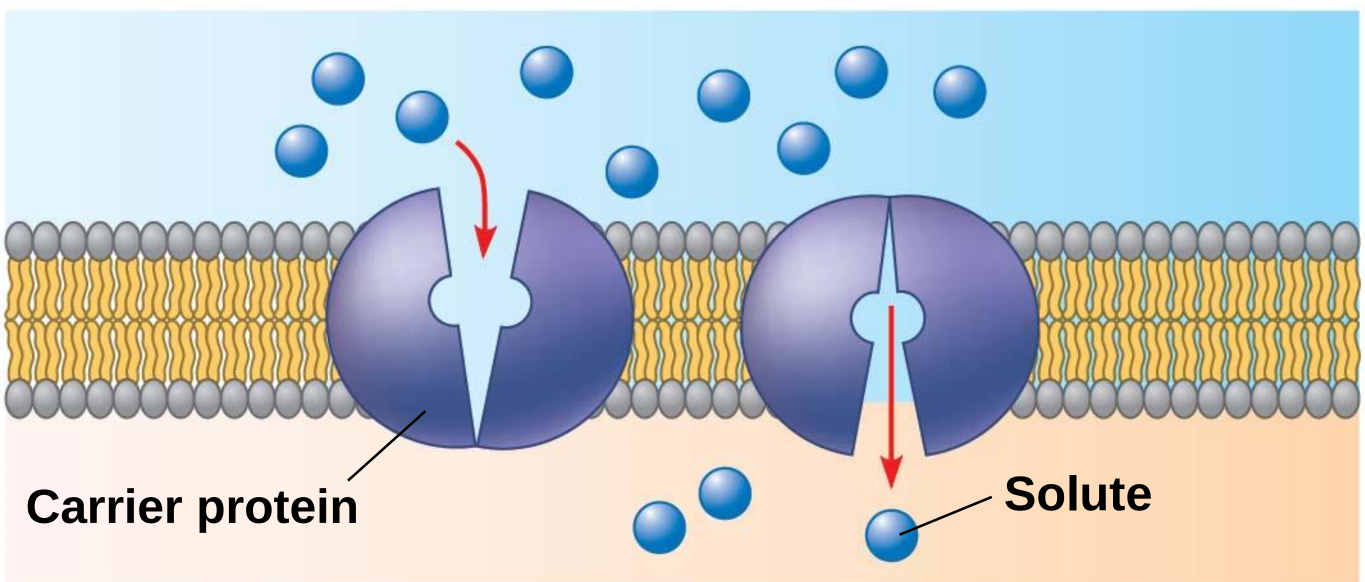
- In **facilitated diffusion**, transport proteins speed the passive movement of molecules across the plasma membrane
- Channel proteins provide corridors that allow a specific molecule or ion to cross the membrane
- Channel proteins include
  - Aquaporins, for facilitated diffusion of water
  - **Ion channels** that open or close in response to a stimulus (**gated channels**)

- Carrier proteins undergo a subtle change in shape that translocates the solute-binding site across the membrane
- The shape change may be triggered by binding and release of the transported molecule
- No net energy input is required

Figure 5.13



(a) A channel protein



(b) A carrier protein

Concept 5.4: Active transport uses energy to move solutes against their gradients

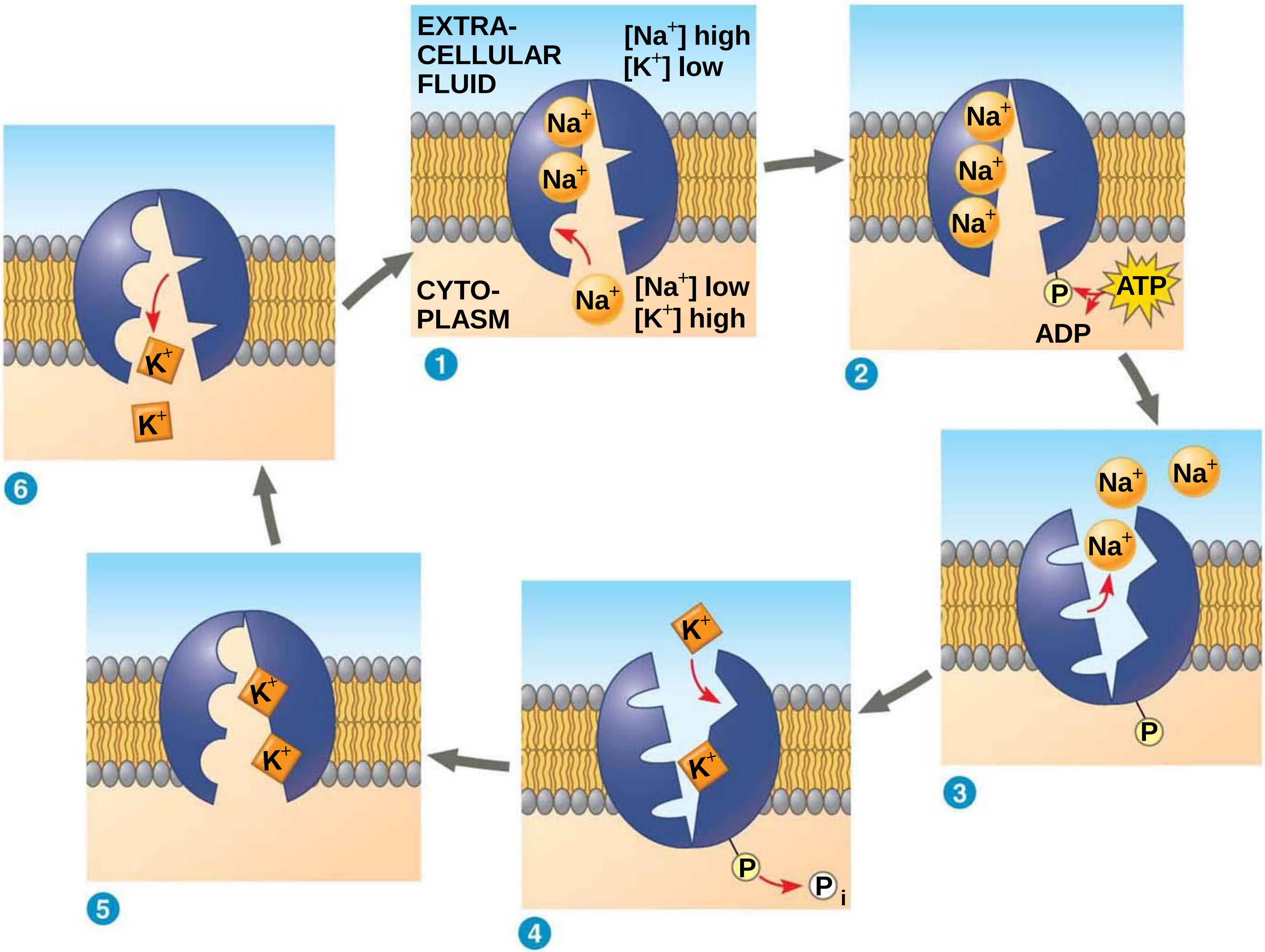
- Facilitated diffusion speeds transport of a solute by providing efficient passage through the membrane but does not alter the direction of transport
- Some transport proteins, however, can move solutes against their concentration gradients

The Need for Energy in Active Transport

- **Active transport** moves substances against their concentration gradients
- Active transport requires energy, usually in the form of ATP

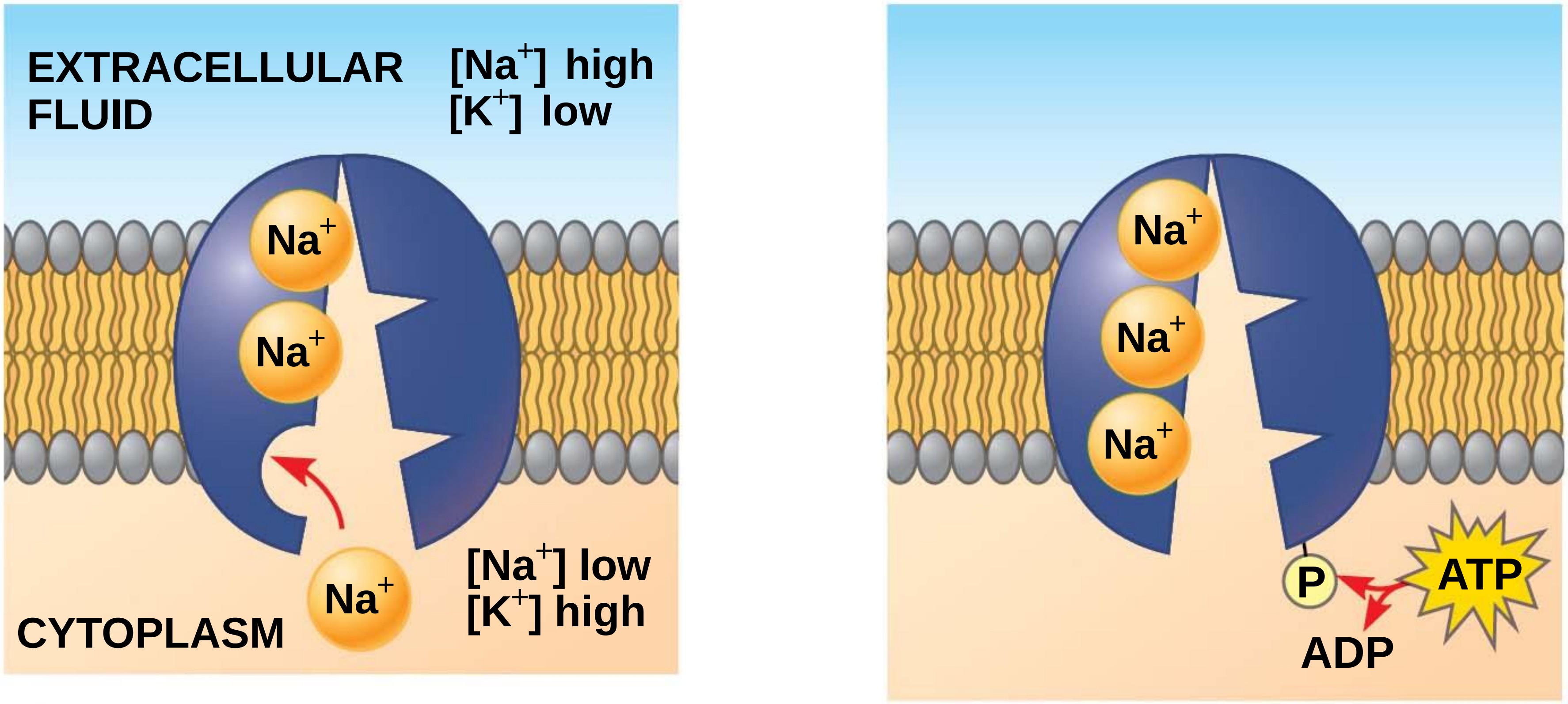
- Active transport allows cells to maintain concentration gradients that differ from their surroundings
- The **sodium-potassium pump** is one type of active transport system

Figure 5.14



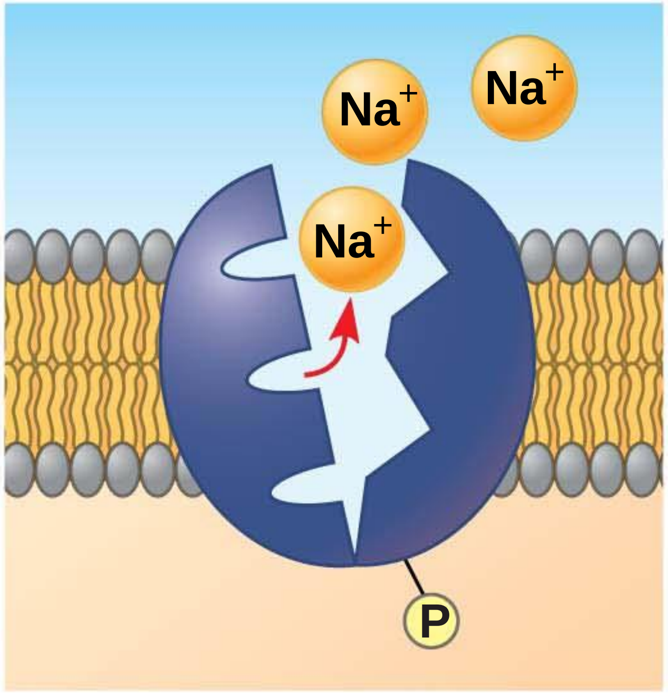
EXTRA-
CELLULAR
FLUID
[Na+] high
[K+] low
Na+
Na+
Na+
CYTO-
PLASM
[Na+] low
[K+] high
1
Na+
Na+
Na+
P
ATP
ADP
2
Na+
Na+
Na+
P
3
K+
K+
P
P
i
4
K+
K+
5
K+
K+
6

Figure 5.14-1

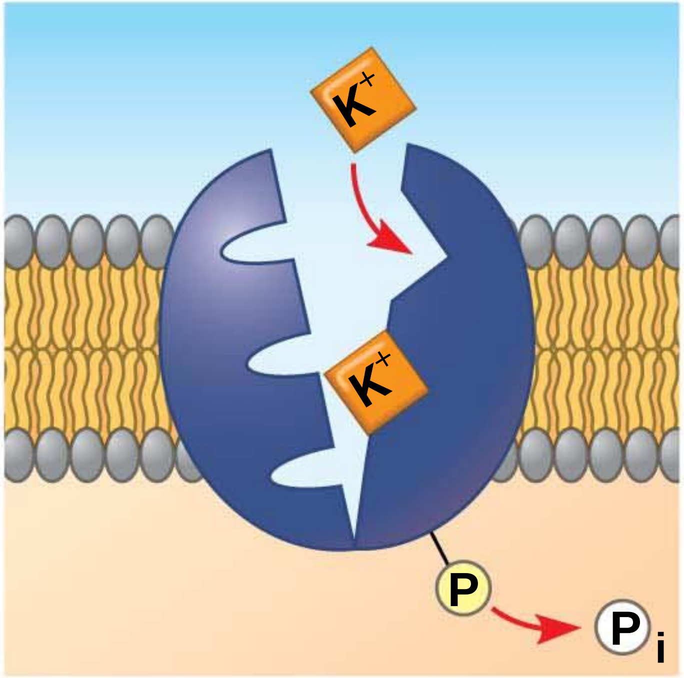


1 Cytoplasmic Na^+ binds to the sodium-potassium pump. The affinity for Na^+ is high when the protein has this shape.

2 Na^+ binding stimulates phosphorylation by ATP.

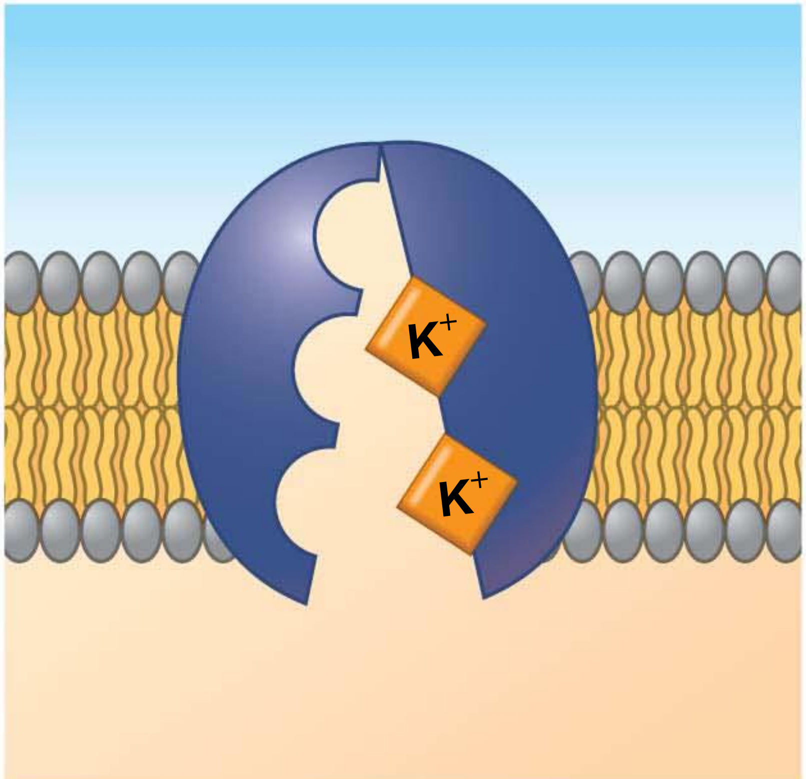


3 **Phosphorylation leads to a change in protein shape, reducing its affinity for Na^+, which is released outside.**

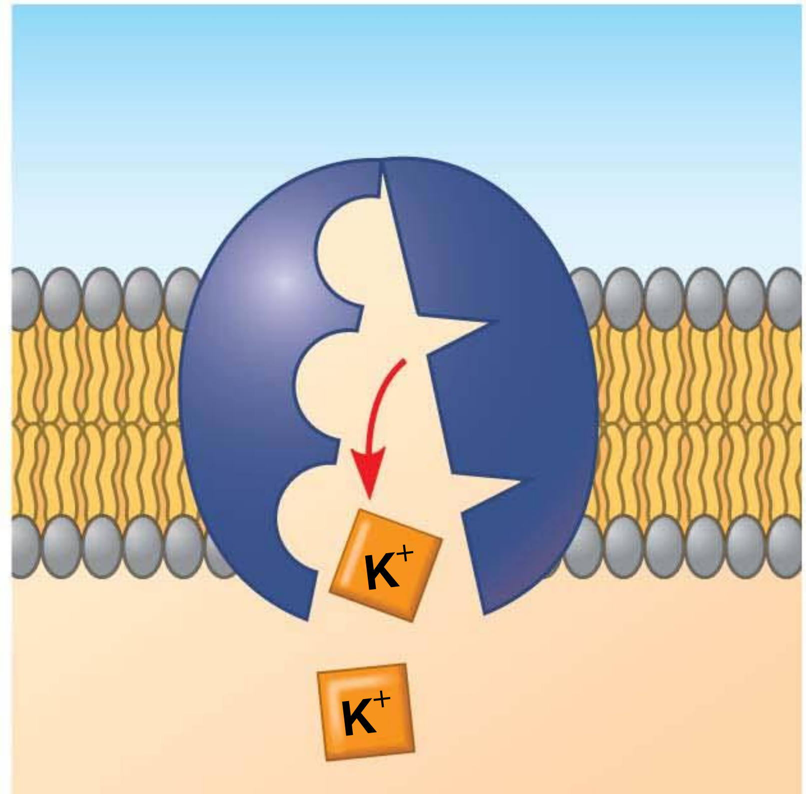


4 **The new shape has a high affinity for K^+, which binds on the extracellular side and triggers release of the phosphate group.**

Figure 5.14-3

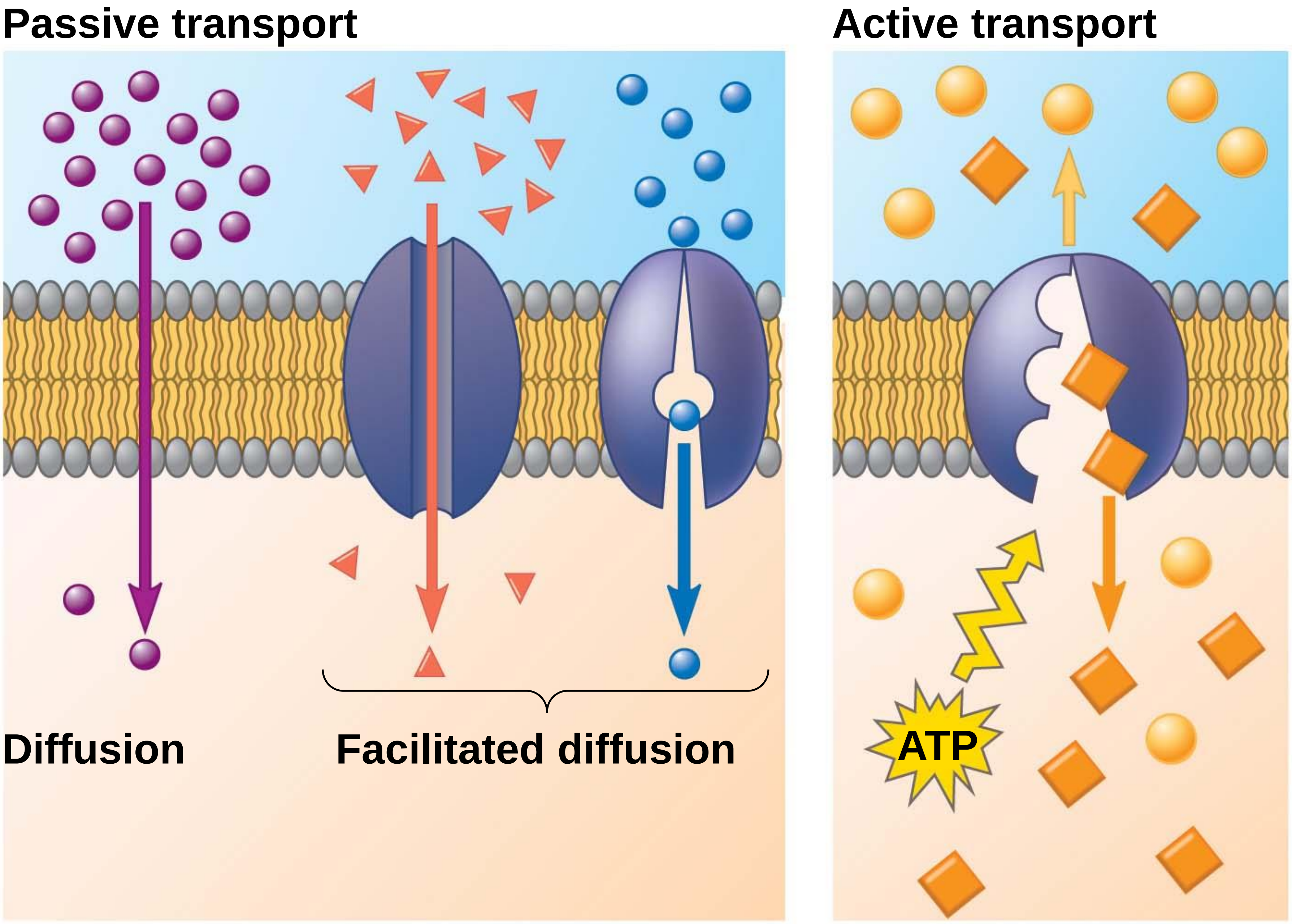


5 Loss of the phosphate group restores the protein's original shape, which has a lower affinity for K^+.



6 K^+ is released; affinity for Na^+ is high again, and the cycle repeats.

Figure 5.15


Passive transport
Active transport
Diffusion
Facilitated diffusion
ATP

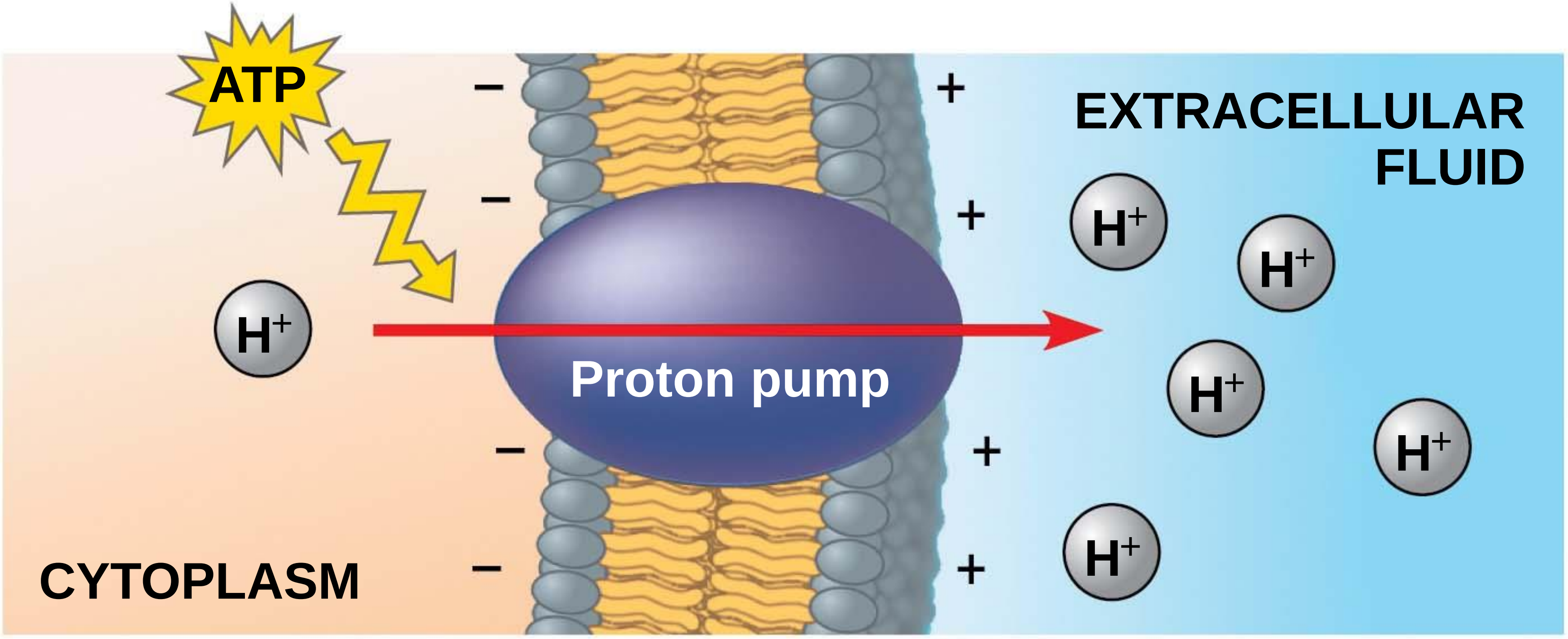
How Ion Pumps Maintain Membrane Potential

- **Membrane potential** is the voltage across a membrane
- Voltage is created by differences in the distribution of positive and negative ions across a membrane

- Two combined forces, collectively called the **electrochemical gradient**, drive the diffusion of ions across a membrane
  - A chemical force (the ion’s concentration gradient)
  - An electrical force (the effect of the membrane potential on the ion’s movement)

- An **electrogenic pump** is a transport protein that generates voltage across a membrane
- The sodium-potassium pump is the major electrogenic pump of animal cells
- The main electrogenic pump of plants, fungi, and bacteria is a **proton pump**
- Electrogenic pumps help store energy that can be used for cellular work

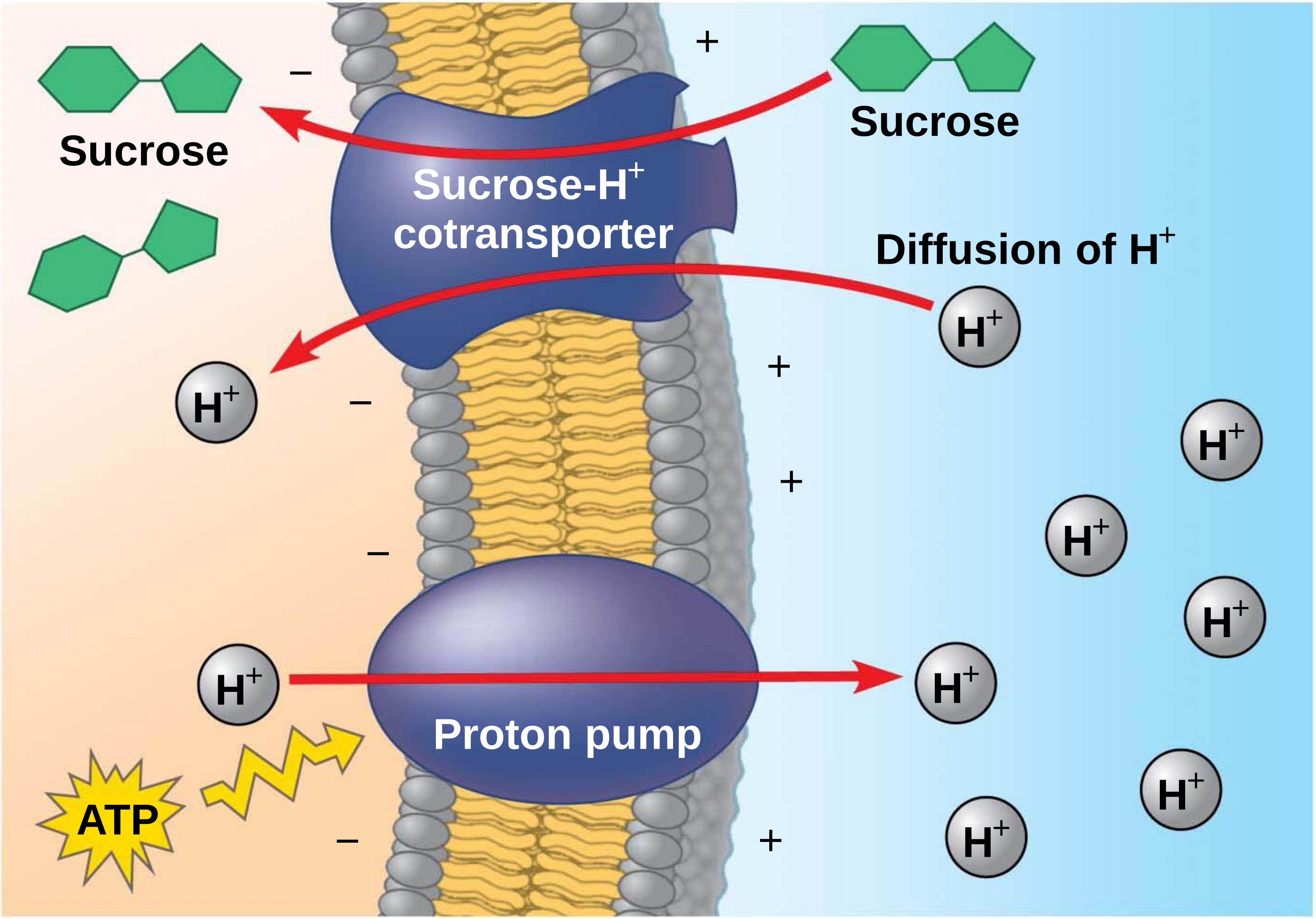
Figure 5.16



Cotransport: Coupled Transport by a Membrane Protein

- **Cotransport** occurs when active transport of a solute indirectly drives transport of other solutes
- Plant cells use the gradient of hydrogen ions generated by proton pumps to drive active transport of nutrients into the cell

Figure 5.17



Sucrose
Sucrose
Sucrose-H+
cotransporter
Diffusion of H+
H+
Proton pump
ATP

Concept 5.5: Bulk transport across the plasma membrane occurs by exocytosis and endocytosis

- Water and small solutes enter or leave the cell through the lipid bilayer or by means of transport proteins
- Large molecules, such as polysaccharides and proteins, cross the membrane in bulk by means of vesicles
- Bulk transport requires energy

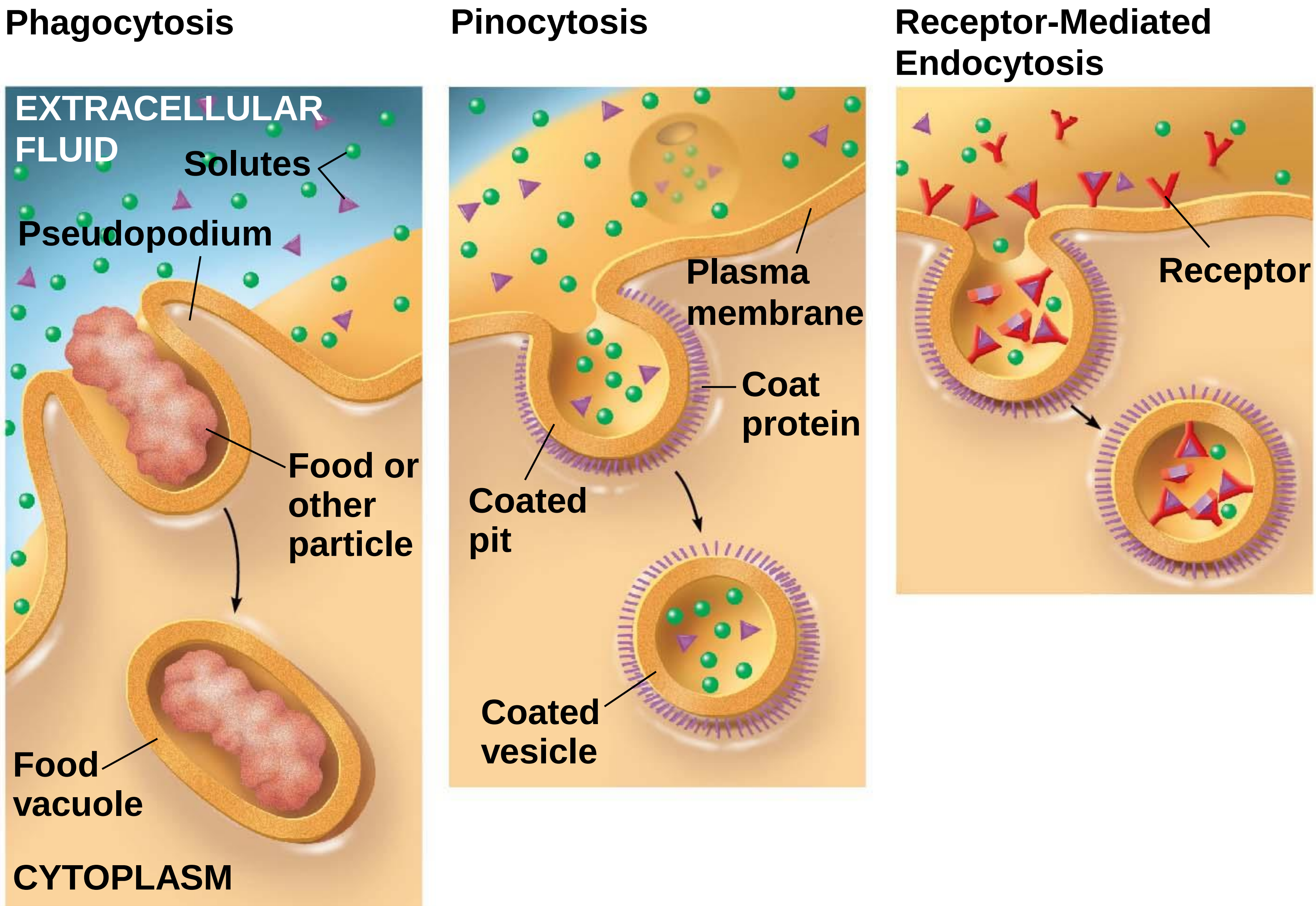
Exocytosis

- In **exocytosis**, transport vesicles migrate to the membrane, fuse with it, and release their contents
- Many secretory cells use exocytosis to export products

Endocytosis

- In **endocytosis**, the cell takes in molecules and particulate matter by forming new vesicles from the plasma membrane
- Endocytosis is a reversal of exocytosis, involving different proteins
- There are three types of endocytosis
  - Phagocytosis (“cellular eating”)
  - Pinocytosis (“cellular drinking”)
  - Receptor-mediated endocytosis

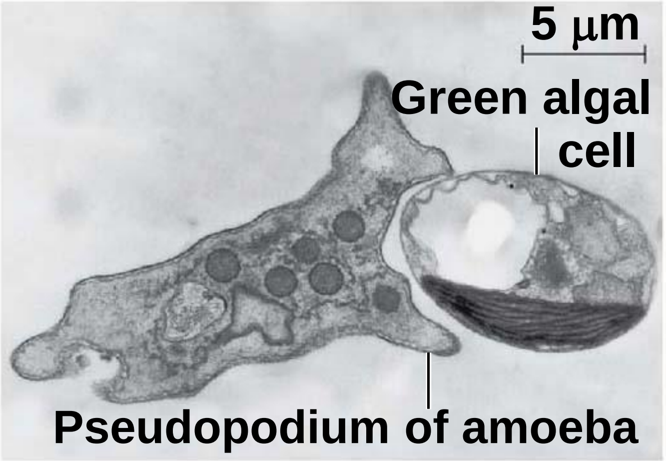
Figure 5.18



Phagocytosis
EXTRACELLULAR FLUID
Solutes
Pseudopodium
Food or other particle
Food vacuole
CYTOPLASM
Pinocytosis
Plasma membrane
Coat protein
Coated pit
Coated vesicle
Receptor-Mediated Endocytosis
Receptor

Figure 5.18-1

Phagocytosis



An amoeba engulfing a green algal cell via phagocytosis (TEM)

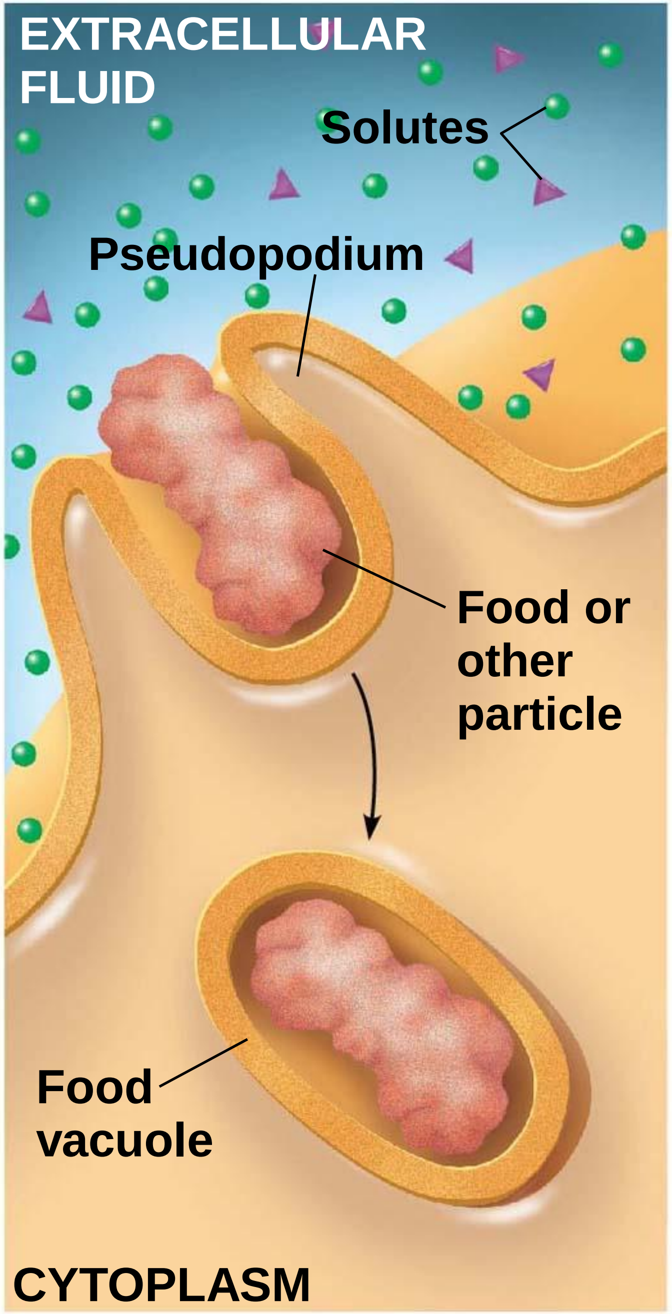
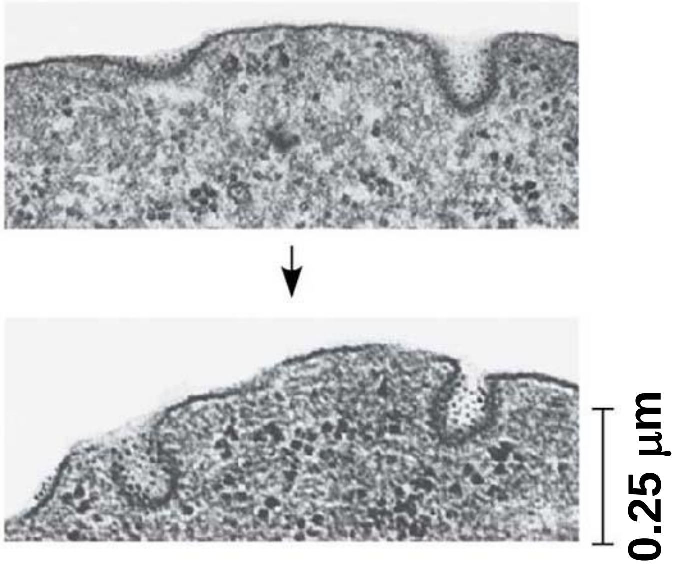


Figure 5.18-2

Pinocytosis



Pinocytotic vesicles forming (TEMs)

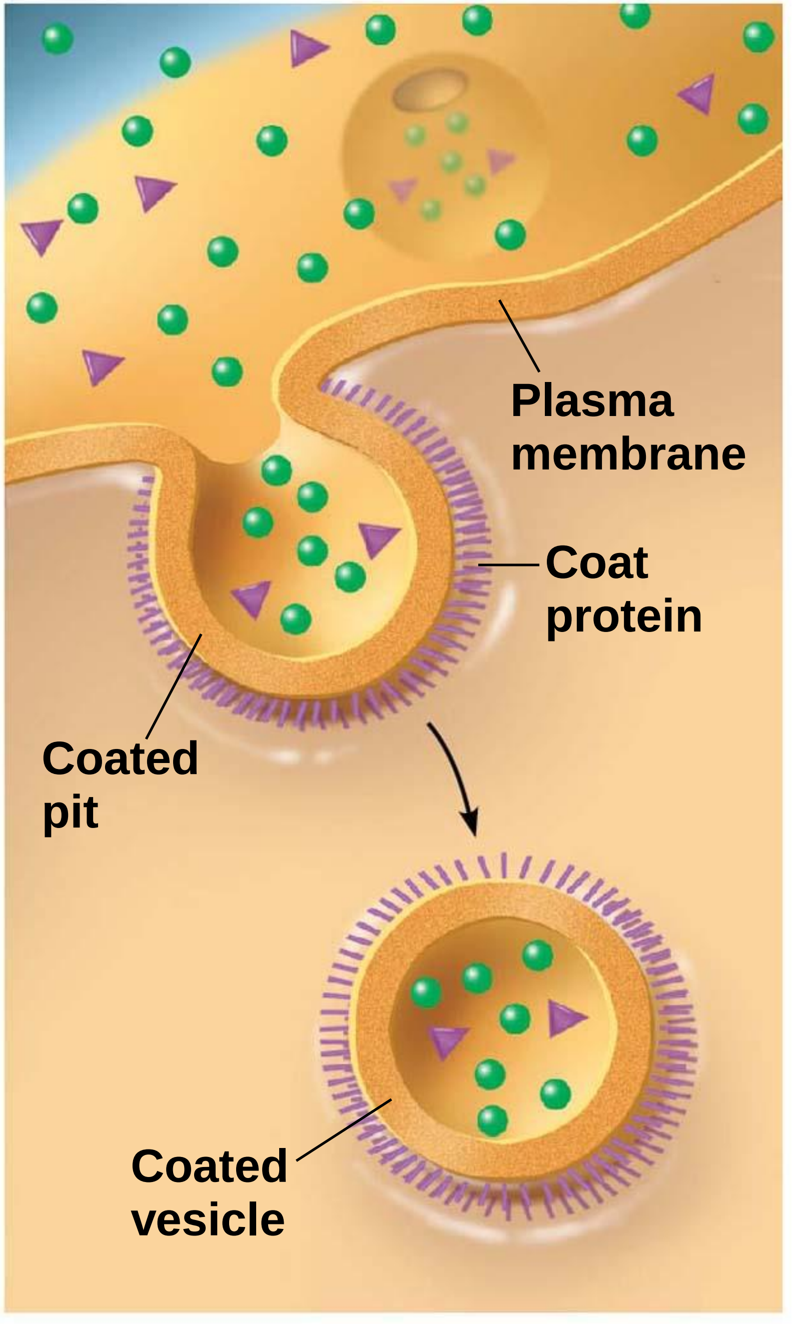
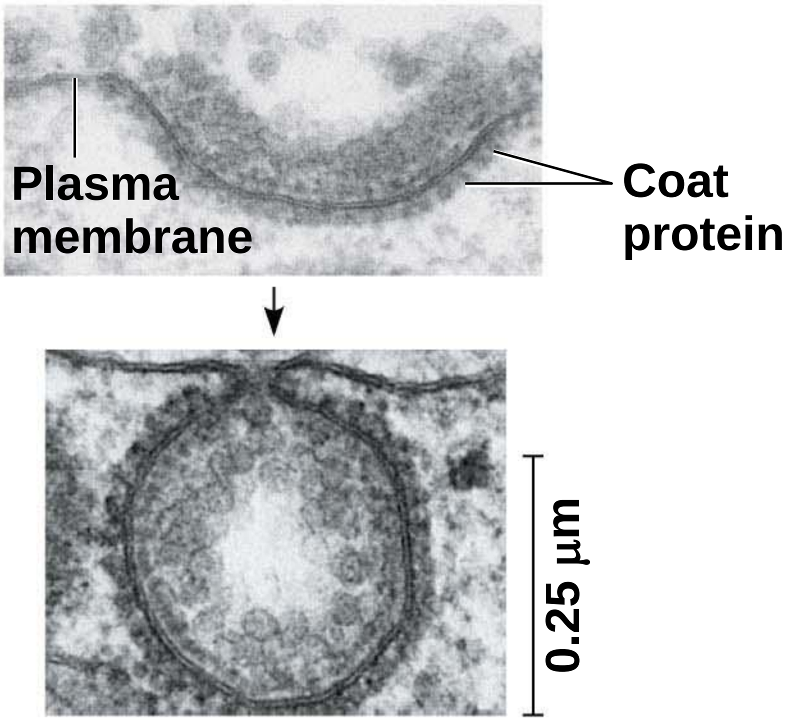


Figure 5.18-3

Receptor-Mediated Endocytosis



Top: **A coated pit**
Bottom: **A coated vesicle forming during receptor-mediated endocytosis (TEMs)**

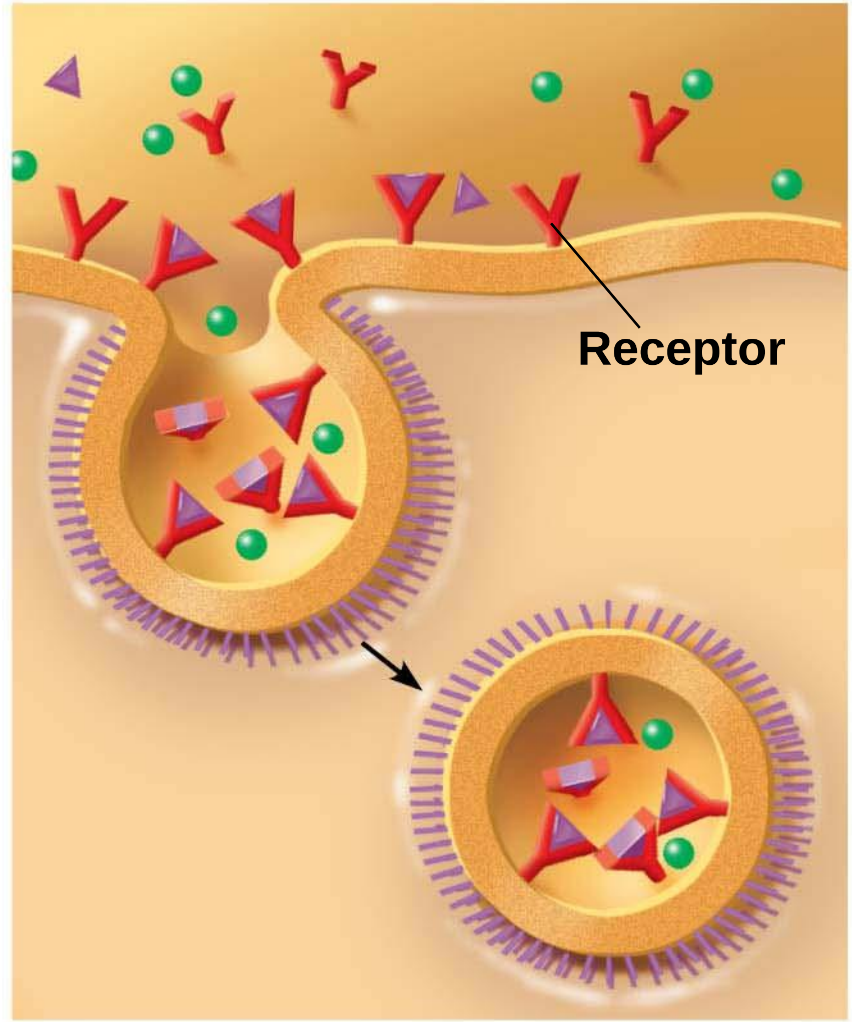
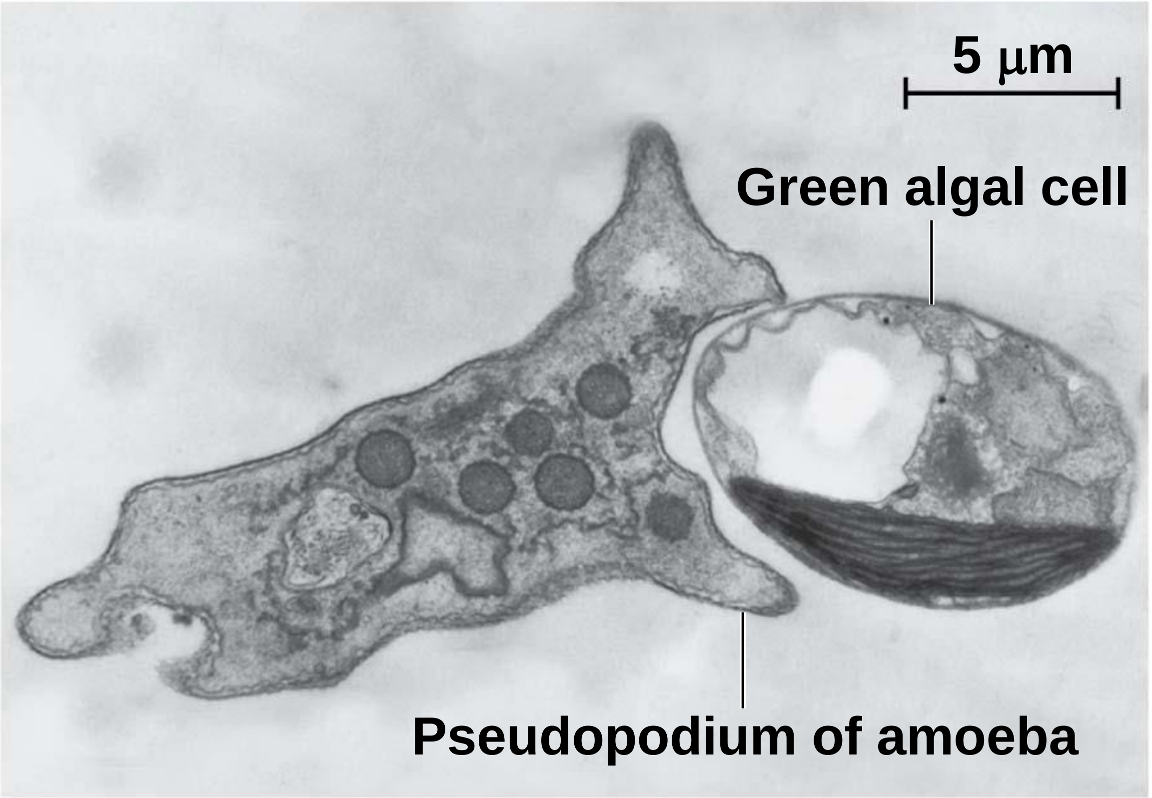
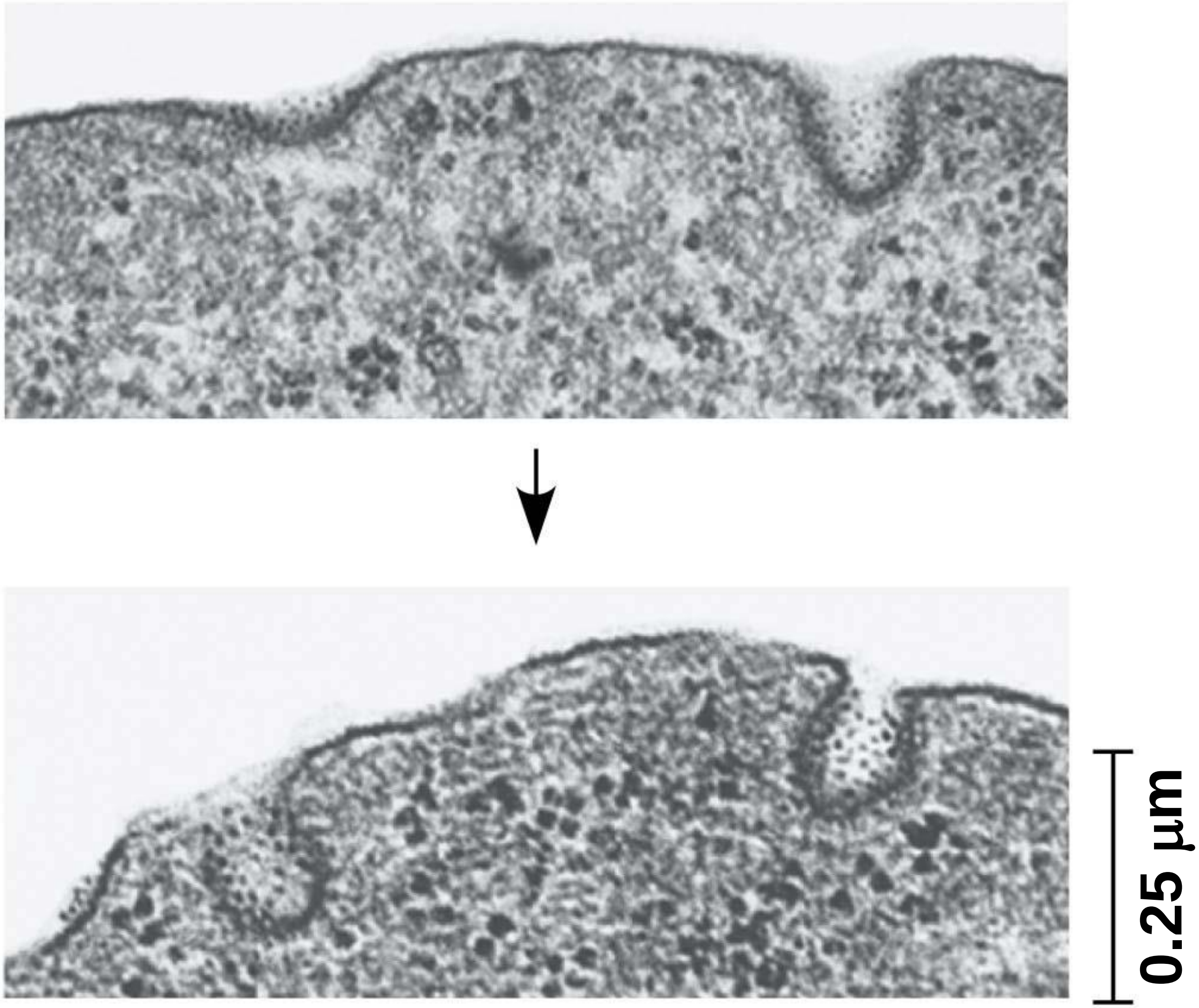


Figure 5.18-4

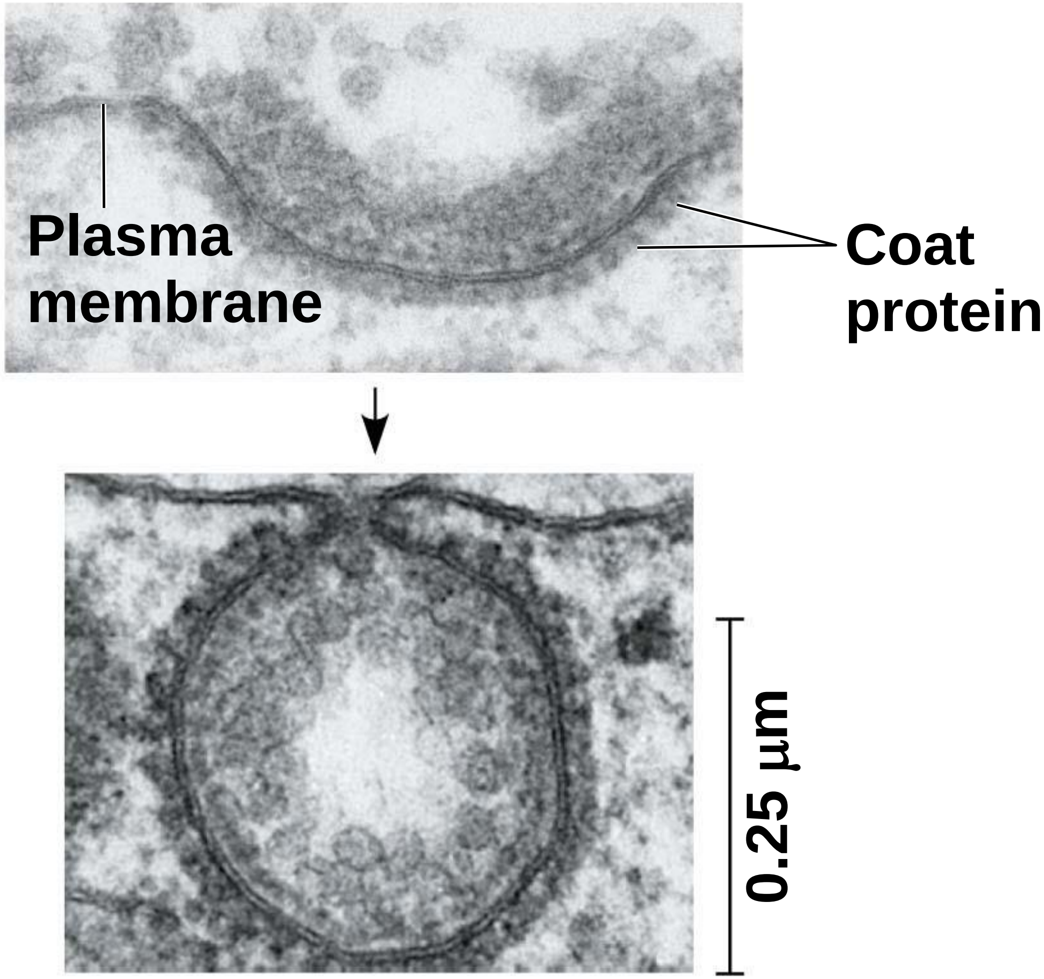


An amoeba engulfing a green algal cell via phagocytosis (TEM)



Pinocytotic vesicles forming (TEMs)

Figure 5.18-6



***Top*: A coated pit**
***Bottom*: A coated vesicle forming during receptor-mediated endocytosis (TEMs)**

Concept 5.6: The plasma membrane plays a key role in most cell signaling

- In multicellular organisms, cell-to-cell communication allows the cells of the body to coordinate their activities
- Communication between cells is also essential for many unicellular organisms

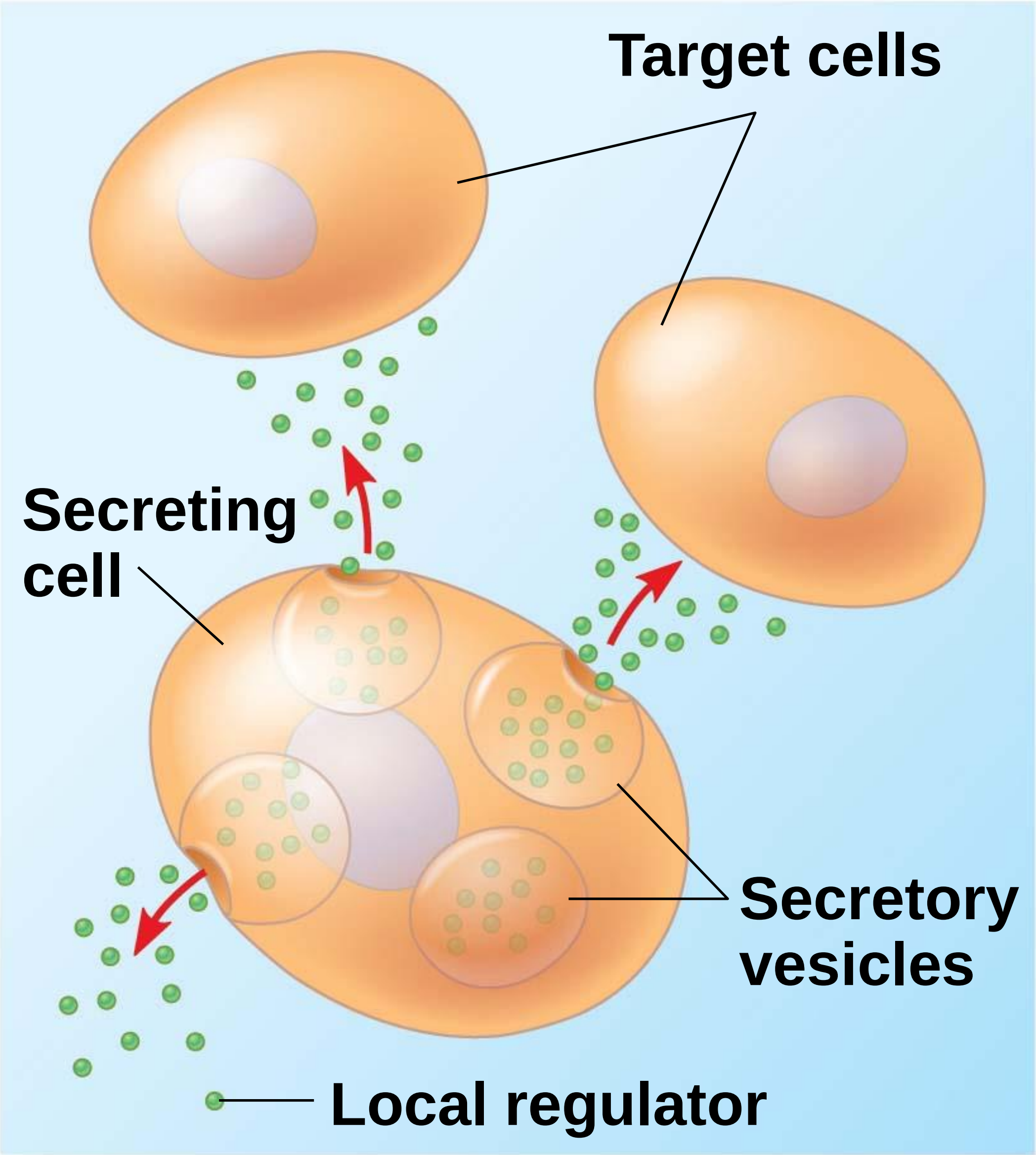
Local and Long-Distance Signaling

- Eukaryotic cells may communicate by direct contact
- Animal and plant cells have junctions that directly connect the cytoplasm of adjacent cells
- These are called gap junctions (animal cells) and plasmodesmata (plant cells)
- The free passage of substances in the cytosol from one cell to another is a type of local signaling

- In many other cases of local signaling, messenger molecules are secreted by a signaling cell
- These messenger molecules, called local regulators, travel only short distances
- One class of these, growth factors, stimulates nearby cells to grow and divide
- This type of local signaling in animal cells is called paracrine signaling

Figure 5.19-1

Local signaling

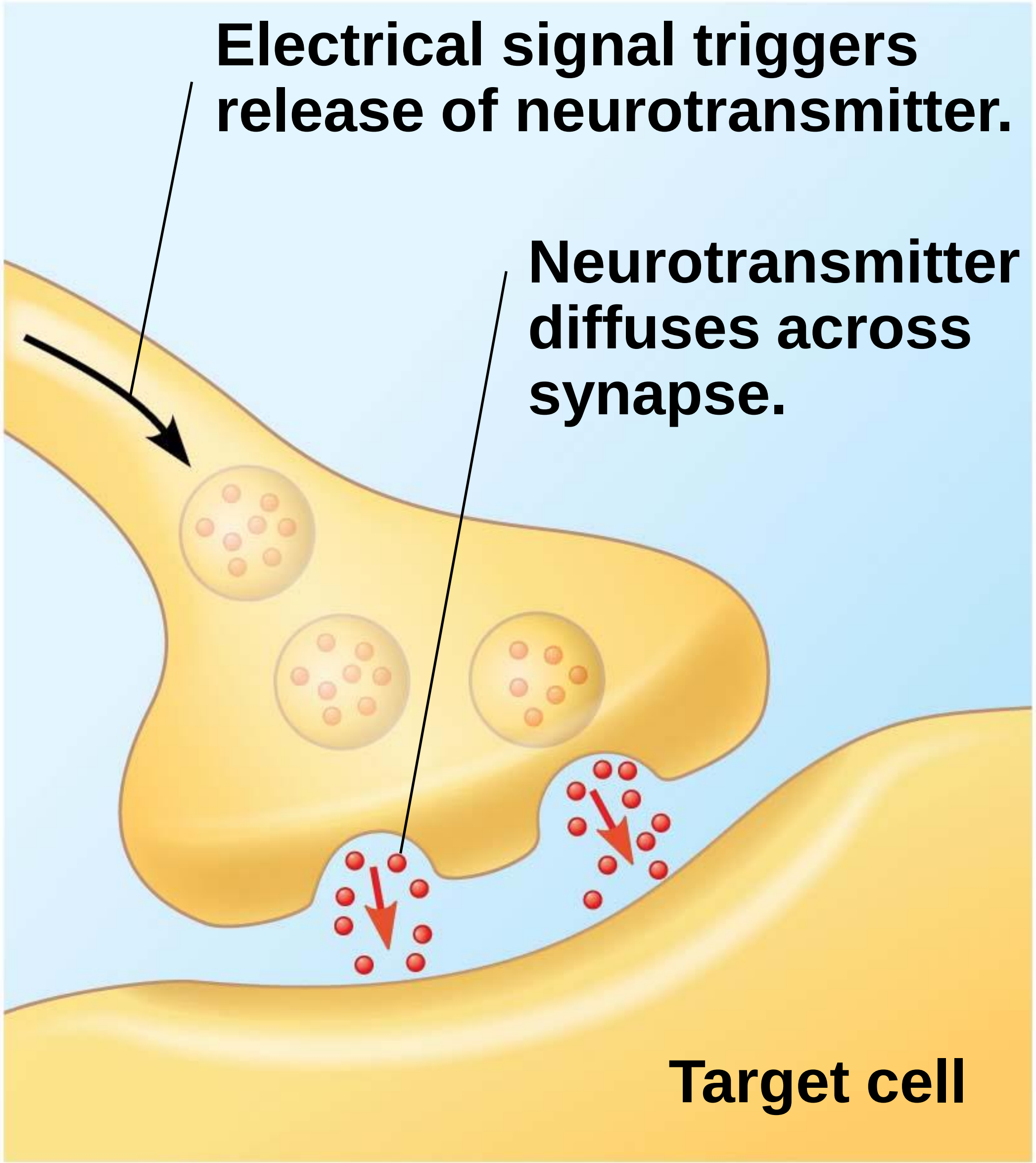


(a) Paracrine signaling

- Another more specialized type of local signaling occurs in the animal nervous system
- This synaptic signaling consists of an electrical signal moving along a nerve cell that triggers secretion of neurotransmitter molecules
- These diffuse across the space between the nerve cell and its target, triggering a response in the target cell

Figure 5.19-2

Local signaling

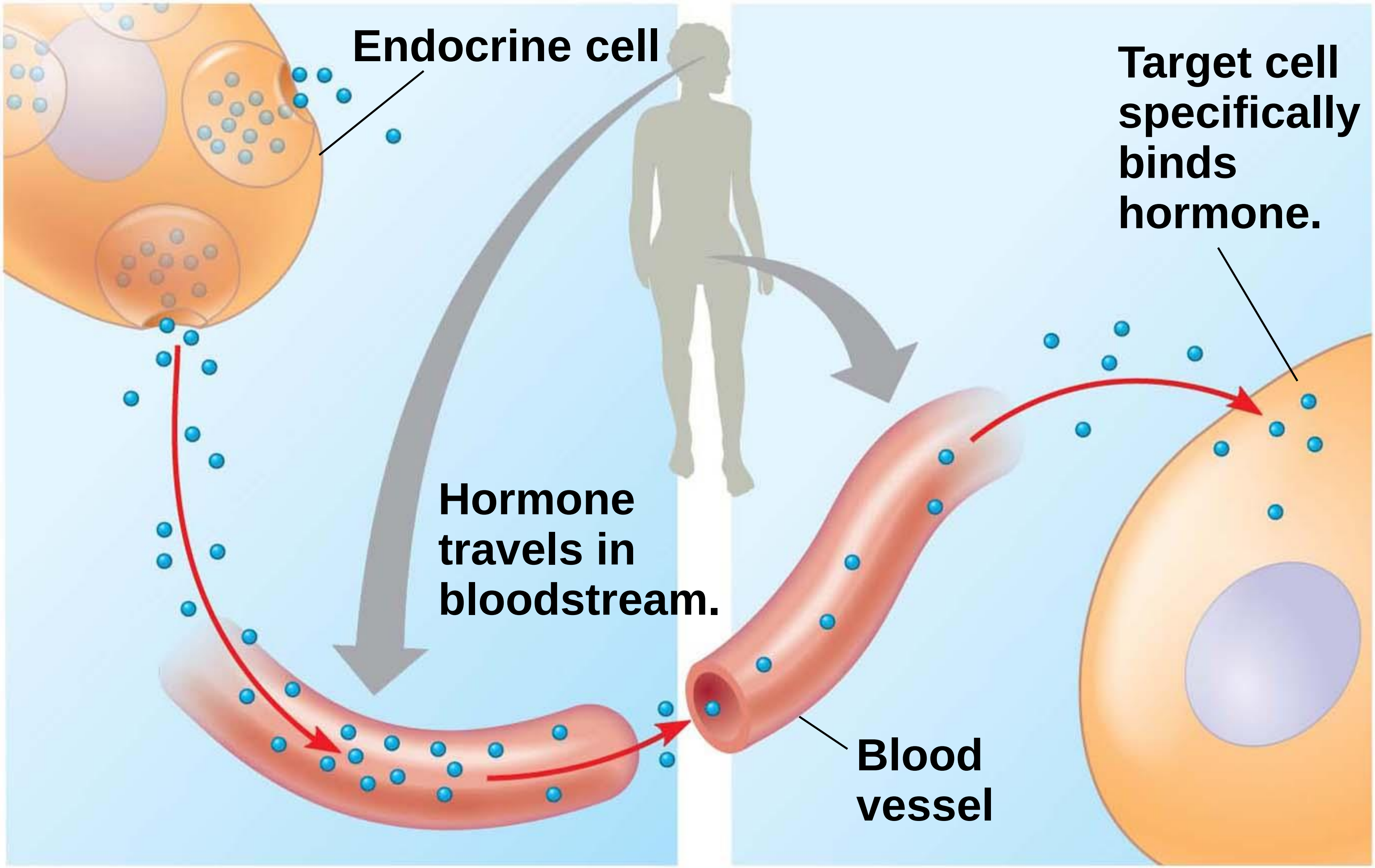


(b) Synaptic signaling

- In long-distance signaling, plants and animals use chemicals called **hormones**
- In hormonal signaling in animals (called endocrine signaling), specialized cells release hormone molecules that travel via the circulatory system
- Hormones vary widely in size and shape

Figure 5.19-3

Long-distance signaling



(c) Endocrine (hormonal) signaling

The Three Stages of Cell Signaling: *A Preview*

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

Figure 5.20-s1

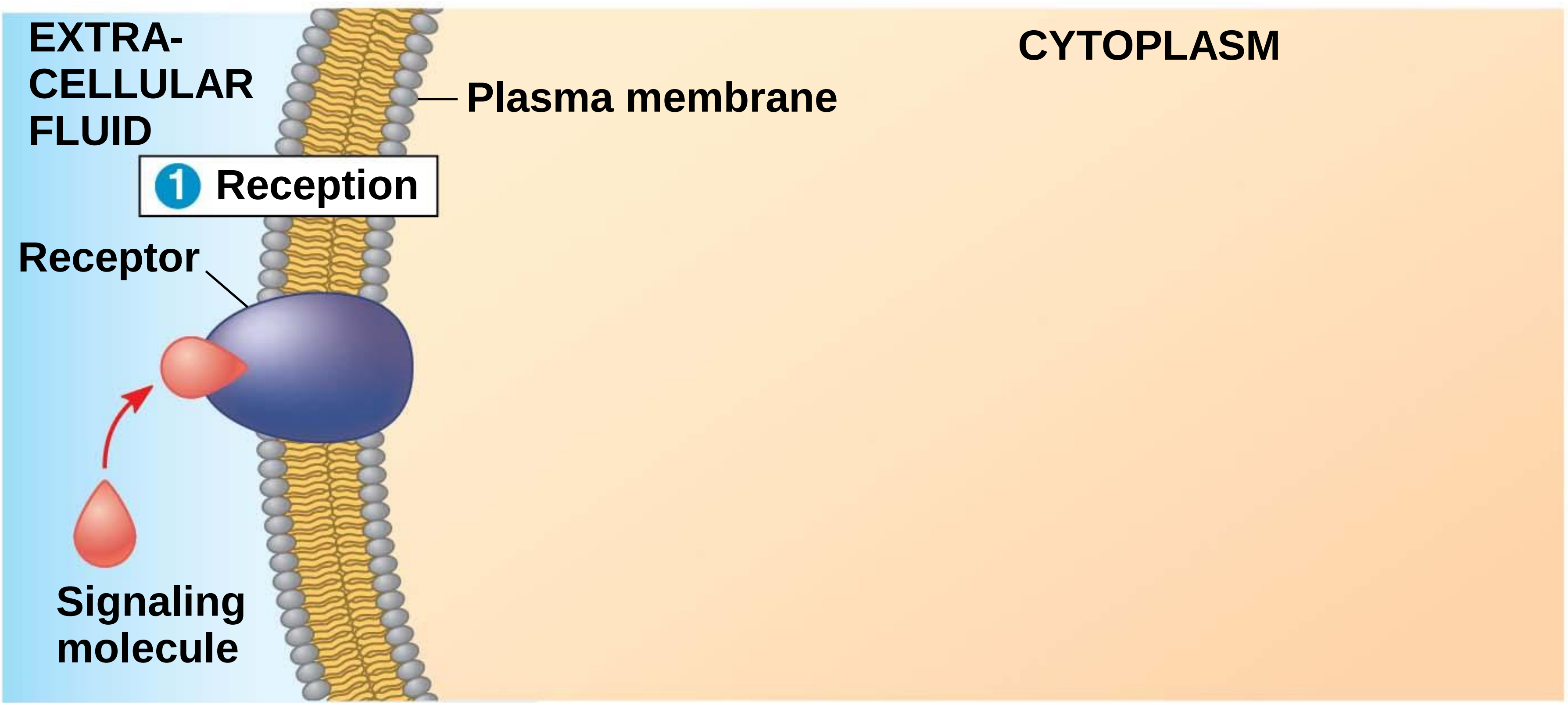


Figure 5.20-s2

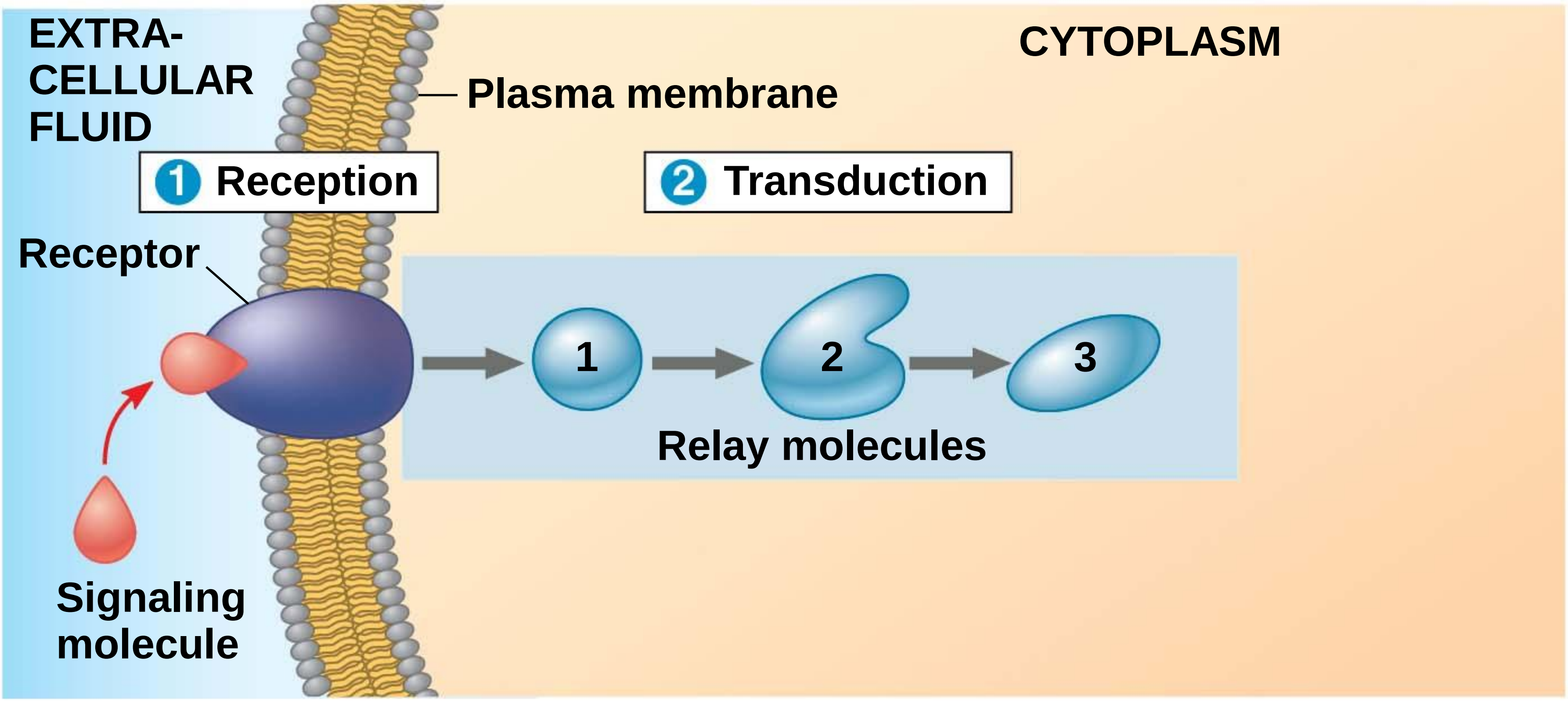
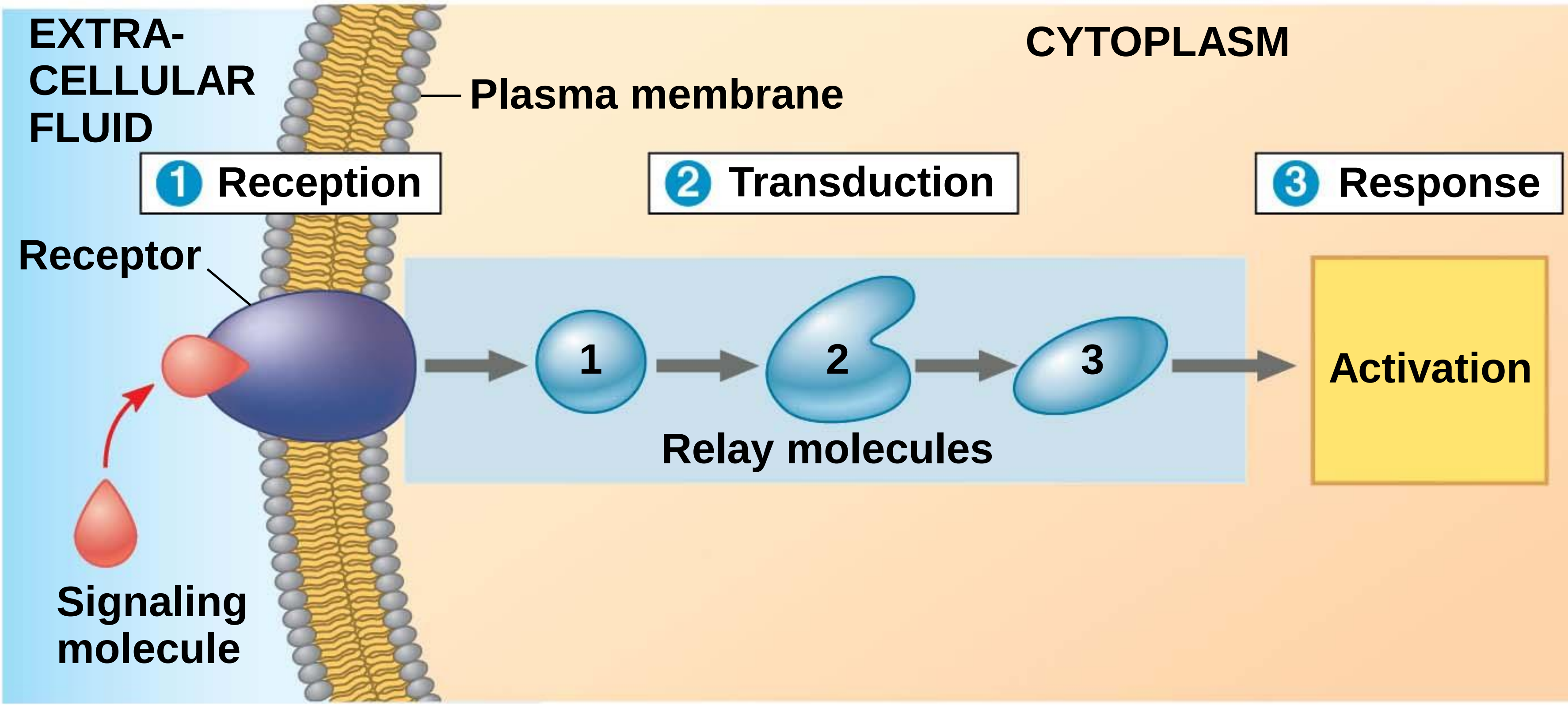


Figure 5.20-s3



Reception, the Binding of a Signaling Molecule to a Receptor Protein

- The binding between a signal molecule (**ligand**) and receptor is highly specific
- Ligand binding generally causes a shape change in the receptor
- Many receptors are directly activated by this shape change
- Most signal receptors are plasma membrane proteins

Receptors in the Plasma Membrane

- Most water-soluble signal molecules bind to specific sites on receptor proteins that span the plasma membrane
- There are two main types of membrane receptors
  - G protein-coupled receptors
  - Ligand-gated ion channels

- **G protein-coupled receptors** (**GPCRs**) are plasma membrane receptors that work with the help of a **G protein**
- G proteins bind to the energy-rich molecule GTP
- Many G proteins are very similar in structure
- GPCR pathways are extremely diverse in function

Figure 5.21-s1

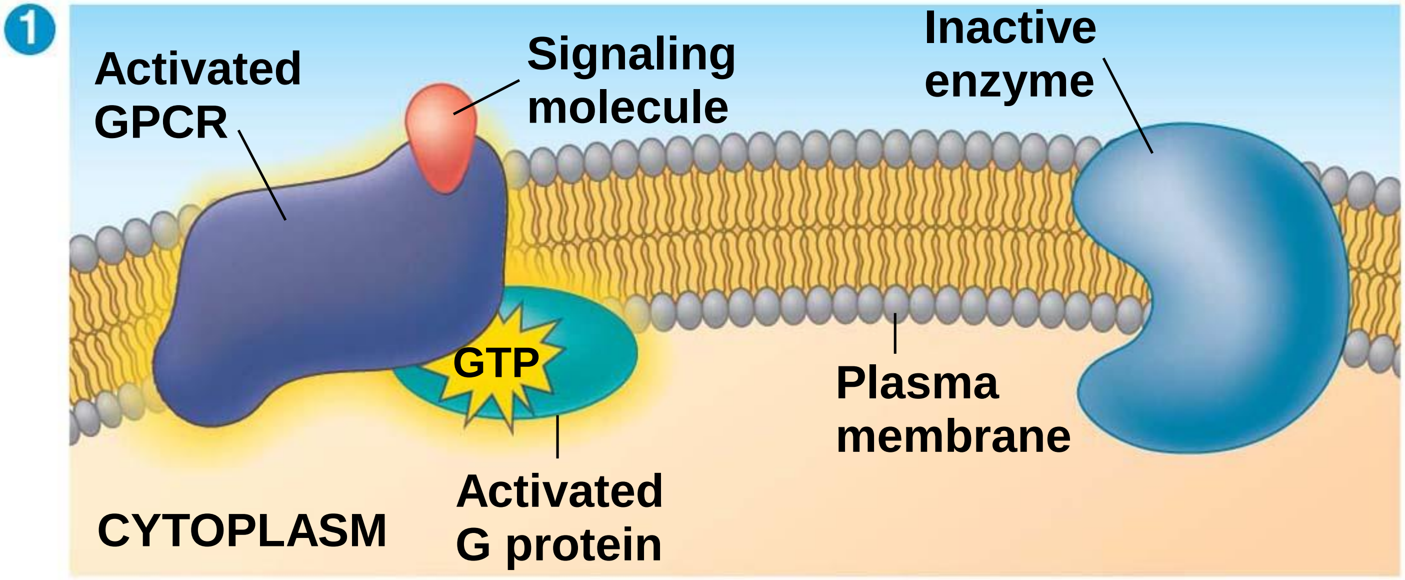
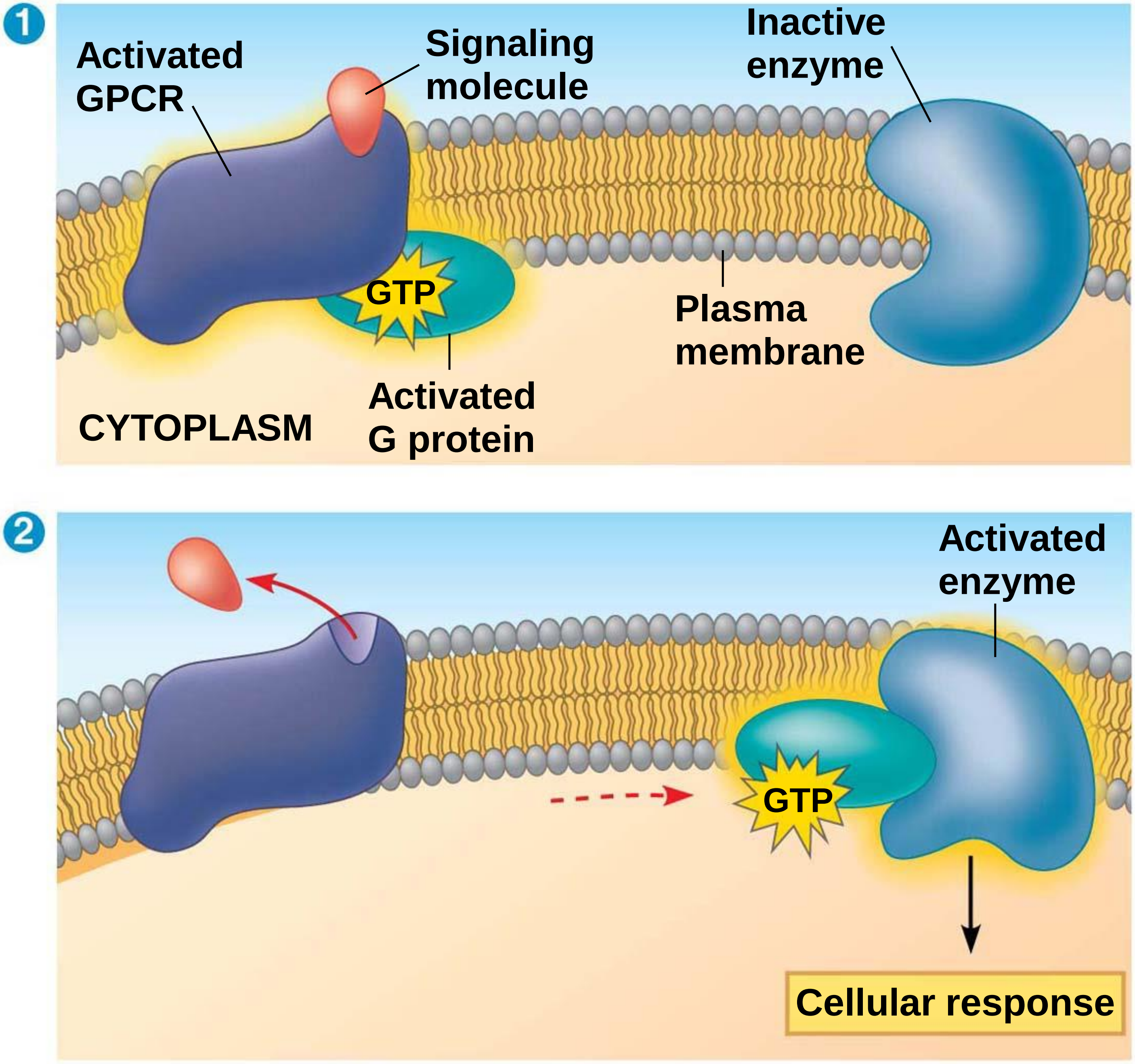


Figure 5.21-s2



- A **ligand-gated ion channel** receptor acts as a "gate" for ions 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
- Ligand-gated ion channels are very important in the nervous system
- The diffusion of ions through open channels may trigger an electric signal

Figure 5.22-s1

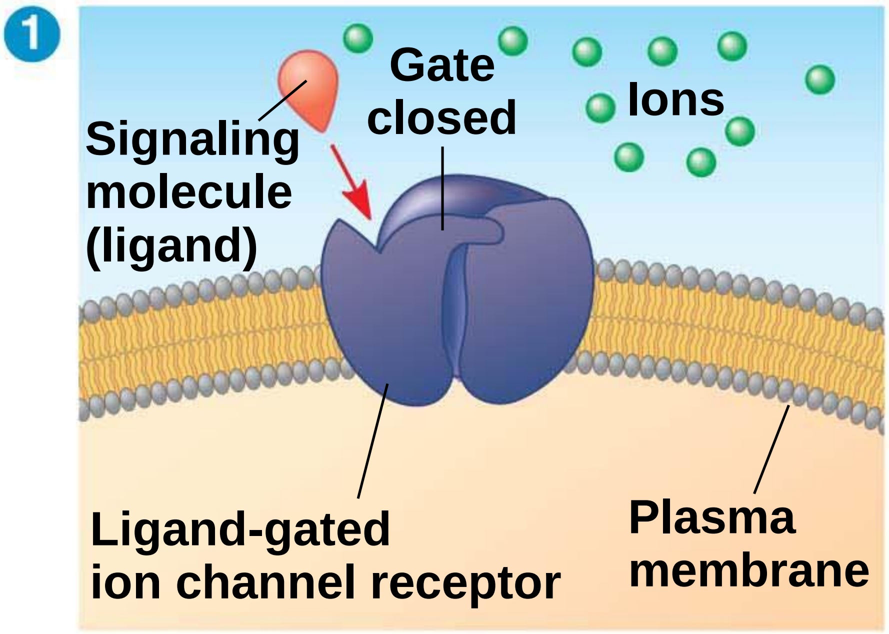


Figure 5.22-s2

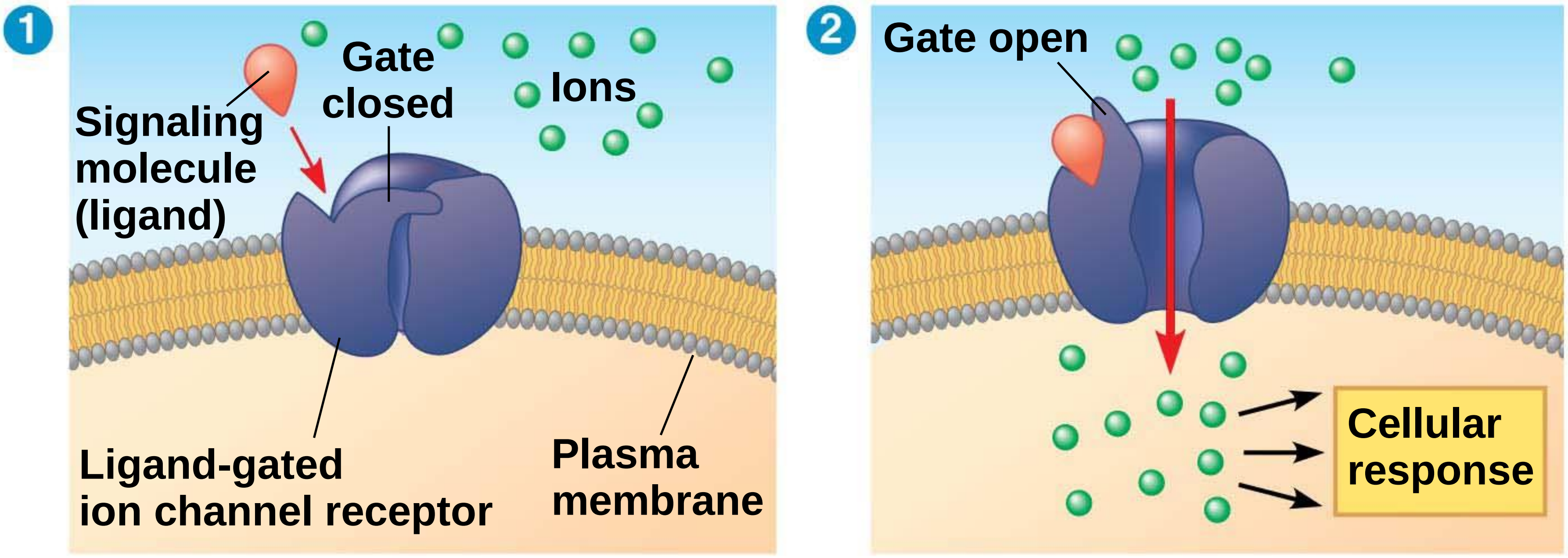
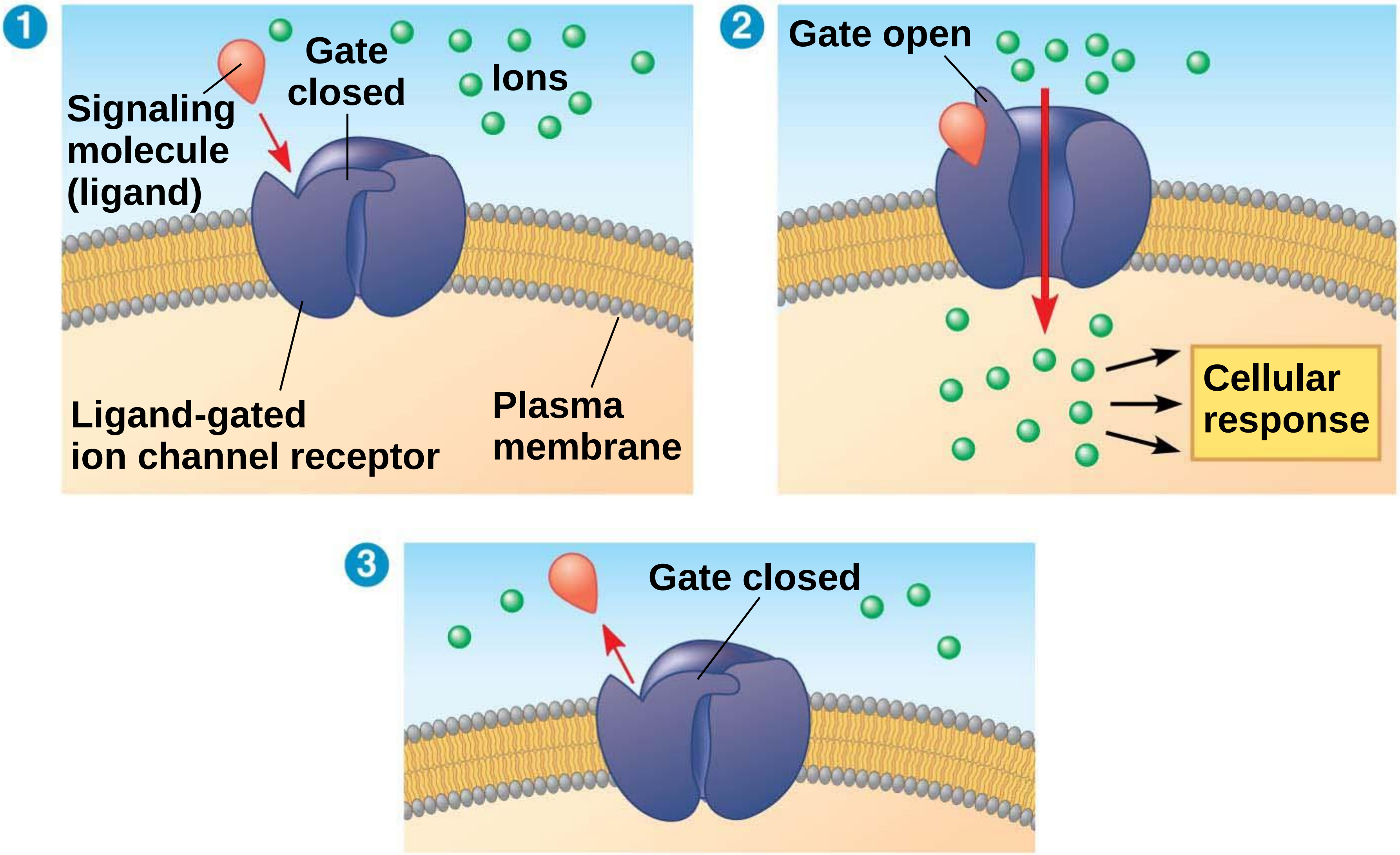


Figure 5.22-s3

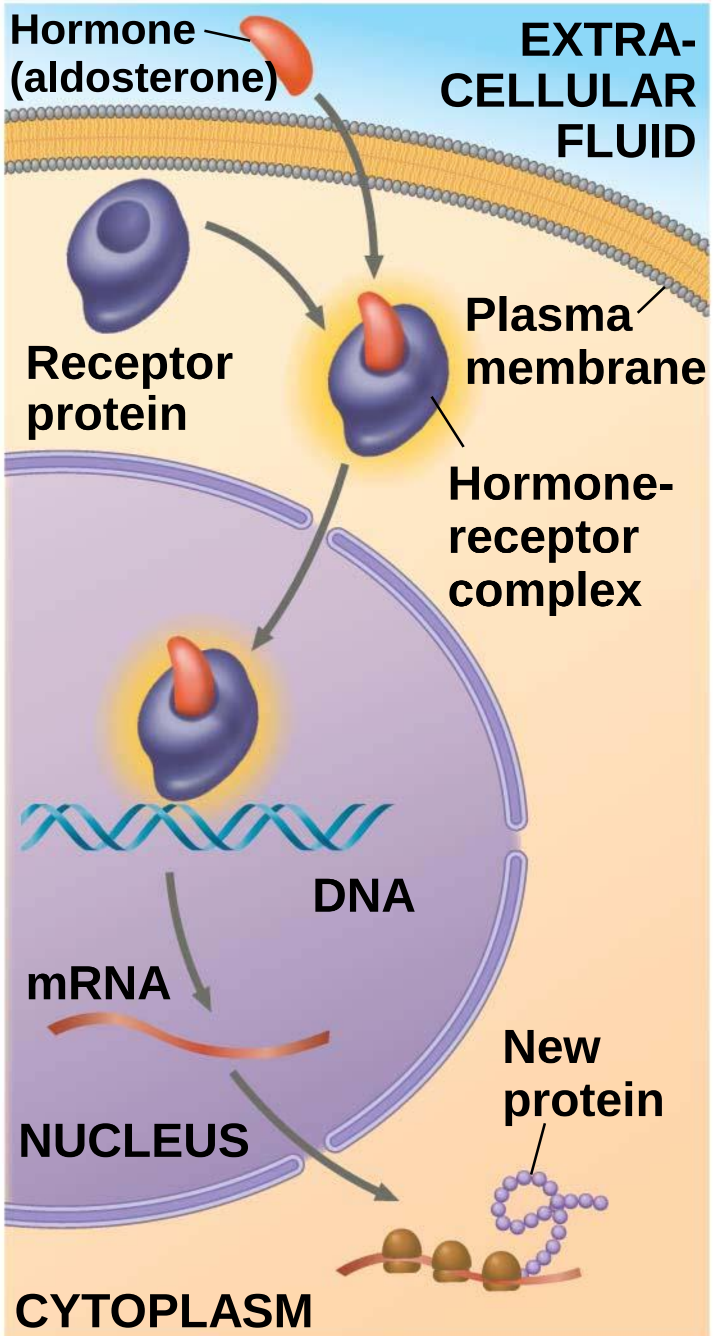


Intracellular Receptors

- Intracellular receptor proteins are found in the cytosol 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 and nitric oxide (NO) in both plants and animals

- Aldosterone behaves similarly to other steroid hormones
- It is secreted by cells of the adrenal gland and enters cells all over the body, but only kidney cells contain receptor cells for aldosterone
- The hormone binds the receptor protein and activates it
- The active form of the receptor enters the nucleus, acts as a transcription factor, and activates genes that control water and sodium flow

Figure 5.23



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

Transduction by Cascades of Molecular Interactions

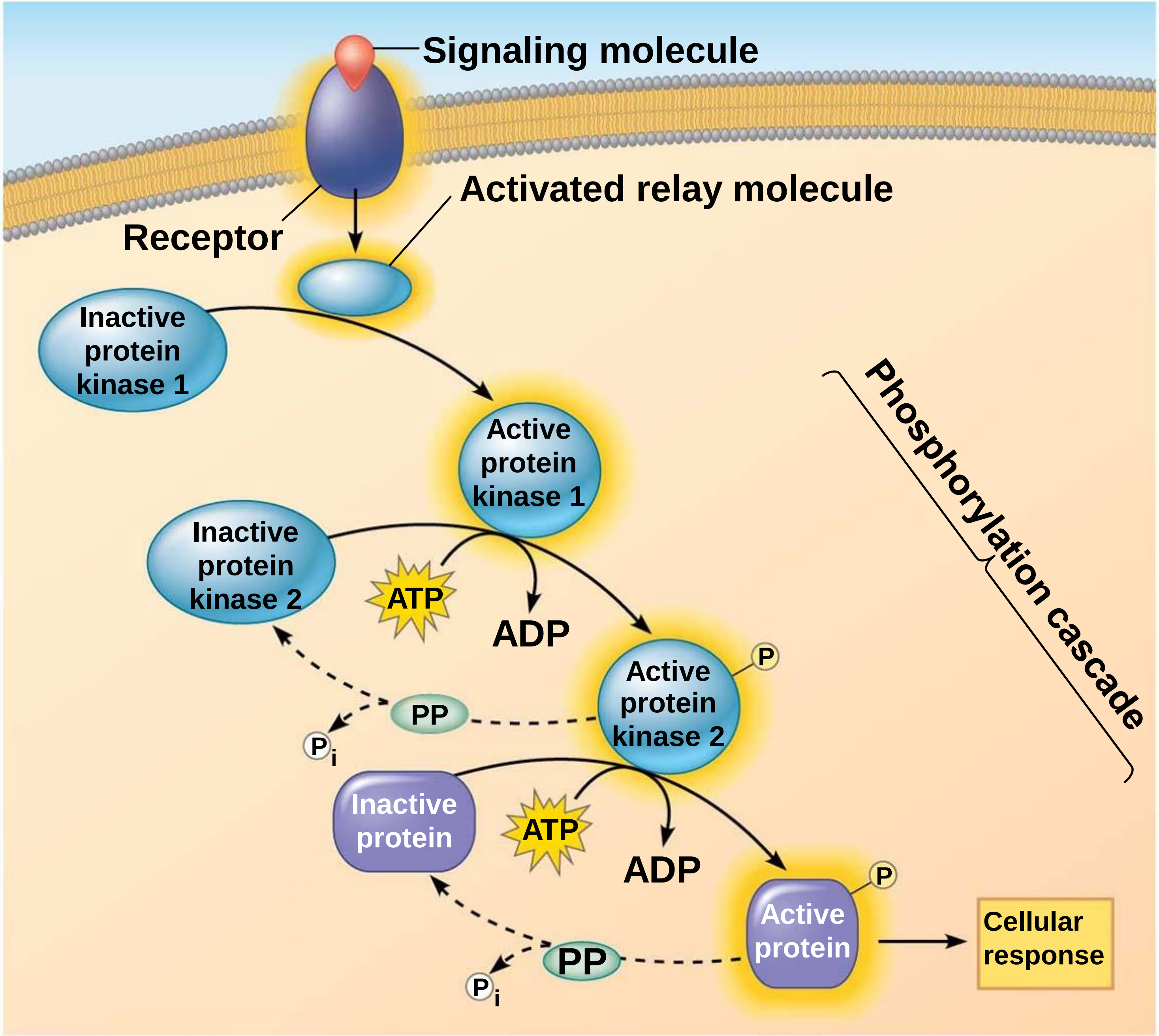
- Signal transduction usually involves multiple steps
- Multistep pathways can amplify a signal: A few molecules can produce a large cellular response
- Multistep pathways provide more opportunities for coordination and regulation of the cellular response than simpler systems do

- The molecules that relay a signal from receptor to response are often proteins
- Like falling dominoes, 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 are a widespread cellular mechanism for regulating protein activity
- **Protein kinases** transfer phosphates from ATP to protein, a process called phosphorylation
- A signaling pathway involving phosphorylation and dephosphorylation can be referred to as a **phosphorylation cascade**
- The addition of phosphate groups often changes the form of a protein from inactive to active

Figure 5.24



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

Figure 5.24-1

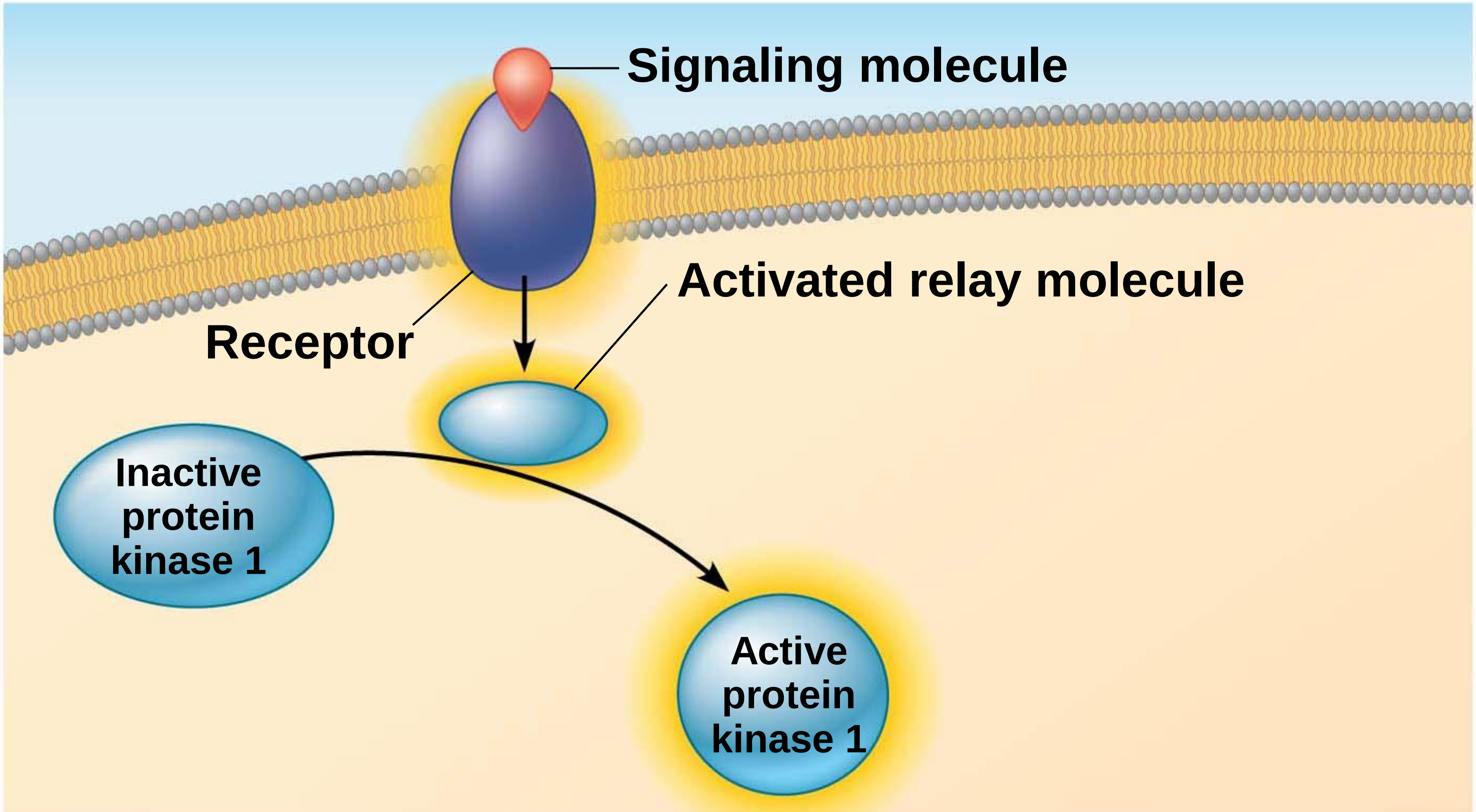
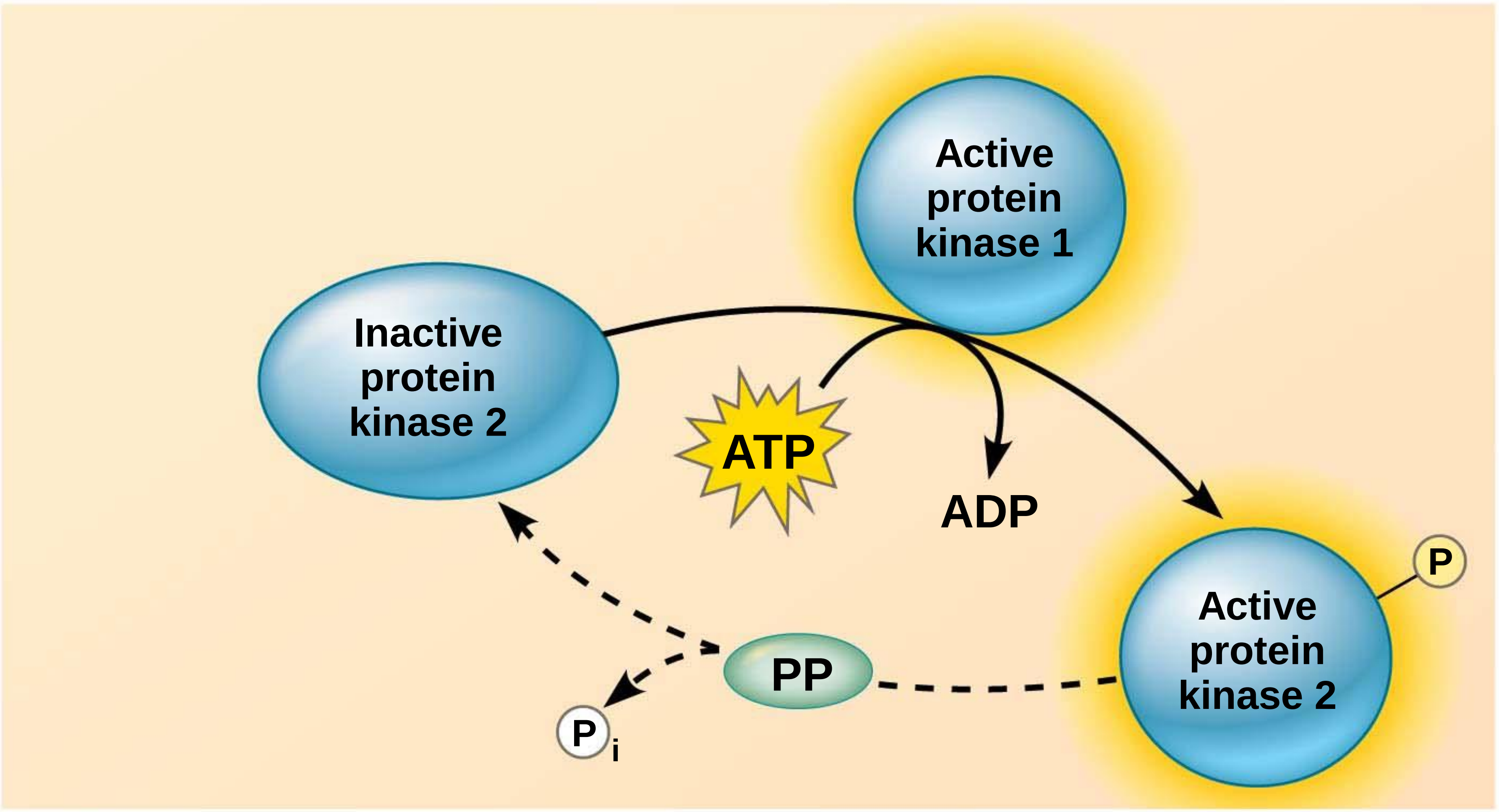
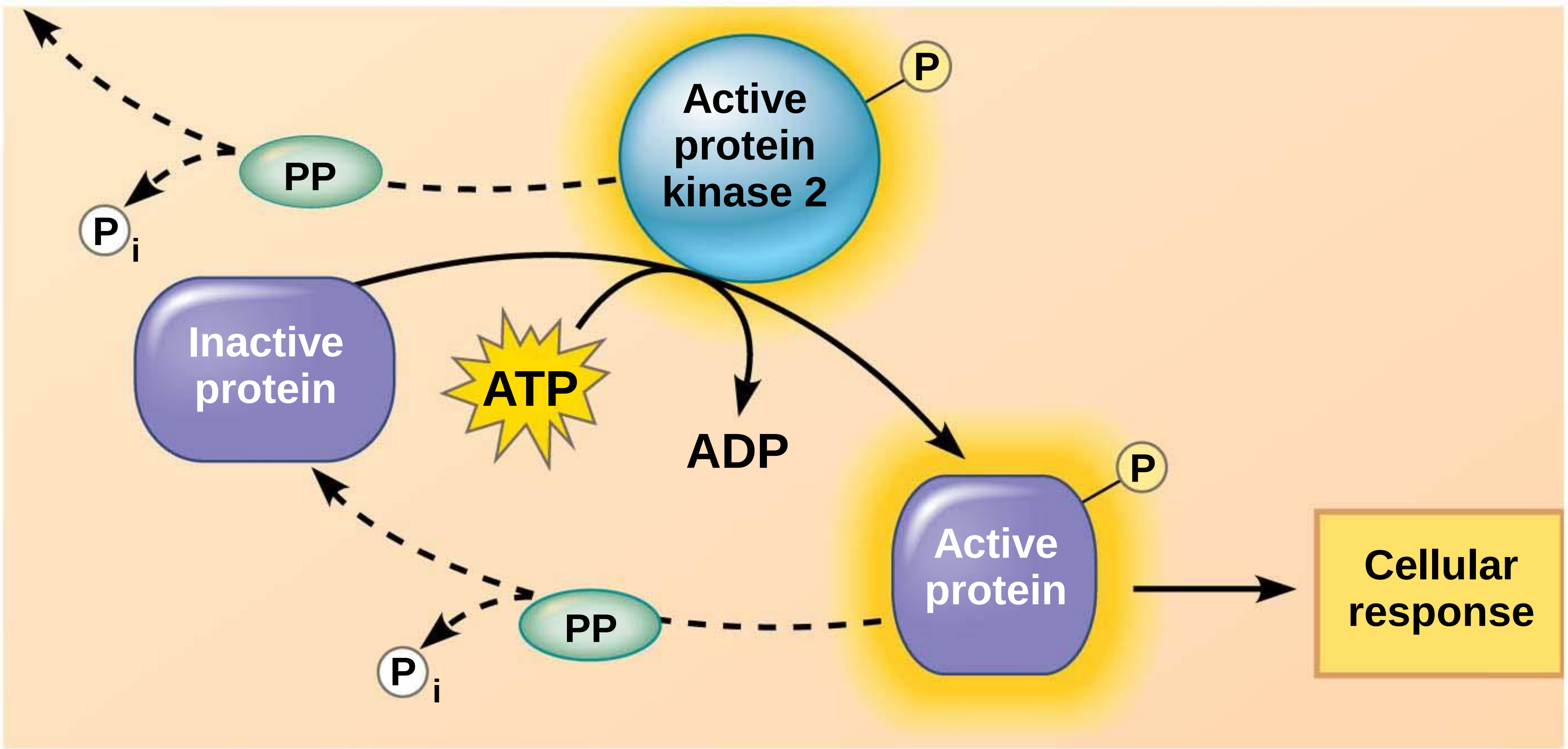

Signaling molecule
Activated relay molecule
Receptor
Inactive
protein
kinase 1
Active
protein
kinase 1

Figure 5.24-2



Active protein kinase 1
Inactive protein kinase 2
ATP
ADP
P
Active protein kinase 2
PP
P i

Figure 5.24-3



P
Active
protein
kinase 2
PP
P
i
Inactive
protein
ATP
ADP
P
Active
protein
Cellular
response
PP
P
i

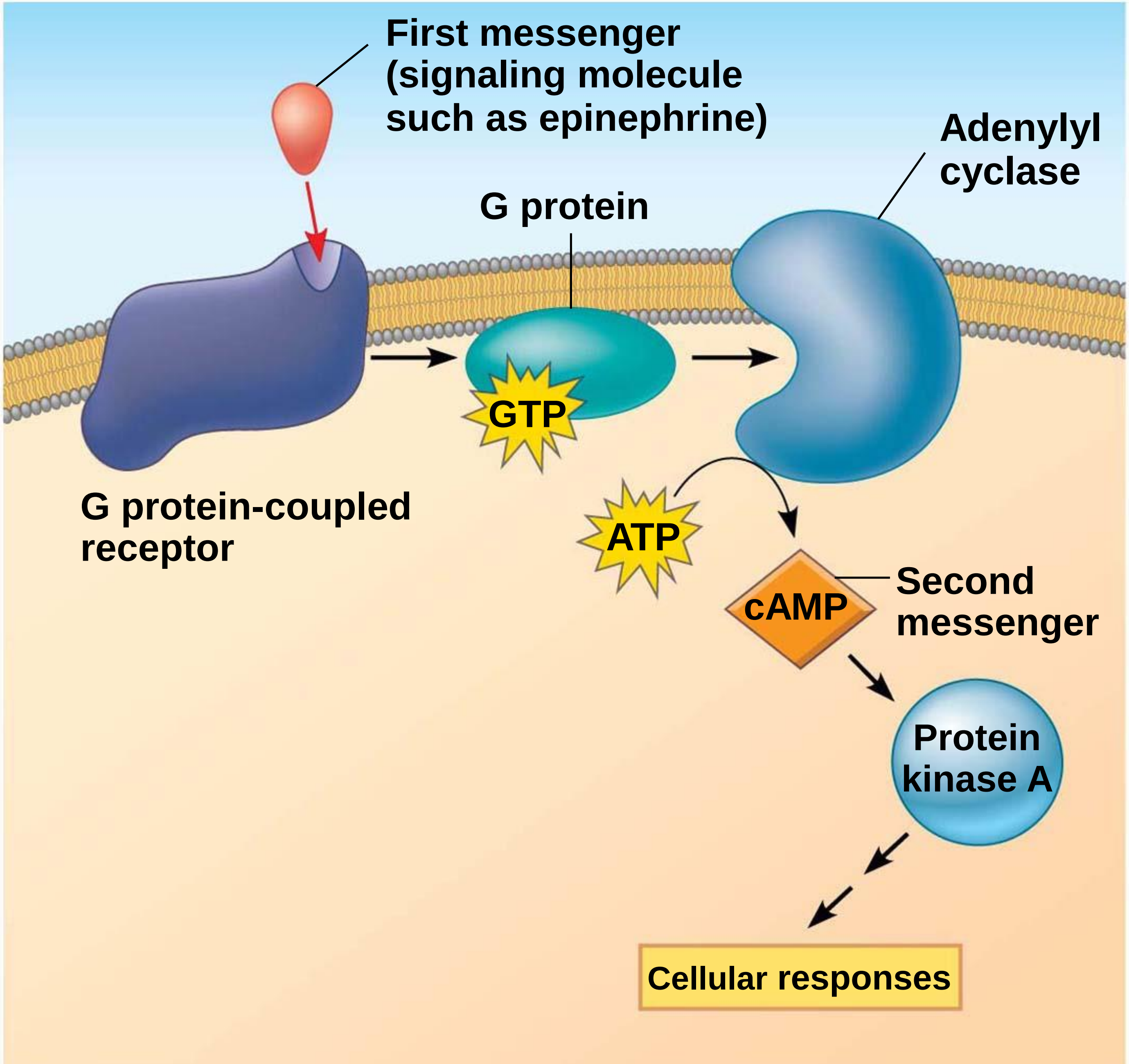
- **Protein phosphatases** remove the phosphates from proteins, a process called dephosphorylation
- Phosphatases provide a mechanism for turning off the signal transduction pathway
- They also make protein kinases available for reuse, enabling the cell to respond to the signal again

Small Molecules and Ions as Second Messengers

- The extracellular signal molecule (ligand) that binds to the receptor is a pathway's "first messenger"
- **Second messengers** are small, nonprotein, water-soluble molecules or ions that spread throughout a cell by diffusion
- Cyclic AMP and calcium ions are common second messengers

- **Cyclic AMP** (**cAMP**) is one of the most widely used second messengers
- Adenylyl cyclase, an enzyme in the plasma membrane, rapidly converts ATP to cAMP in response to a number of extracellular signals
- The immediate effect of cAMP is usually the activation of protein kinase A, which then phosphorylates a variety of other proteins

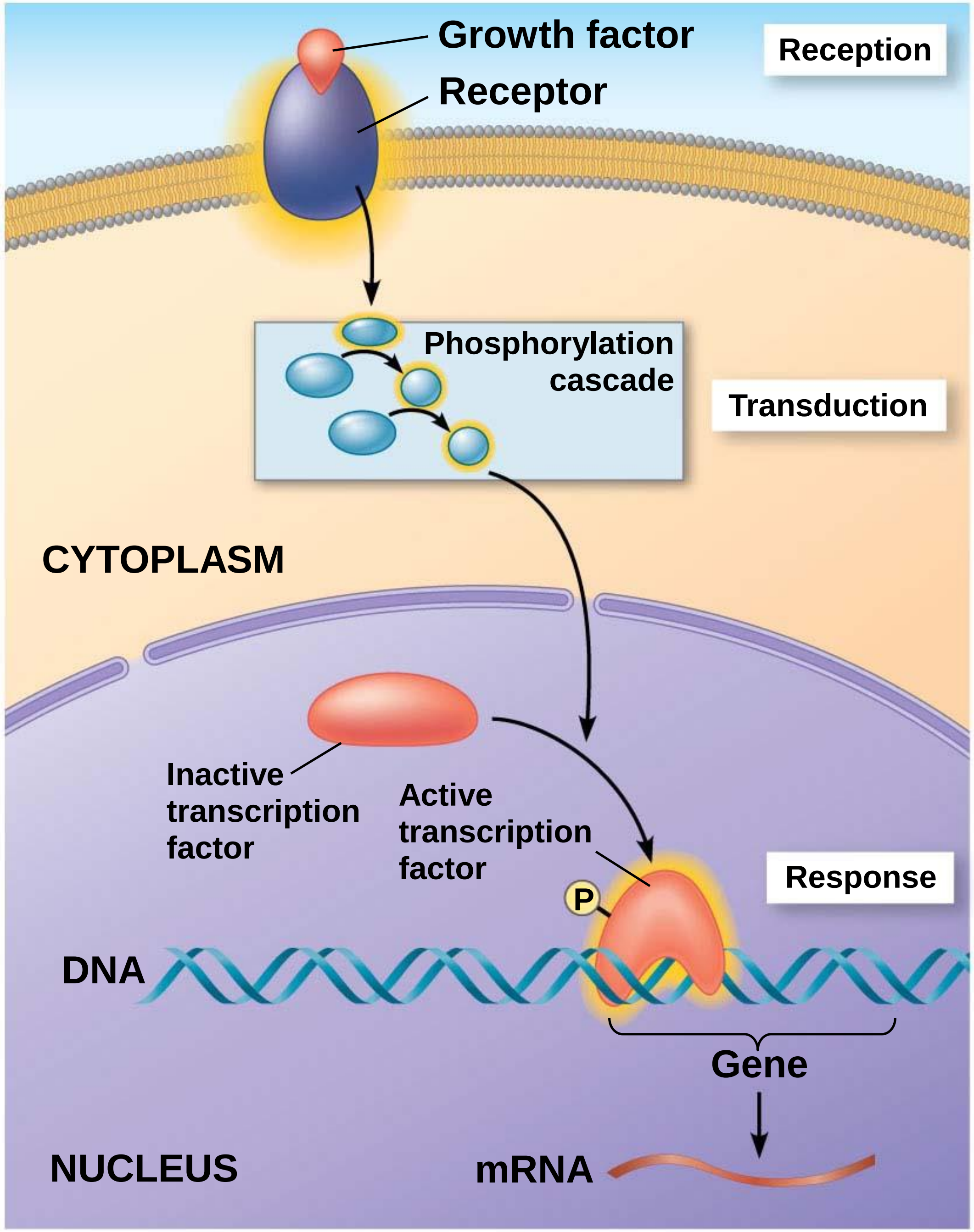
Figure 5.25


First messenger
(signaling molecule
such as epinephrine)
Adenylyl
cyclase
G protein
GTP
G protein-coupled
receptor
ATP
cAMP
Second
messenger
Protein
kinase A
Cellular responses

Response: Regulation of Transcription or Cytoplasmic Activities

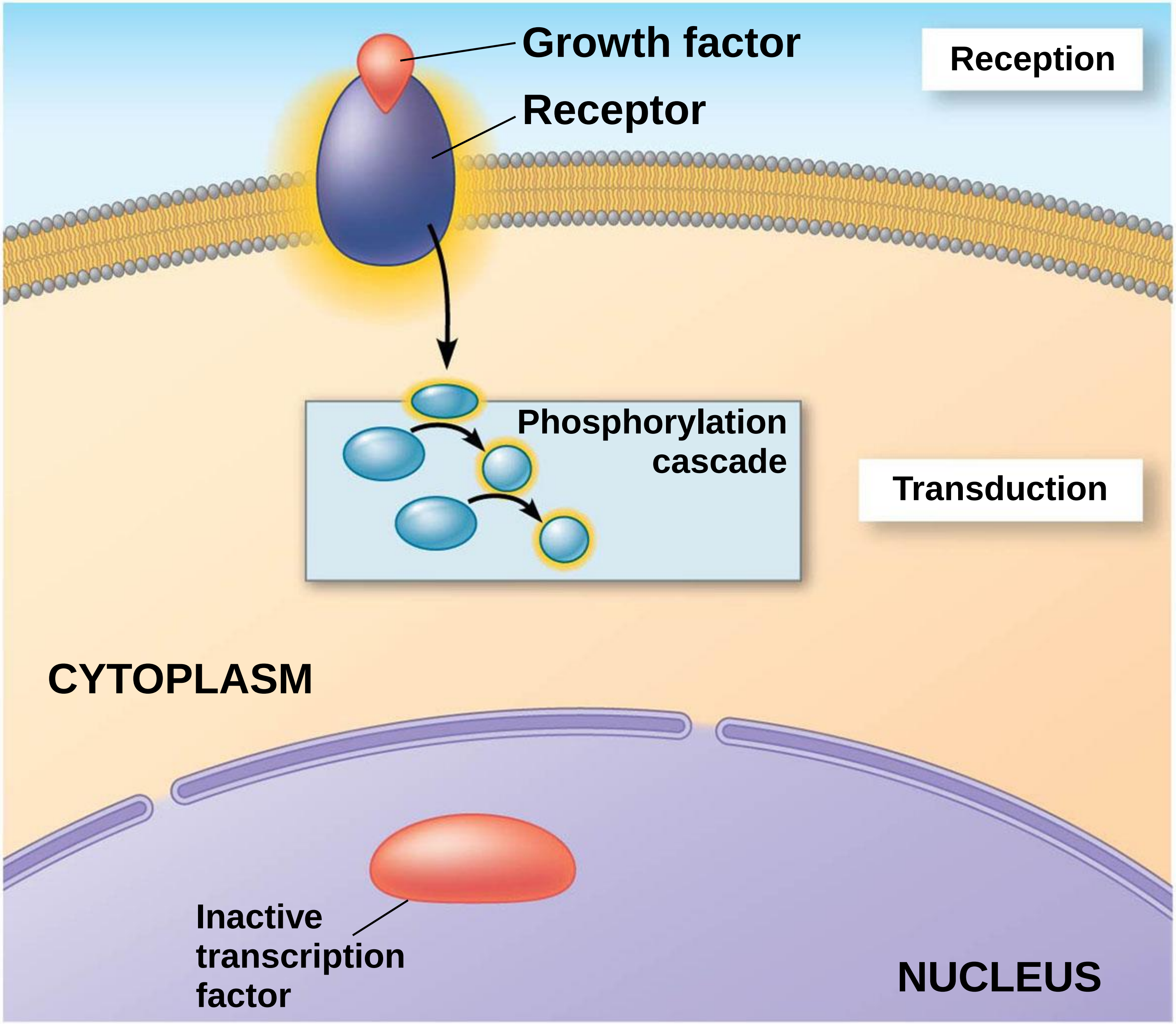
- Ultimately, a signal transduction pathway leads to regulation of one or more cellular activities
- The response may occur in the cytoplasm or in the nucleus
- Many signaling pathways regulate the synthesis of enzymes or other proteins, usually by turning genes on or off in the nucleus
- The final activated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

Figure 5.26



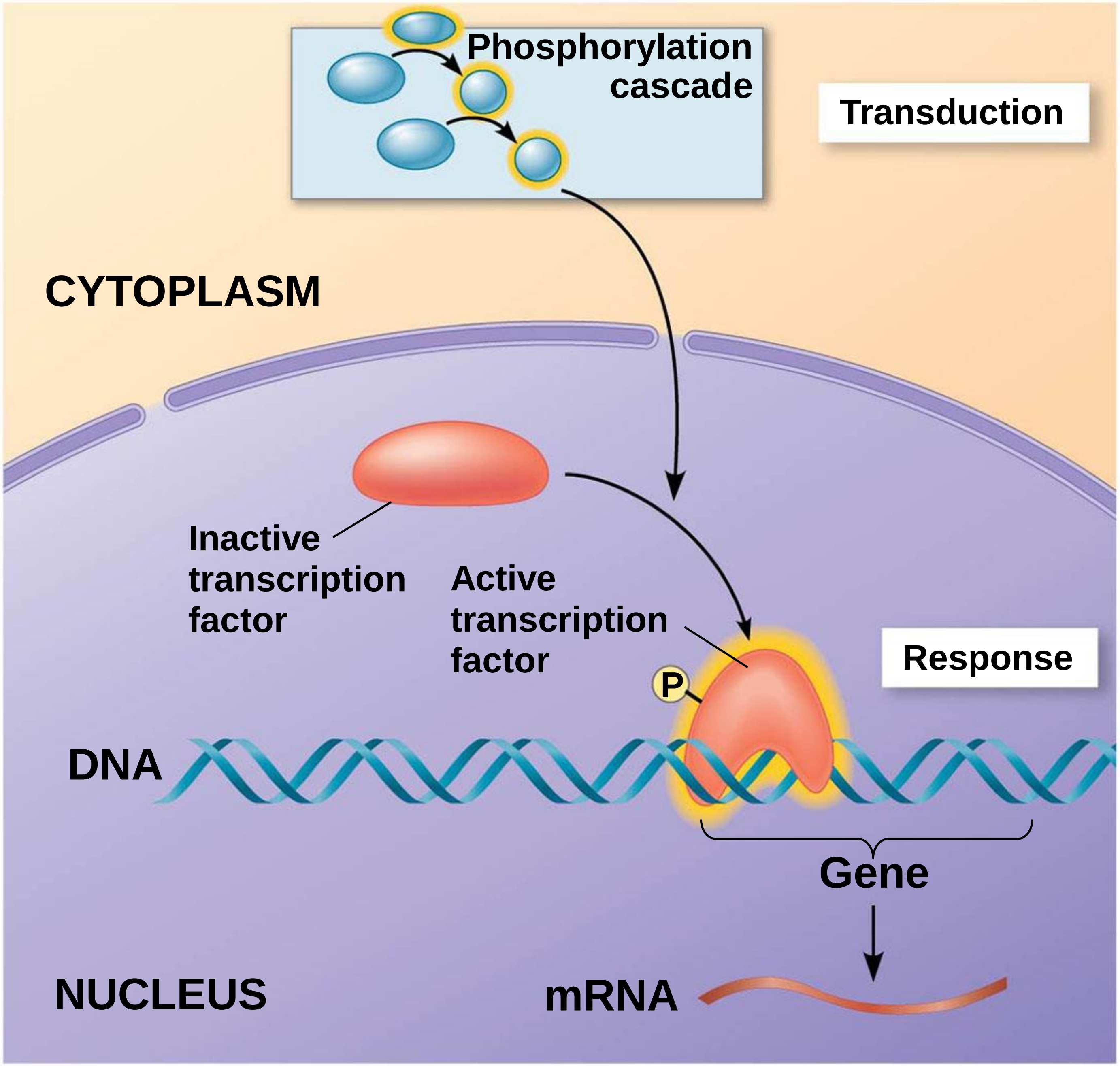
Growth factor
Receptor
Reception
Phosphorylation cascade
Transduction
CYTOPLASM
Inactive transcription factor
Active transcription factor
P
Response
DNA
Gene
NUCLEUS
mRNA

Figure 5.26-1



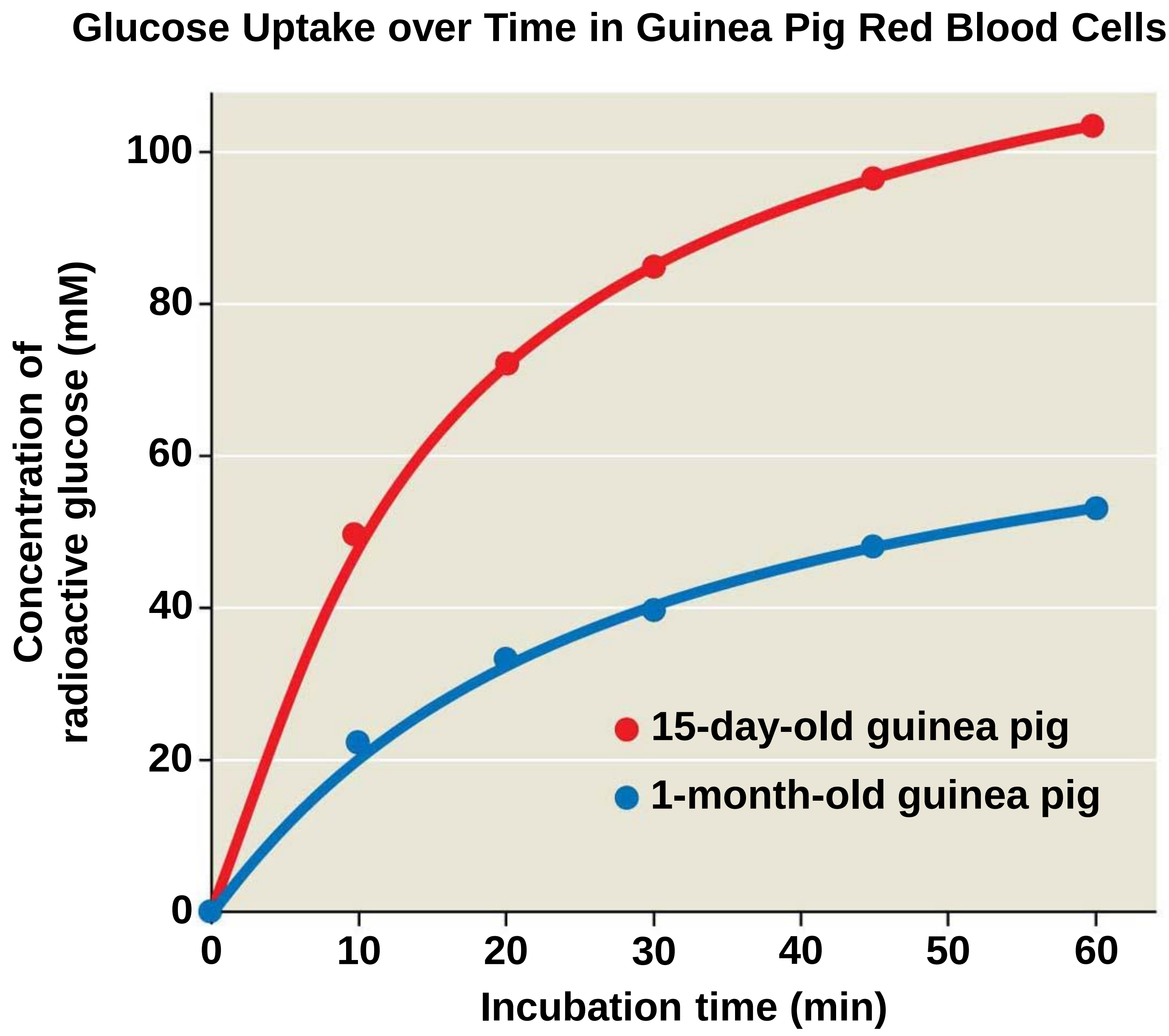
Growth factor
Receptor
Reception
Phosphorylation cascade
Transduction
CYTOPLASM
Inactive transcription factor
NUCLEUS

Figure 5.26-2


Phosphorylation
cascade
Transduction
CYTOPLASM
Inactive
transcription
factor
Active
transcription
factor
P
Response
DNA
Gene
NUCLEUS
mRNA

- Other pathways regulate the activity of enzymes rather than their synthesis, such as the opening of an ion channel or a change in cell metabolism

Figure 5.UN01-1



Data from T. Kondo and E. Beutler, Developmental changes in glucose transport of guinea pig erythrocytes, *Journal of Clinical Investigation* 65:1–4 (1980).

Figure 5.UN01-2

15-day-old and 1-month-old guinea pigs

Figure 5.UN02

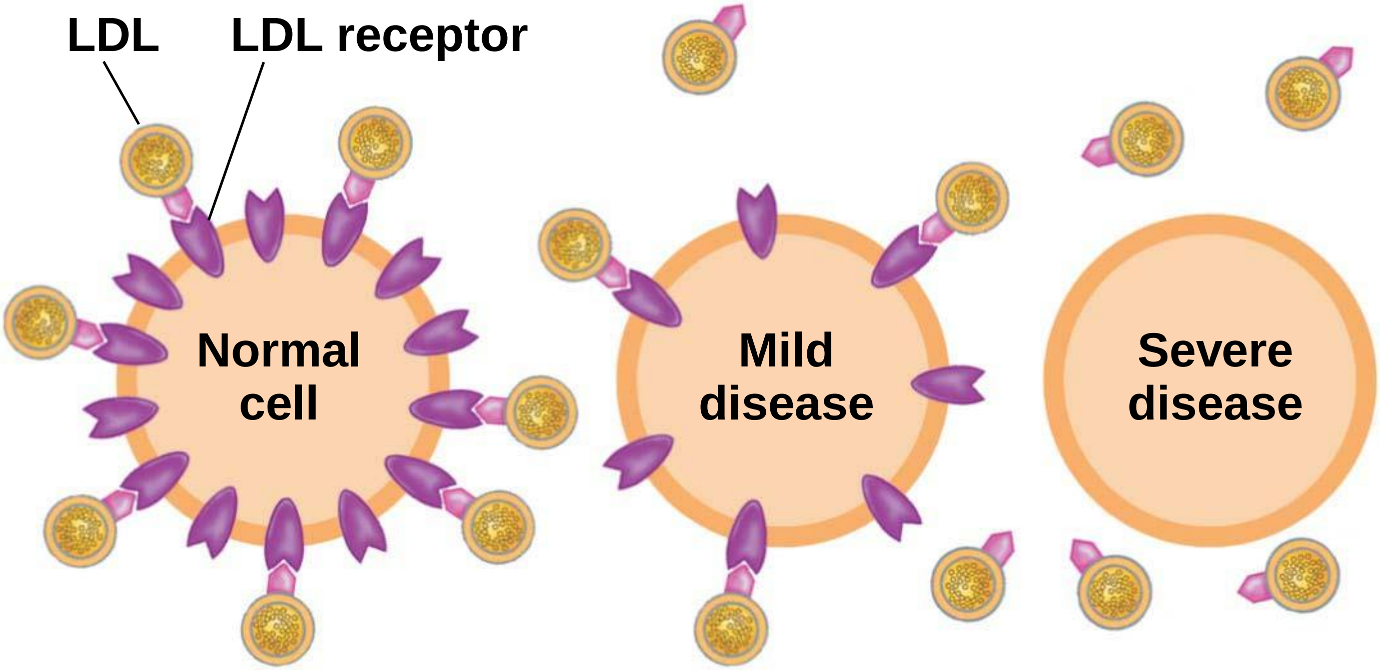


Figure 5.UN03

This image cannot currently be displayed.

Figure 5.UN04

Passive transport: Facilitated diffusion

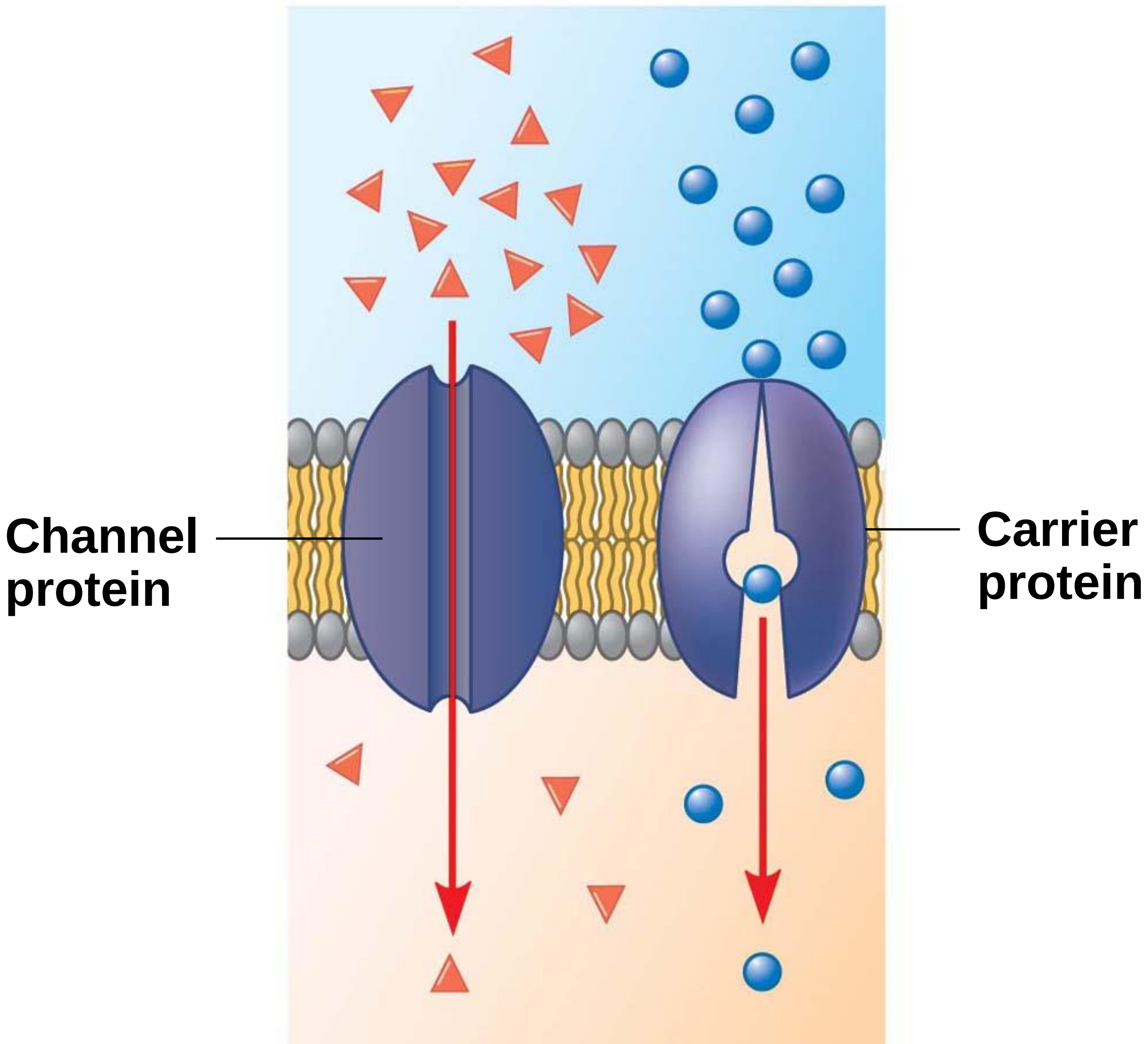


Figure 5.UN05

Active transport

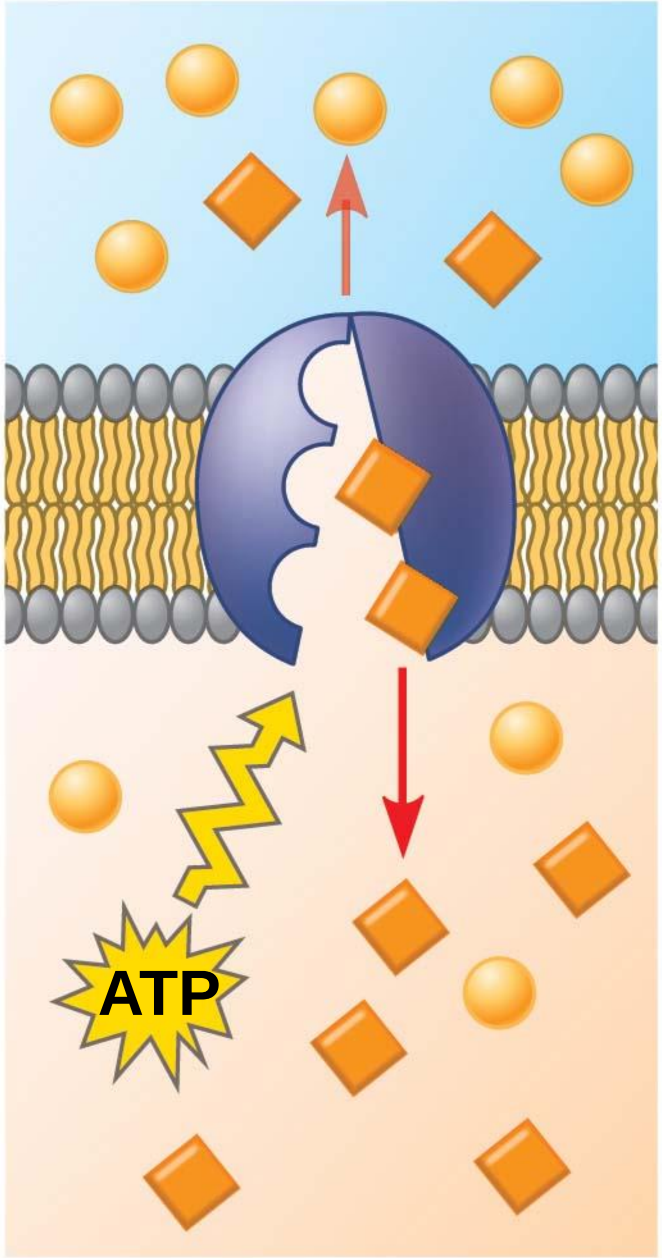


Figure 5.UN06