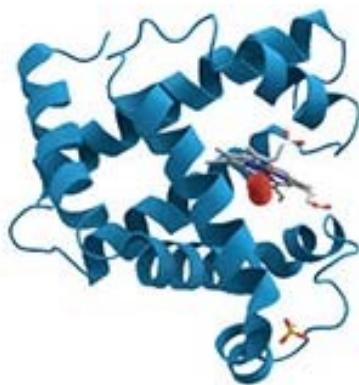
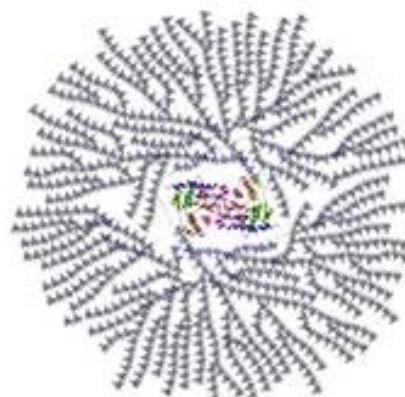


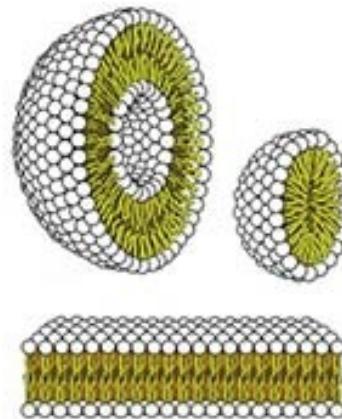
Building Blocks of Life's Complexity



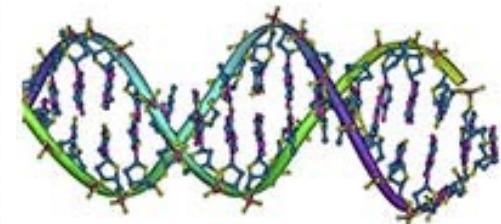
PROTEINS



CARBOHYDRATES

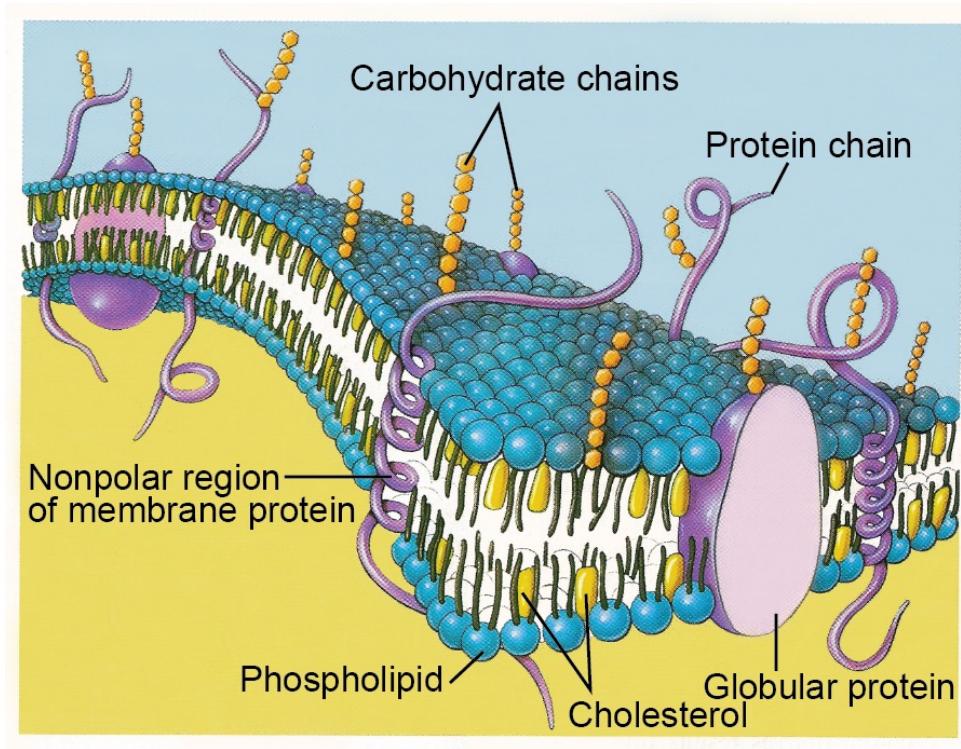


LIPIDS



NUCLEIC ACIDS





Lecture 6

Membrane Structure and Function

Signal-Transduction Pathways

Membrane Structure and Function

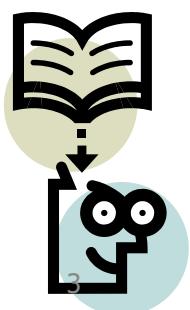
Signal-Transduction Pathways

Lecture Outline:

- Phospholipids and Glycolipids Form Bimolecular Sheets
- Membrane Fluidity
- Proteins and Their Role in Cell Membranes
- Lipids and Their Role in Cell Membranes
- Membrane Proteins As Transporters
- Signal Transduction Depends on Molecular Circuits
- Receptor Proteins
- Metabolism in Context: Insulin Signaling Regulates Metabolism
- Calcium Ion Is a Ubiquitous Cytoplasmic Messenger
- Defects in Signalling Pathways and Diseases

Readings:

Tymochko, Berg, Stryer,
Biochemistry, Ch. 12 - 13
2nd Edition, pp. 195 - 231
3rd Edition, pp. 205-240
4th Edition, pp. 223-263

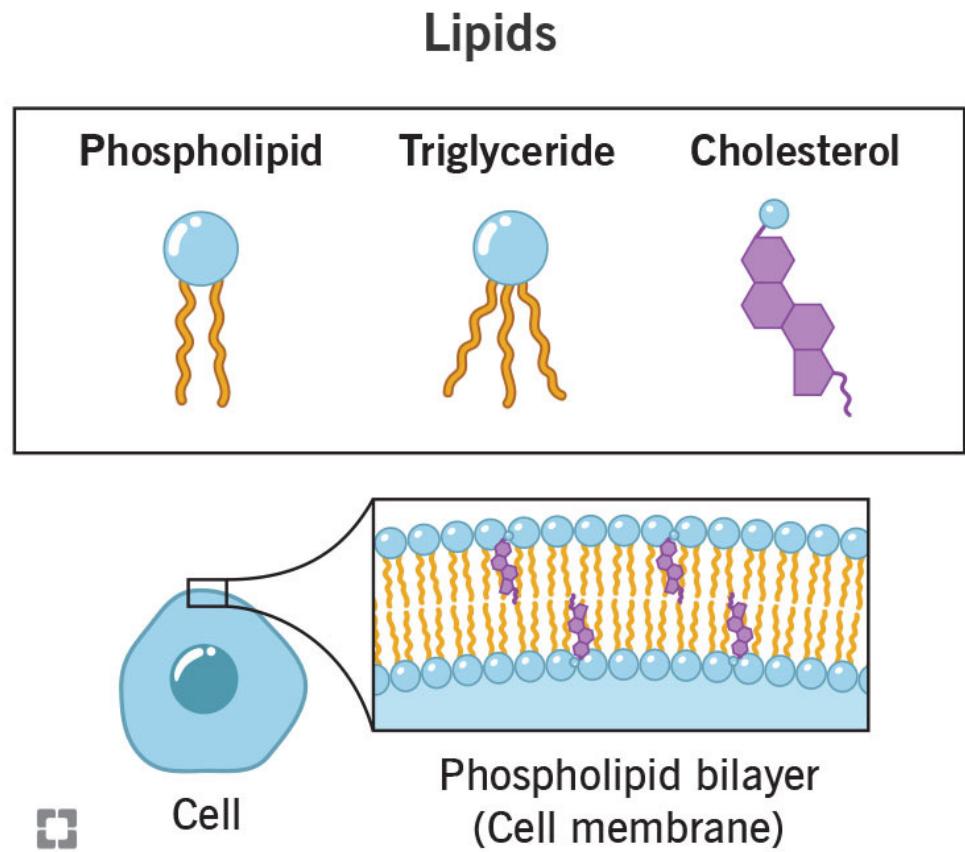


Lipids

- **Lipids** are molecules that are not soluble in water but are soluble in organic solvents.

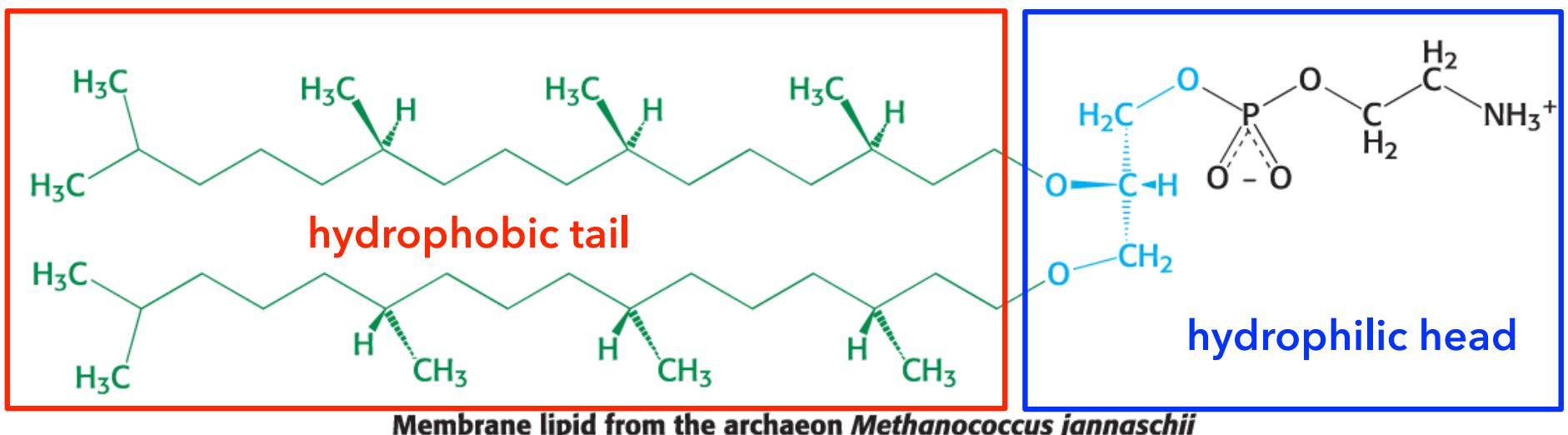
We will examine five classes of lipids:

1. **Free fatty acids:** A common fuel.
2. **Triacylglycerols:** Storage form of fatty acids.
3. **Phospholipids:** Membrane lipids.
4. **Glycolipids:** Membrane lipids composed in part of carbohydrates.
5. **Steroids:** Polycyclic hydrocarbons with a variety of functions.

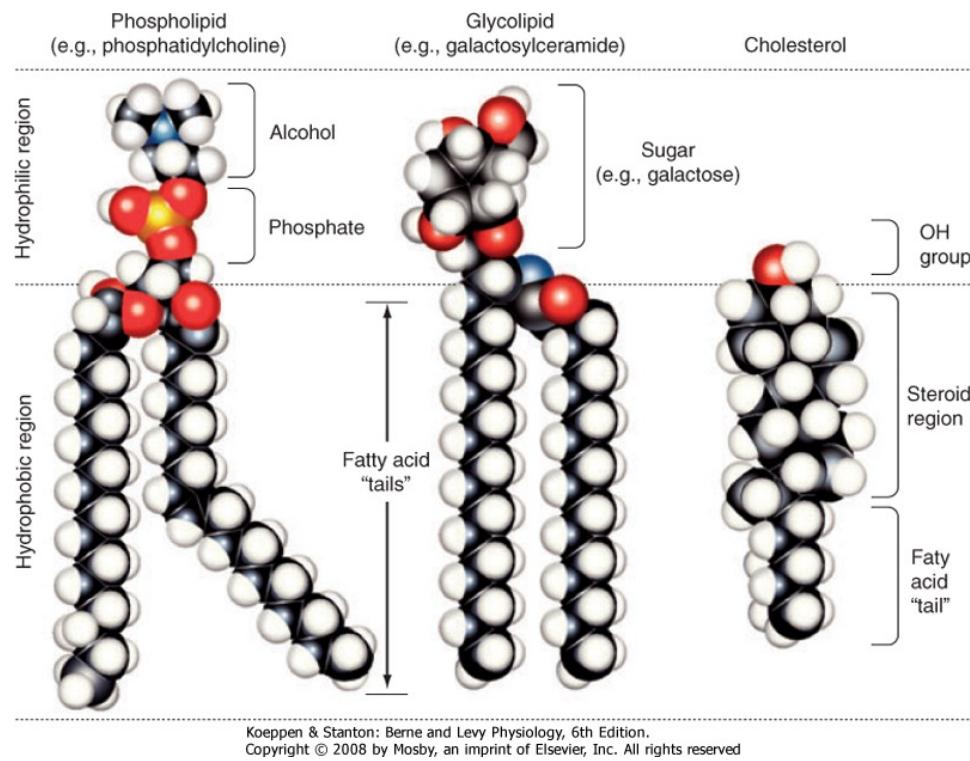


Membrane Lipids

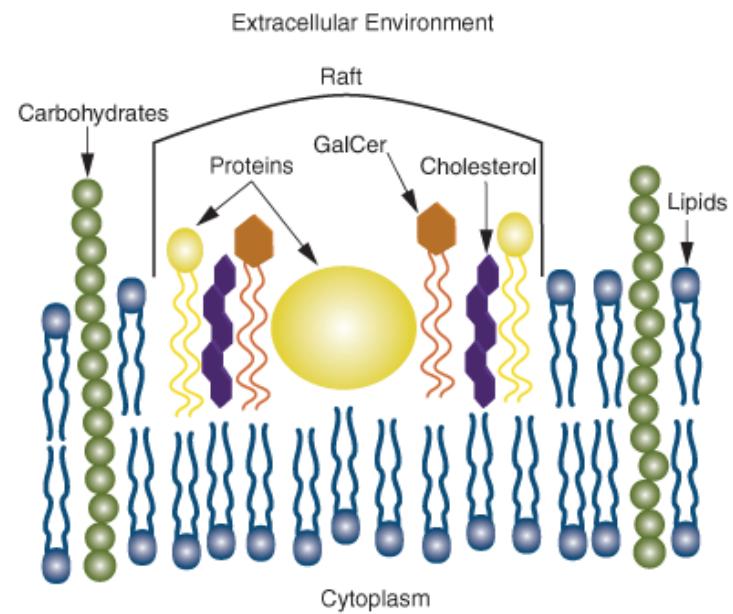
- Membrane lipids are **amphipathic** molecules, containing hydrophobic and hydrophilic properties.
- The fatty acid components provide the hydrophobic properties, while the alcohol and phosphate components, called the polar head group, provide the hydrophilic properties.



Membrane Lipids

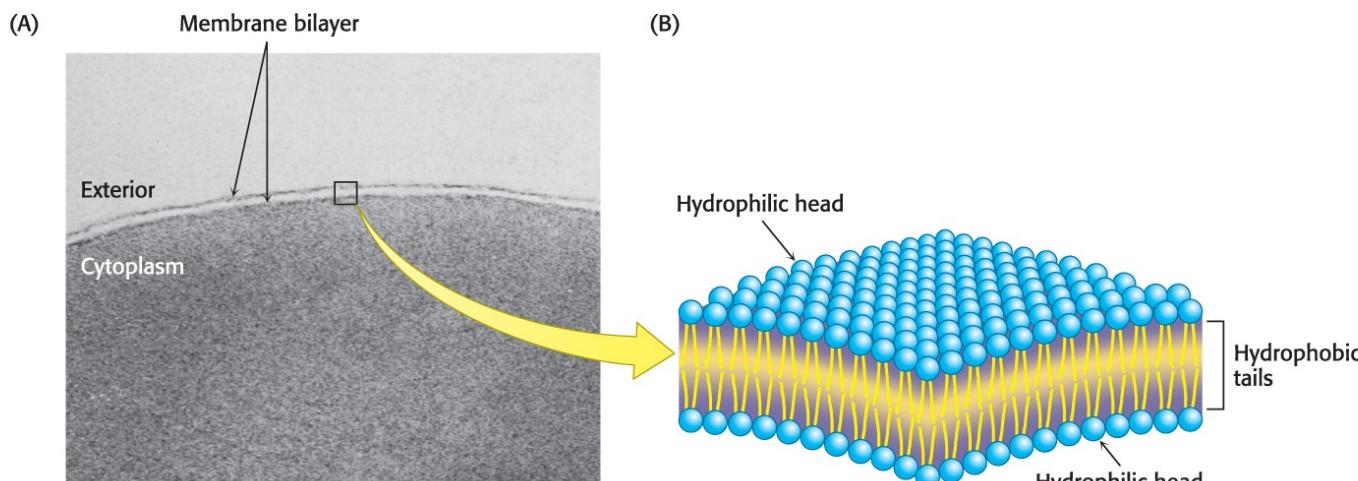


- Proteins are sometimes covalently bound to lipids to localize the protein to the cell membrane.

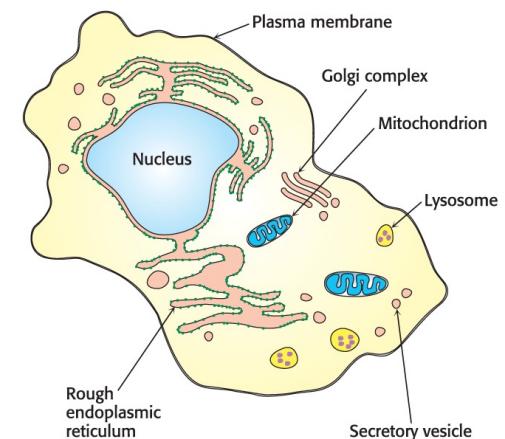


The Membrane

- Membranes are the interface of two environments:
 - In relation to plasma membrane
 - In relation to internal membranes (cellular compartments)
- Membranes are sheet-like structures, two molecules thick, that form closed boundaries.

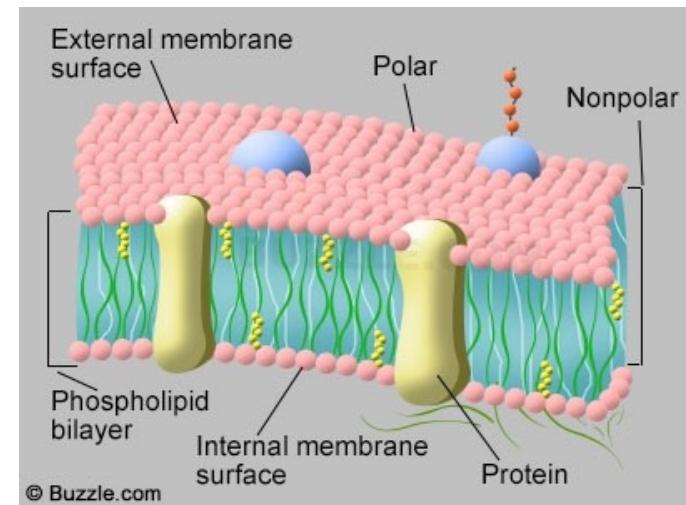


© 1981 The Rockefeller University Press. The Journal of Cell Biology, 1981, 91: 189s–204s. Courtesy of J.D. Robertson.



Characteristics of Membranes

1. Membranes are composed of lipids and proteins, either of which can be decorated with carbohydrates.
2. Membrane lipids are small amphipathic molecules that form closed bimolecular sheets that prevent the movement of polar or charged molecules.
3. Proteins serve to mitigate the impermeability of membranes and allow movement of molecules and information across the cell membrane.
4. Membranes are noncovalent assemblies.
5. Membranes are asymmetric in that the outer surface is always different from the inner surface.
6. Membranes are fluid structures.



Phospholipids and Glycolipids Form Bimolecular Sheets

- Phospholipids and glycolipids form lipid bilayers in aqueous solutions.
- The formation of membranes is powered by the **hydrophobic effect**.
- Liposomes, or lipid vesicles, are aqueous compartments enclosed by a lipid membrane.
- Liposomes, formed by sonicating a mixture of phospholipids in aqueous solution, may be useful as drug-delivery systems.

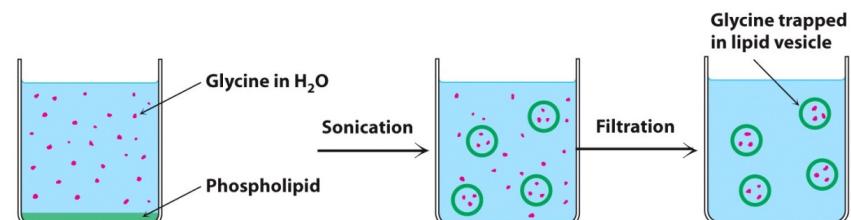
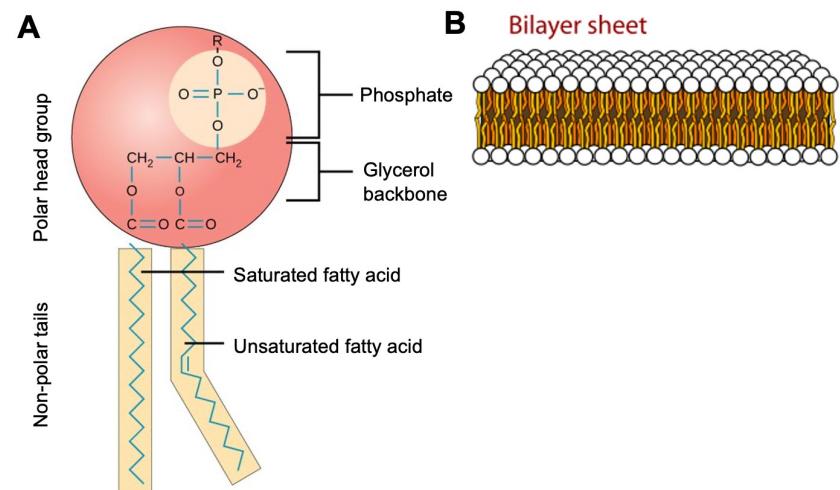
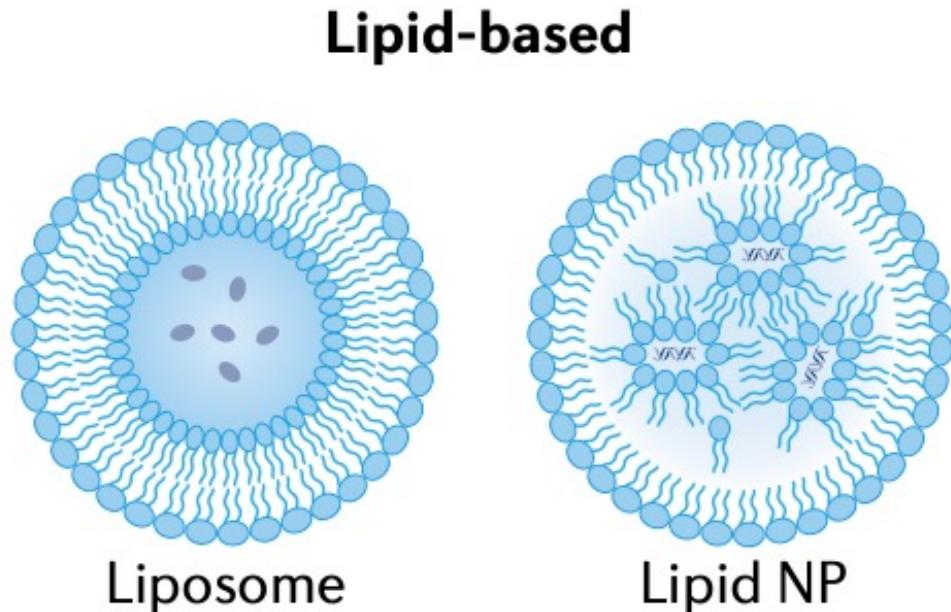


Figure 12.3
Biochemistry: A Short Course, Second Edition
© 2013 W. H. Freeman and Company

Engineering precision nanoparticles for drug delivery

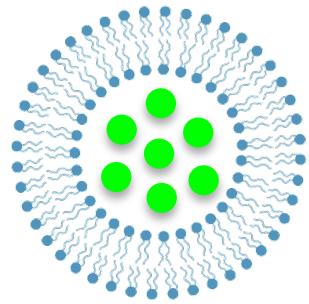
Michael J. Mitchell^{1,2,3,4,5}, Margaret M. Billingsley¹, Rebecca M. Haley¹, Marissa E. Wechsler⁶, Nicholas A. Peppas^{6,7,8,9,10} and Robert Langer¹



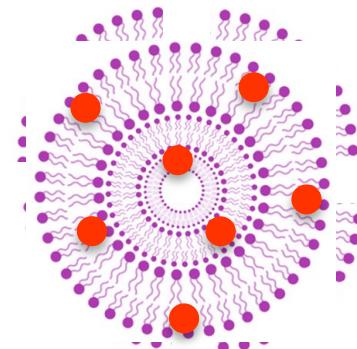
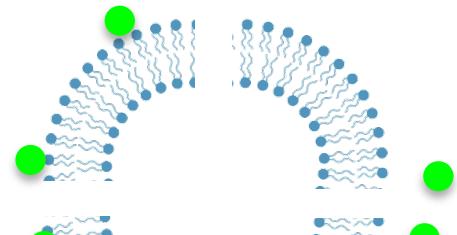
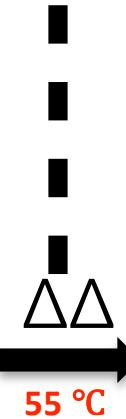
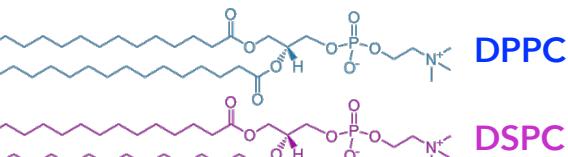
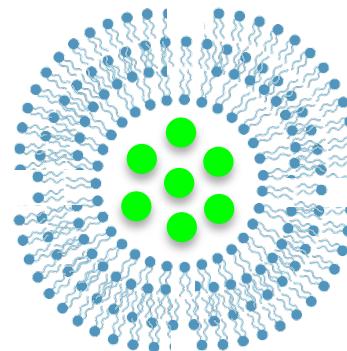
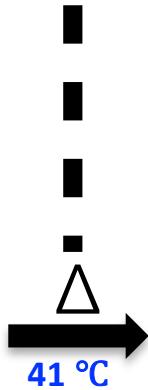
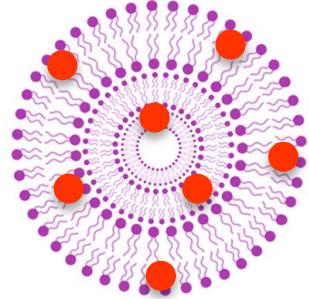
- Formulation simplicity with a range of physicochemical properties
- High bioavailability
- Payload flexibility
- Low encapsulation efficiency

Sequential drug release

DPPC, $T_m = 41^\circ\text{C}$

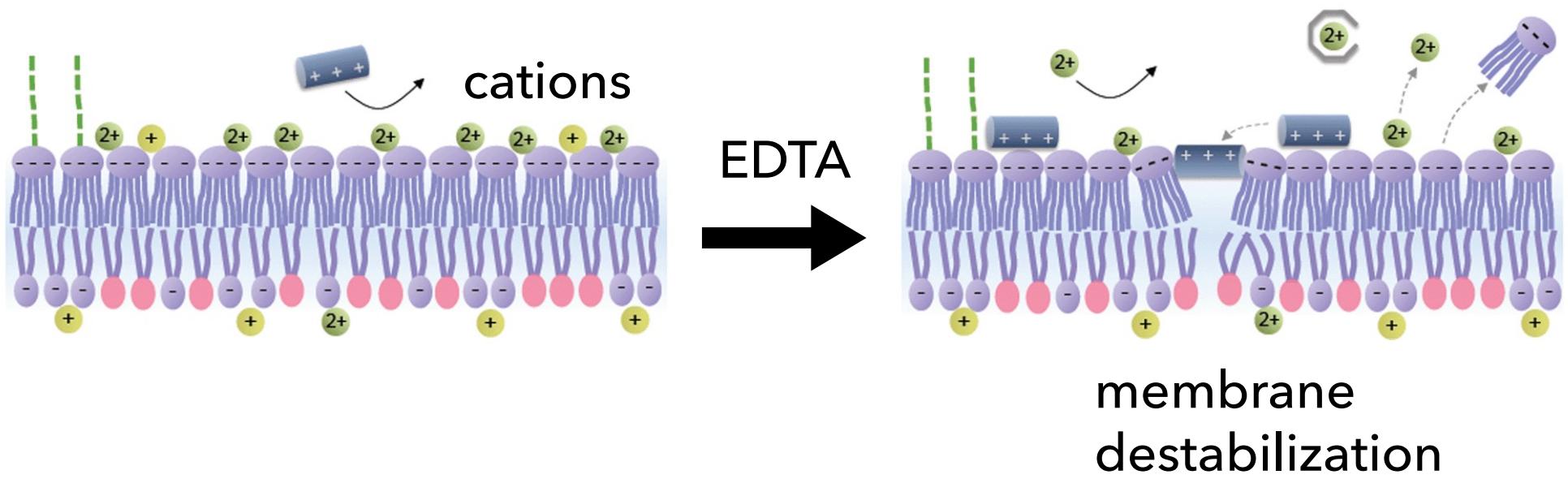


DSPC, $T_m = 55^\circ\text{C}$



● EDTA ● Rifampicin

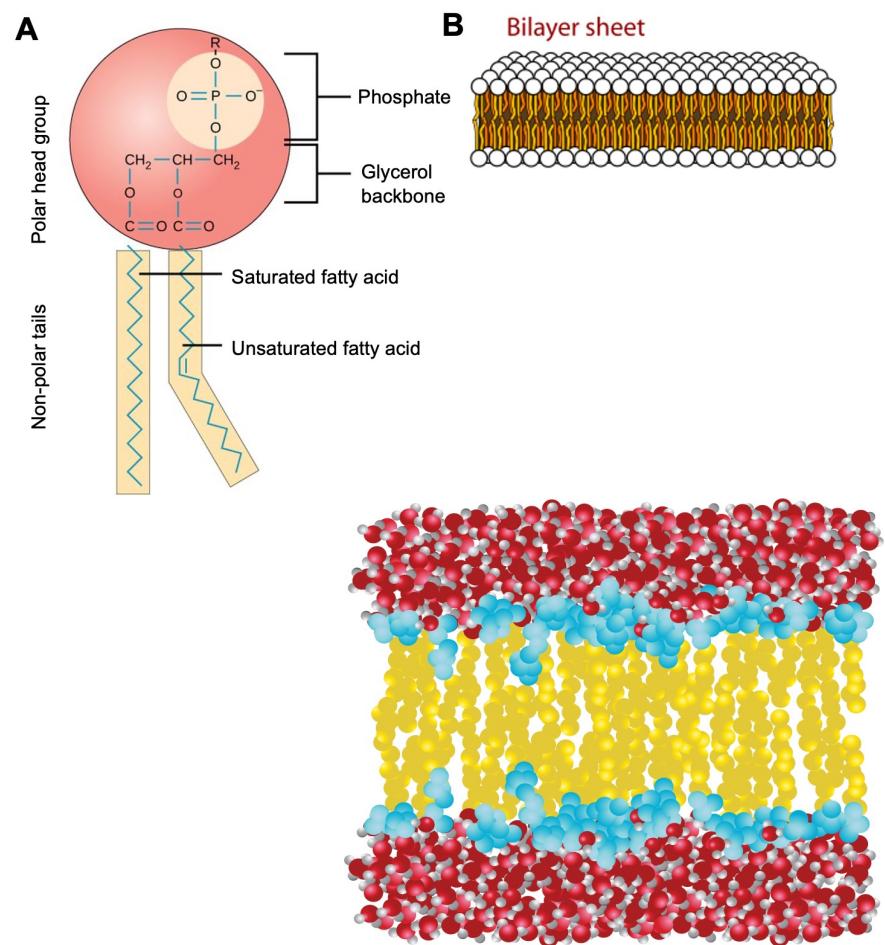
Potentiators enhance membrane permeability



Reid and Speyer, *Journal of Bacteriology*, 1970; Lam et al., *Soft Matter*, 2014.

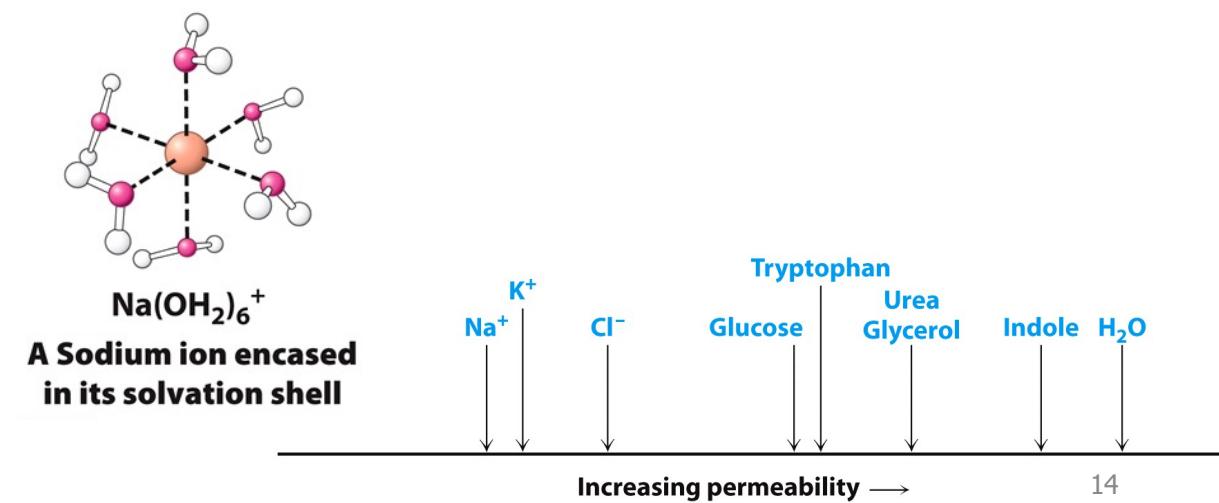
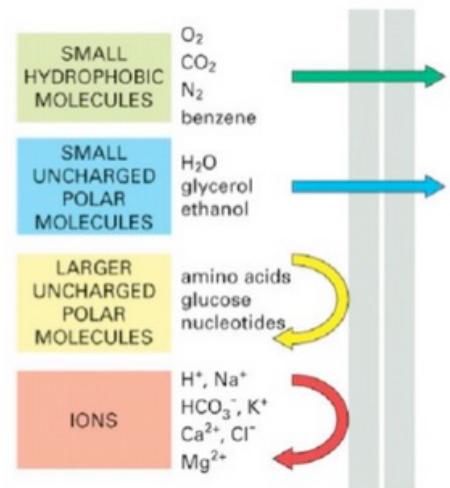
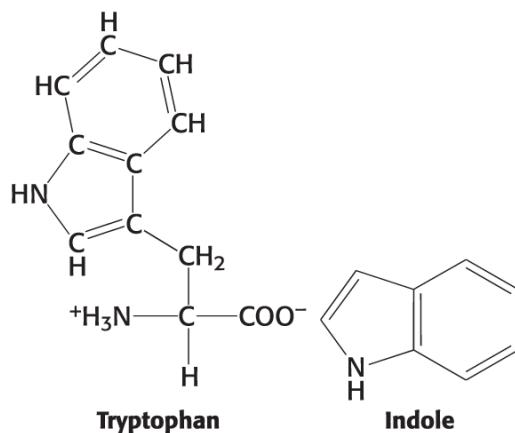
Phospholipids and Glycolipids Form Bimolecular Sheets

- Phospholipids and glycolipids form lipid bilayers in aqueous solutions.
- The formation of membranes is powered by the **hydrophobic effect**.
- Liposomes, or lipid vesicles, are aqueous compartments enclosed by a lipid membrane.
- Liposomes, formed by sonicating a mixture of phospholipids in aqueous solution, may be useful as drug-delivery systems.
- Lipid bilayer membranes have a very low permeability for ions and most polar molecules.



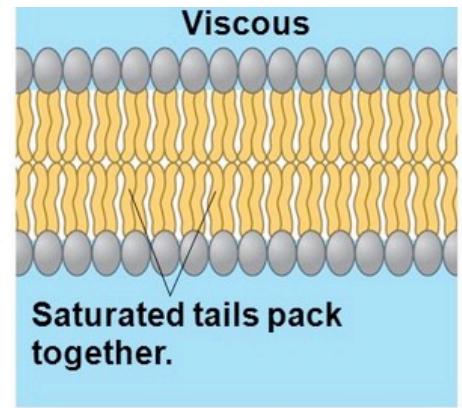
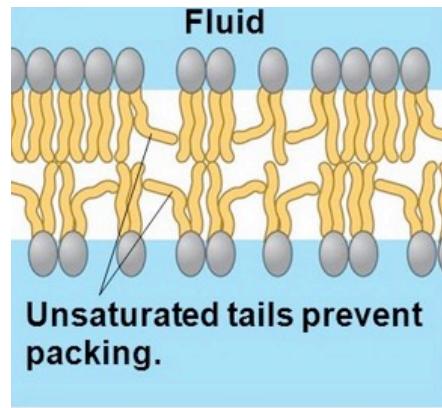
Lipids Bilayers

- The ability of small molecules to cross a membrane is a function of its **hydrophobicity**
- Cell membrane is **semi-permeable** → it's a barrier to most but all molecules
- Indole is more soluble than tryptophan in membranes because it is uncharged.
- Ions cannot cross membranes because of the energy cost of shedding their associated water molecules.



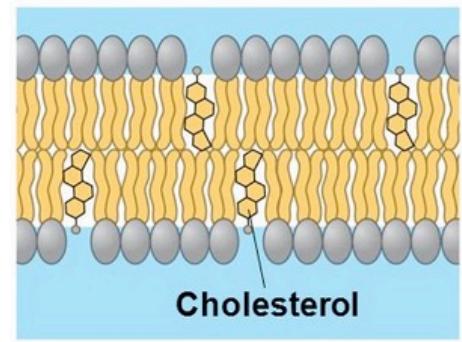
Membrane Fluidity

- Membrane processes depend on the fluidity of the membrane
- The temperature at which a membrane transitions from being highly ordered to very fluid is called the **melting temperature**
- The melting temperature is dependent on the length of the fatty acids in the membrane lipid and the degree of cis unsaturation
- Cholesterol helps to maintain proper membrane fluidity in membranes in animals.



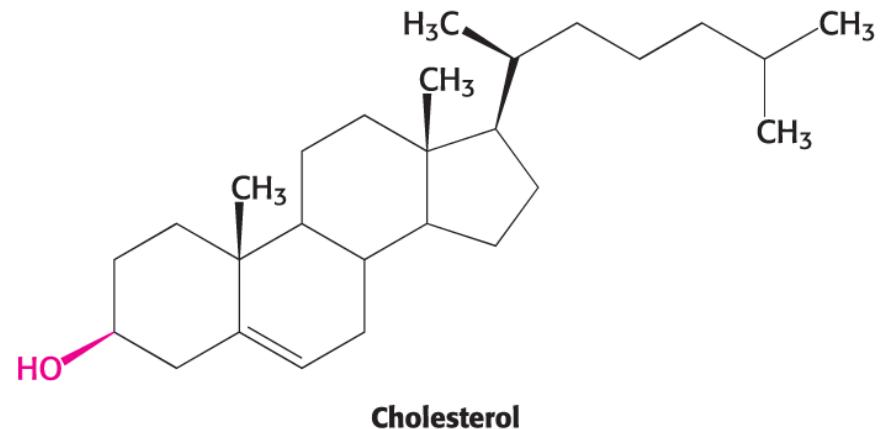
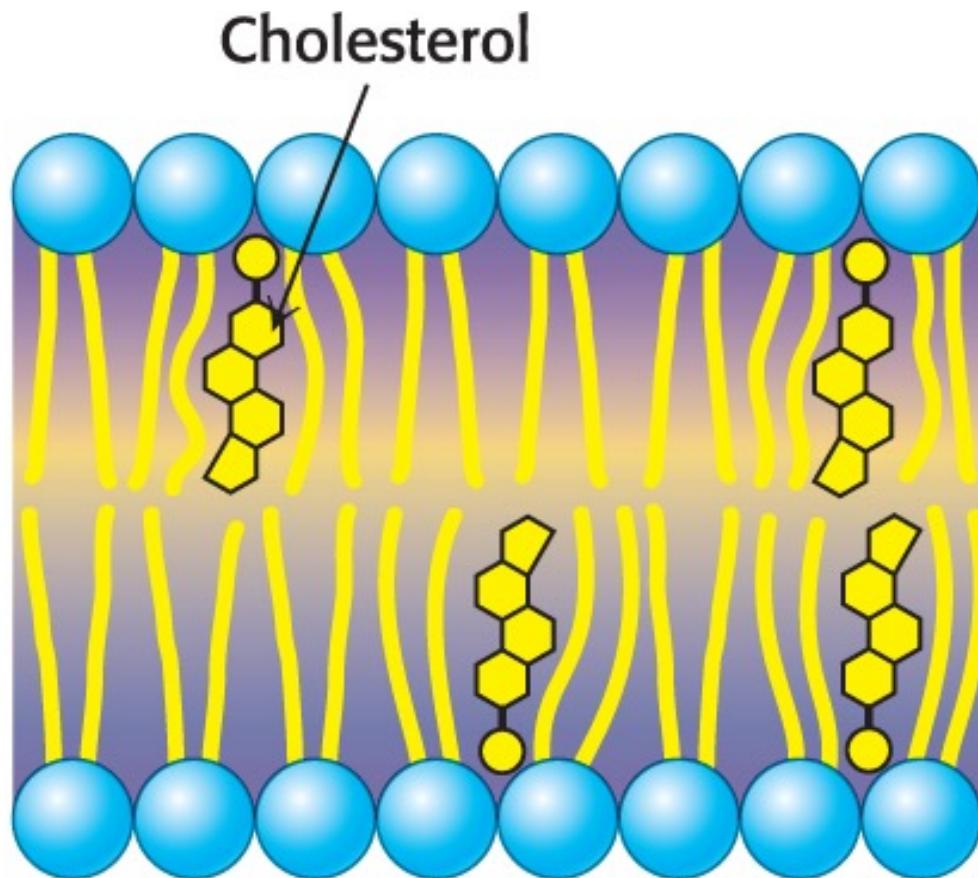
(a) Unsaturated versus saturated hydrocarbon tails

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



lution, Inc.

Cholesterol and Membrane Fluidity



- Cholesterol inserts into bilayers w/ its long axis perpendicular to the plane of the membrane
- Cholesterol disrupts the tight packing of the fatty acid chains, and maintain membrane fluidity

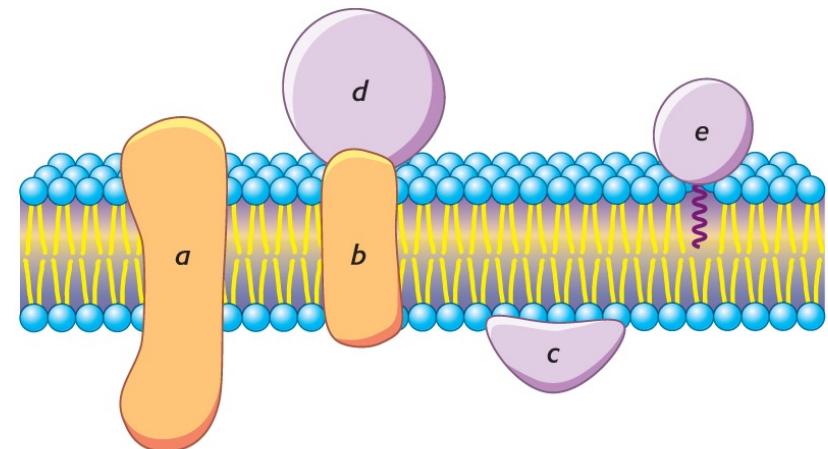
Quick Quiz 1

Which of the following cannot form when phospholipids are combined with water?

- A. bimolecular sheet
- B. liposomes
- C. lipid vesicles
- D. micelles
- E. None of the above

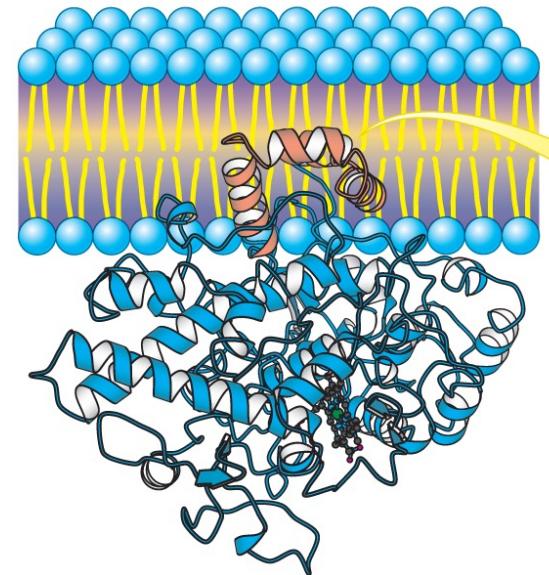
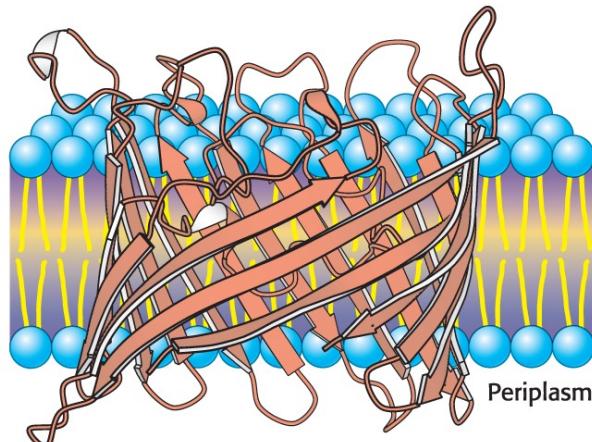
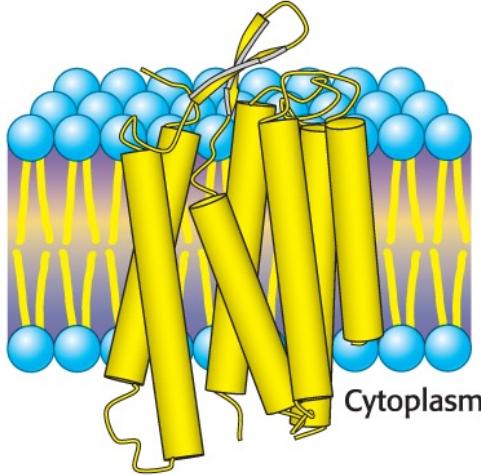
Proteins Associate w/ the Lipid Bilayer in Many Ways

- While membrane lipids establish a permeability barrier, membrane proteins allow transport of molecules and information across the membrane.
- Membranes vary in protein content from as little as 18% to as much as 75%.
- Integral membrane proteins are embedded in the hydrocarbon core of the membrane.
- Peripheral membrane proteins are bound to the polar head groups of membrane lipids or to the exposed surfaces of integral membrane proteins.
- Some proteins are associated with membranes by attachment to a hydrophobic moiety that is inserted into the membrane.



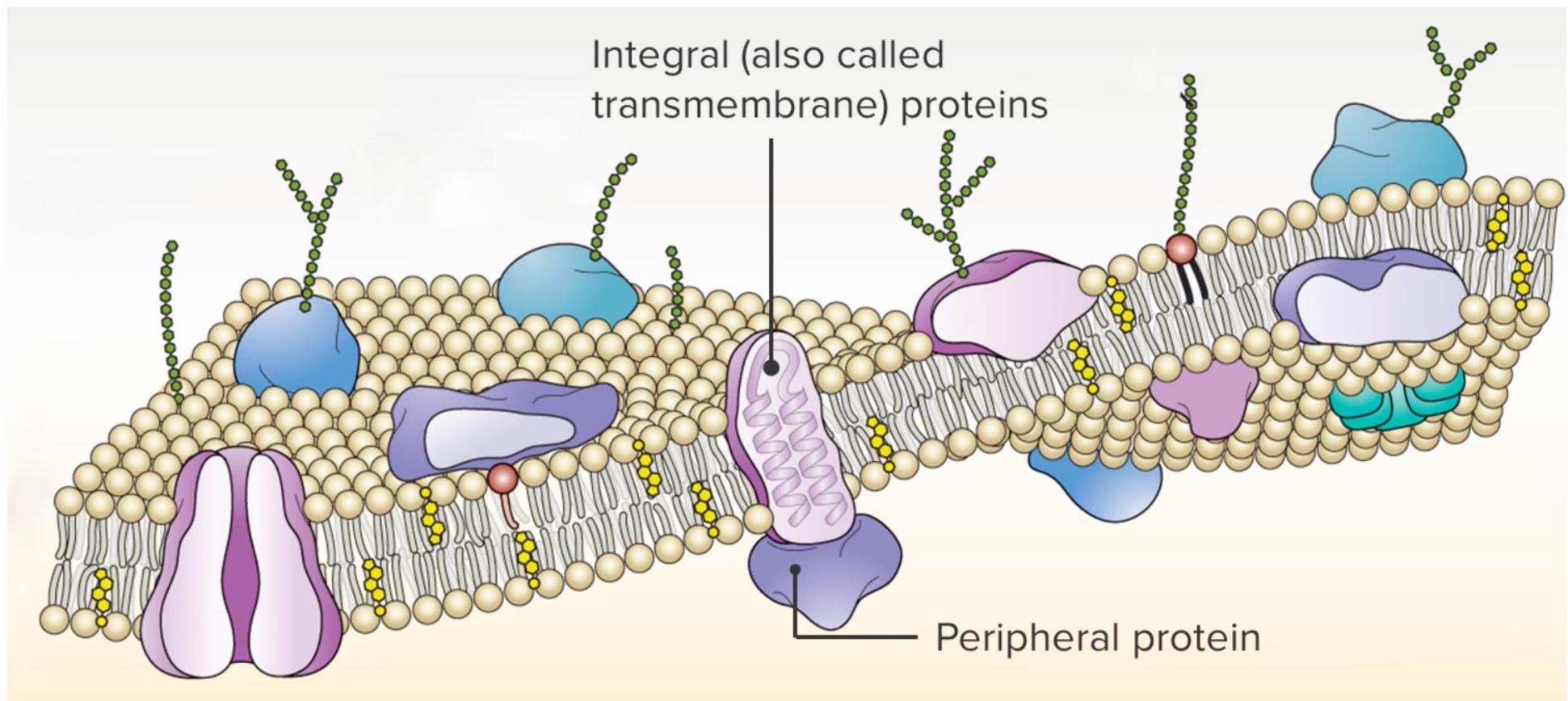
Exercise: Classify the type/nature of membrane proteins in the schematic above.

Proteins Associate w/ the Lipid Bilayer in Many Ways



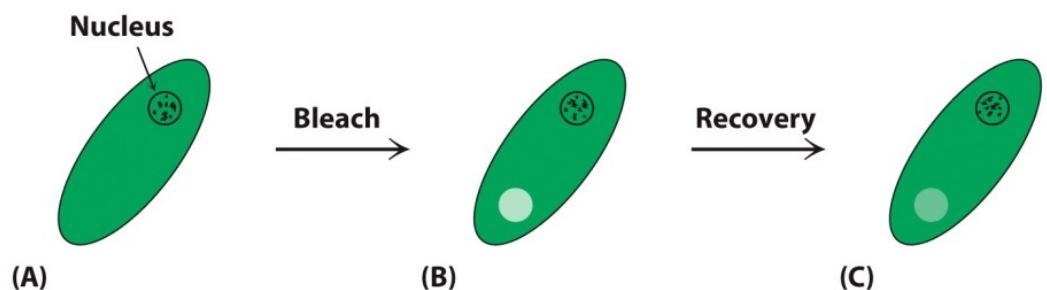
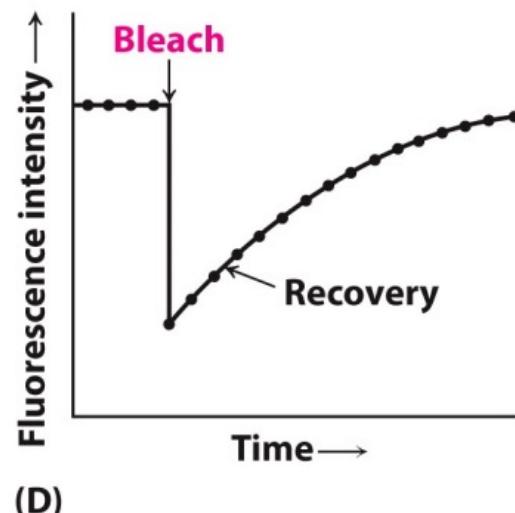
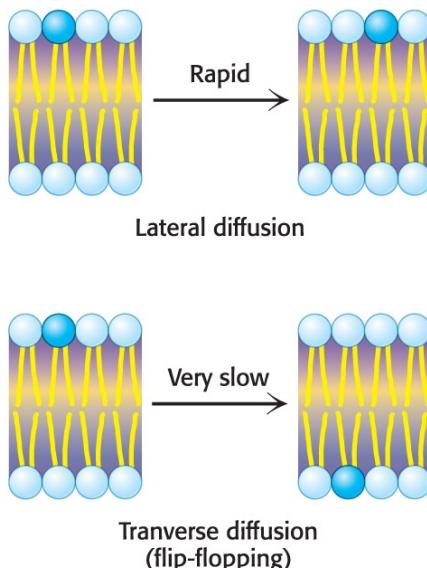
- Membrane-spanning α -helices are a common structural feature of integral membrane proteins.
 - e.g., bacteriorhodopsin
- Other means of embedding integral membrane proteins is by using β strands to form a pore in the membrane or by embedding part of the protein into the membrane.
 - e.g., bacterial porins
- Via partial attachment to the membrane.
 - e.g., prostaglandin H-2 synthase (membrane-bound enzyme)

Two Main Types of Membrane Proteins



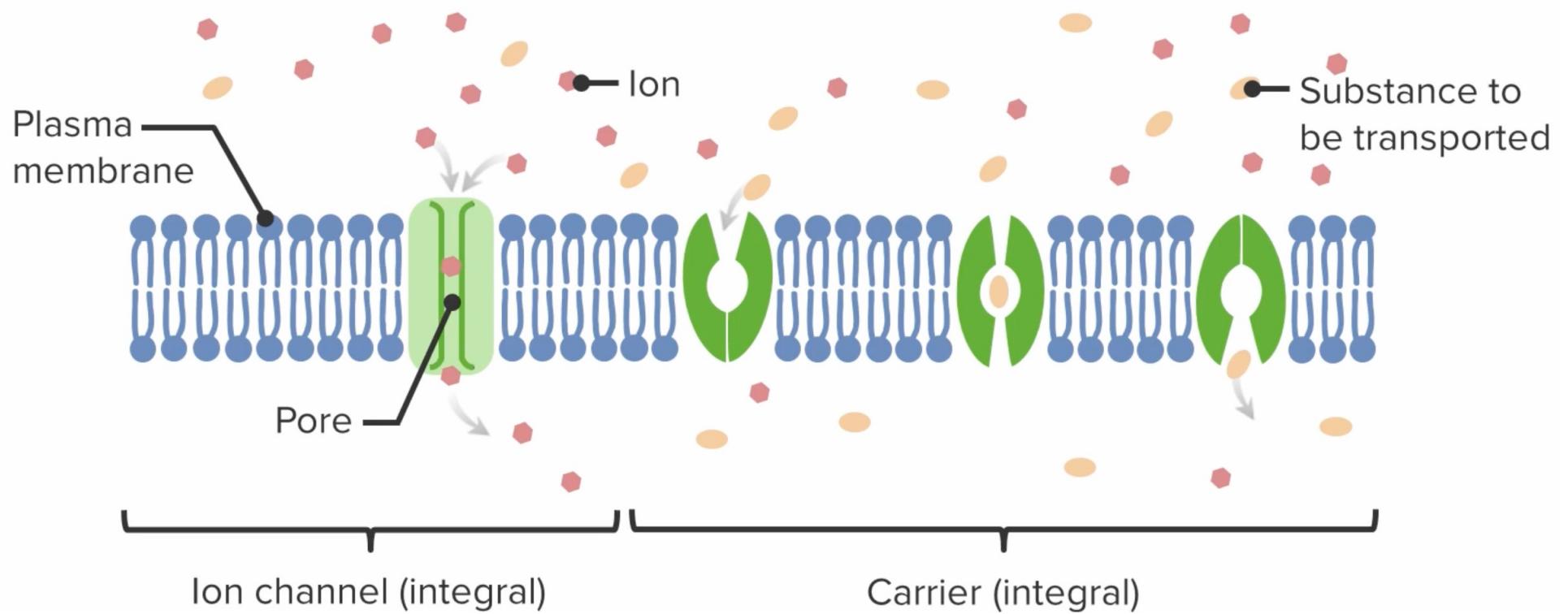
Membranes are not rigid structures

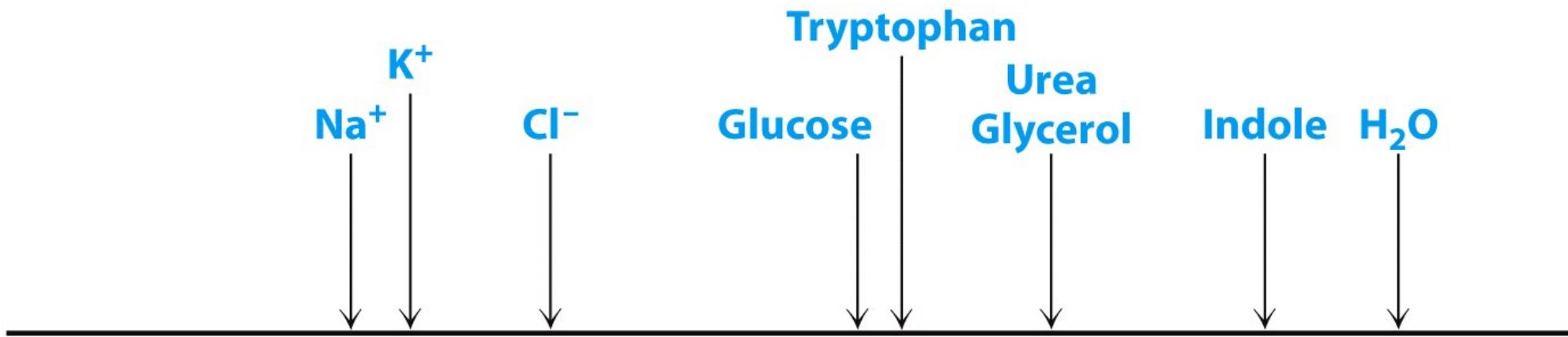
- Lateral diffusion of proteins depends on whether they are attached to other cellular or extracellular components.
- Lipids rapidly diffuse laterally in membranes, although transverse diffusion or flip-flopping is very rare without the assistance of enzymes.



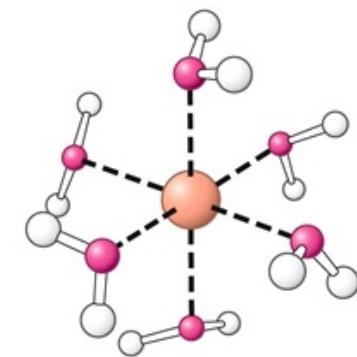
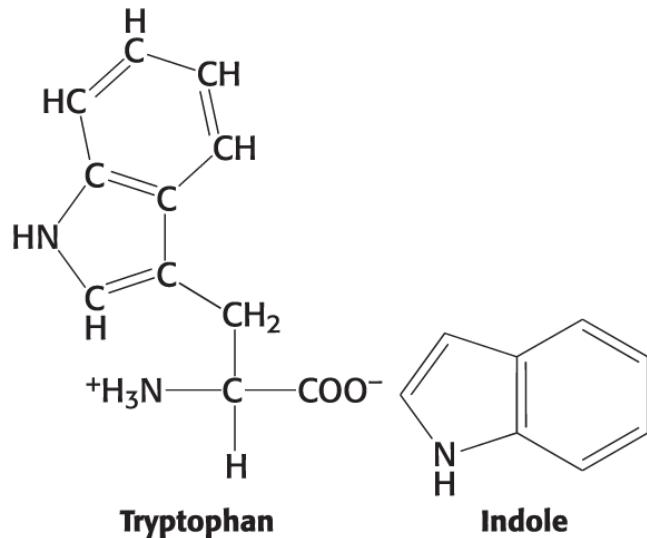
- Fluorescence recovery after photobleaching (FRAP) is a technique that allows the measurement of lateral mobility of membrane components.
- The mobility of the fluorescently labeled component is a function of how rapidly the bleached area recovers fluorescence.
- The prohibition of transverse diffusion accounts for the stability of membrane asymmetry.

Functions of Membrane Proteins



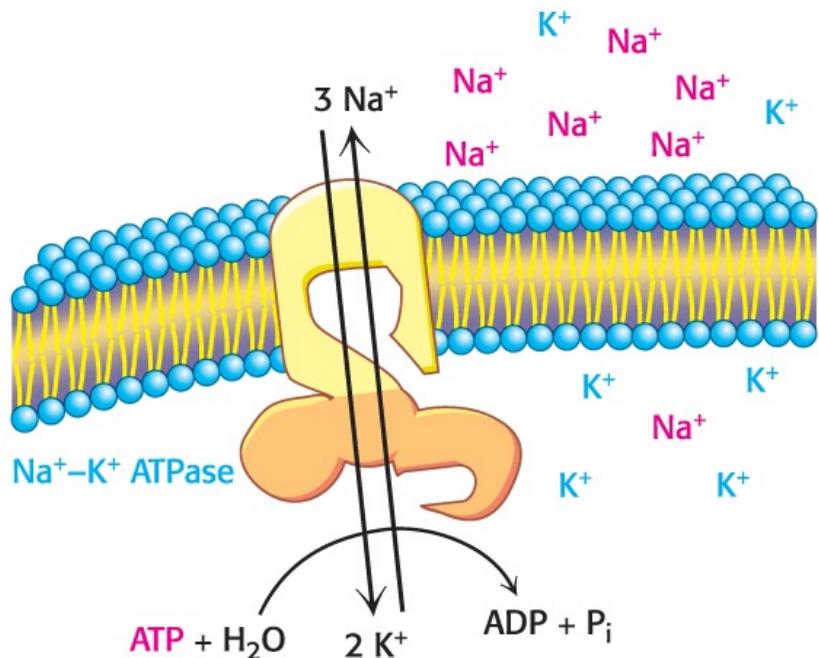


Increasing permeability →



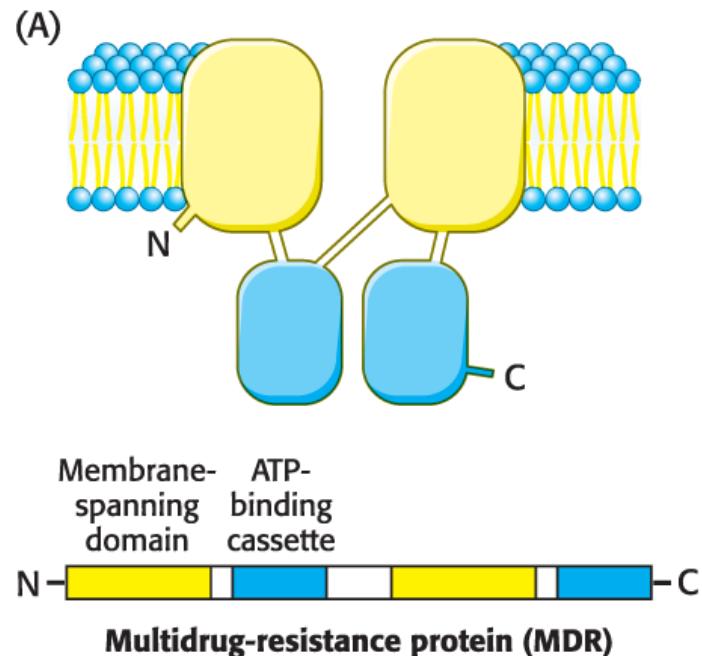
**A Sodium ion encased
in its solvation shell**

The Na⁺-K⁺ ATPase Pump



- an ATP-driven pump
- cells need to maintain an Na⁺-K⁺ gradient → cell volume, muscle excitability, drives secondary active transport (sugars, amino acids)

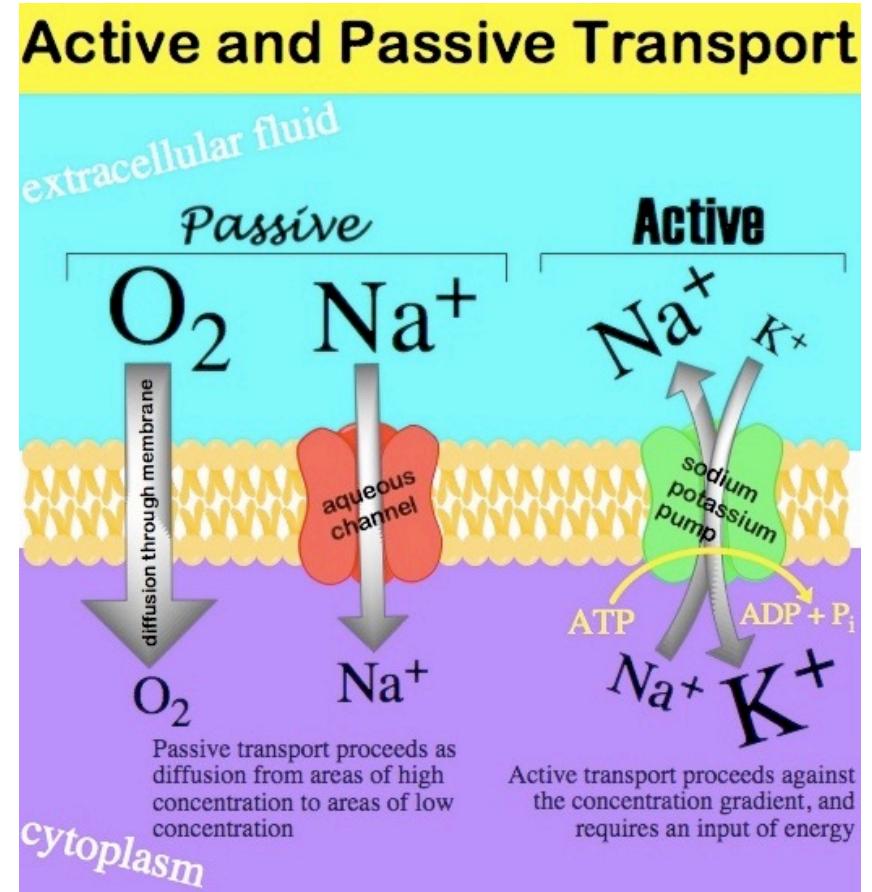
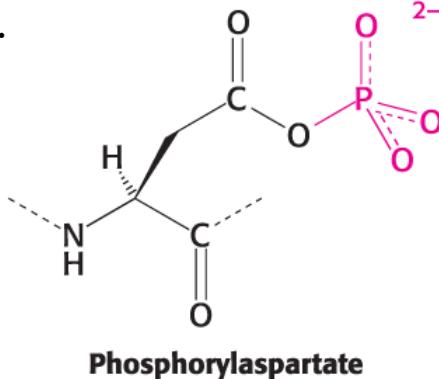
An ABC Transporter



- ATP-binding cassettes (ABCs)
- Multidrug-resistance (MDR) proteins pump the drug out of the cell before it can exert any effects

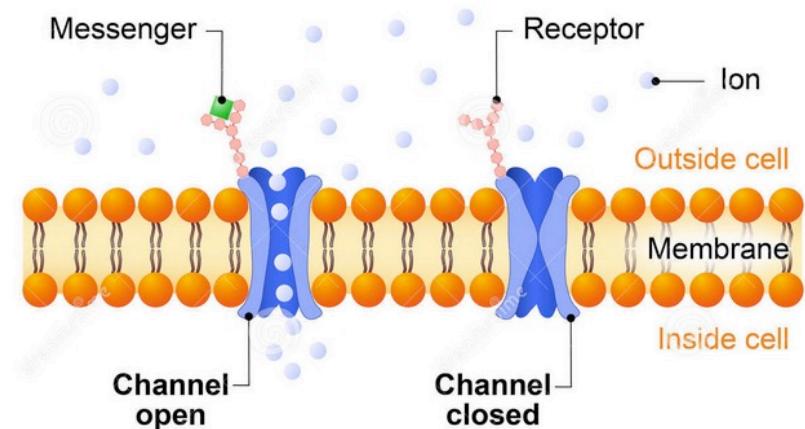
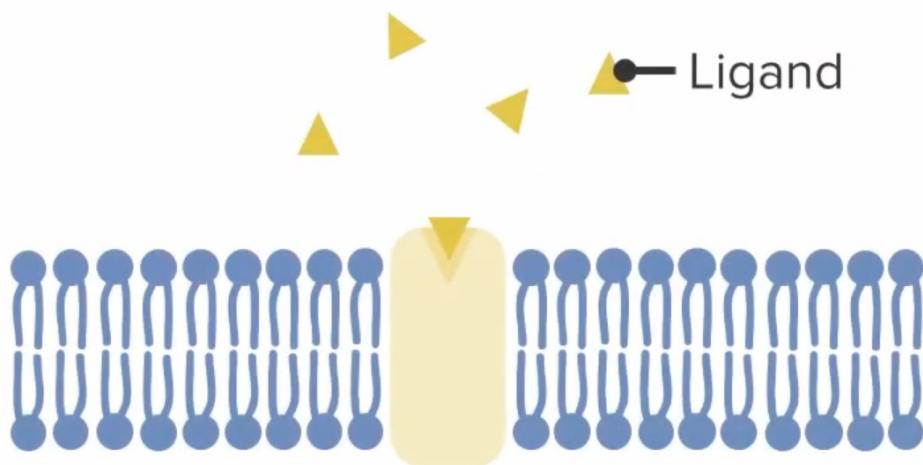
Membrane Proteins As Transporters

- The Na^+-K^+ ATPase or Na^+-K^+ pump uses the energy of ATP hydrolysis to simultaneously pump three Na^+ ions out of the cell and two K^+ ions into the cell **against their concentration gradients**.
- Because the reaction includes an intermediate in which the enzyme is phosphorylated, such pumps are called P-type ATPases.



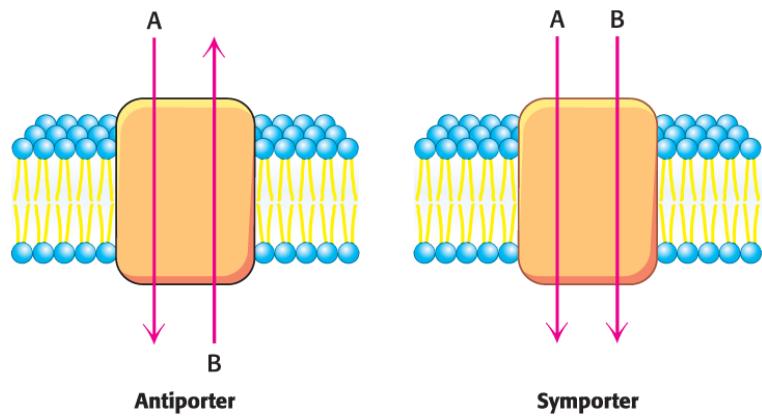
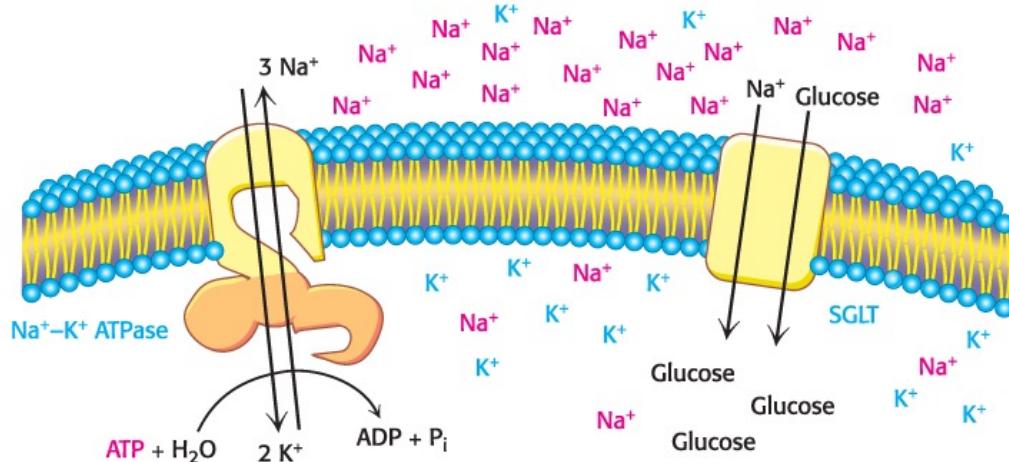
Functions of Membrane Proteins

Ligand-gated ion channel



- Ligand-gated ion channels (LGICs), commonly referred to as ionotropic receptors
- group of transmembrane ion-channel proteins which open to allow ions such as Na^+ , K^+ , Ca^{2+} , and/or Cl^- to pass through the membrane in response to the binding of a chemical messenger (i.e. a ligand), such as a neurotransmitter.

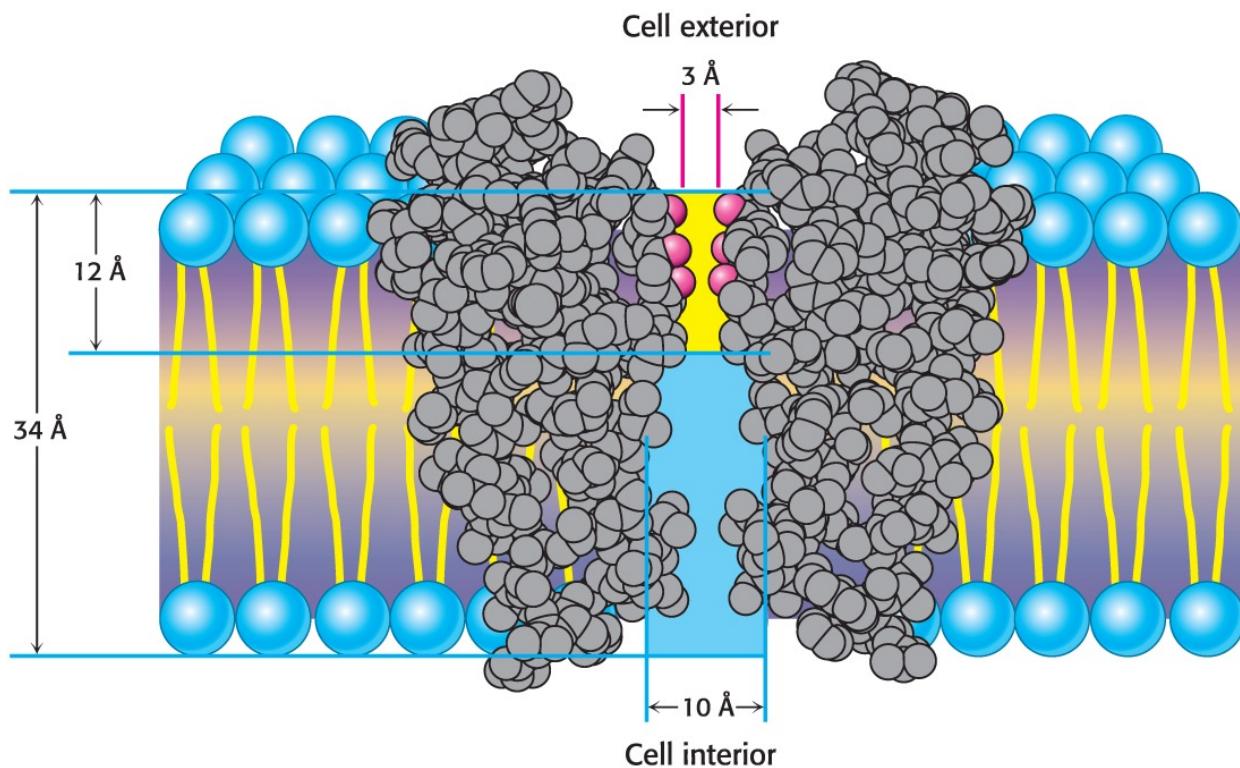
Membrane Proteins As Transporters



- In **secondary active transport**, concentration gradients generated by primary active transport are harvested to move substances across membranes.

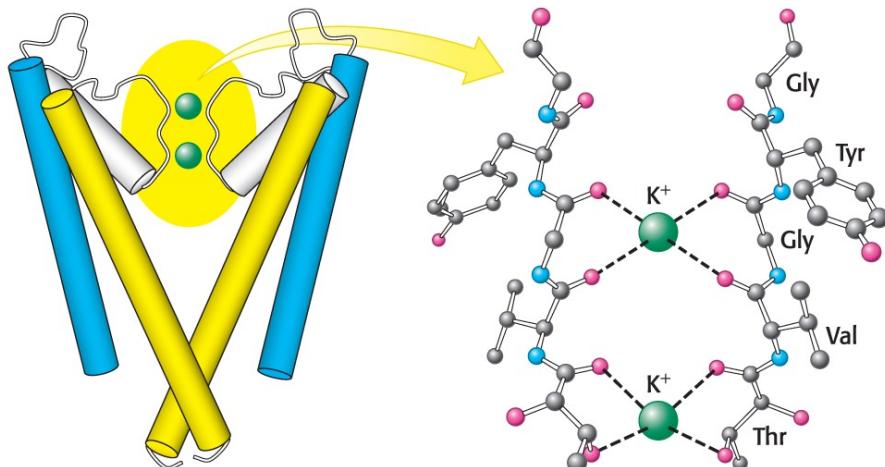
- **Antiporters** → transport two substrates in opposite directions
- **Symporters** → transport two substrates in the same direction (e.g., Na⁺-glucose linked transporter, SGLT)

Ion Channels Response Fast and are Specific

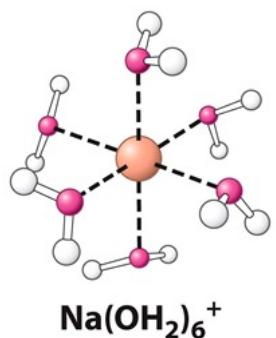


- **The K⁺ channel**
- 100-fold more permeable to K⁺ than Na⁺
- Ions with larger radius cannot pass through
- Na⁺ has a radius smaller than K⁺, so what drives the selectivity?

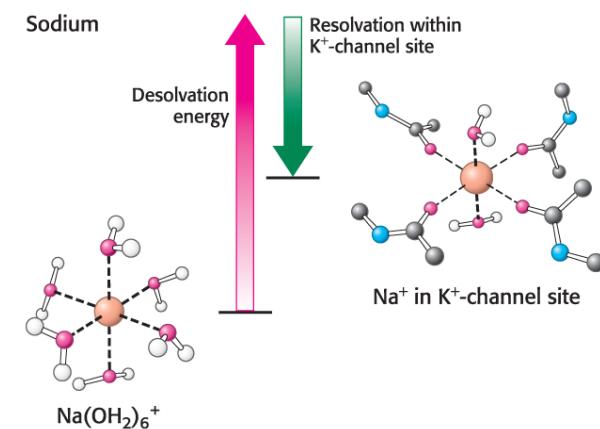
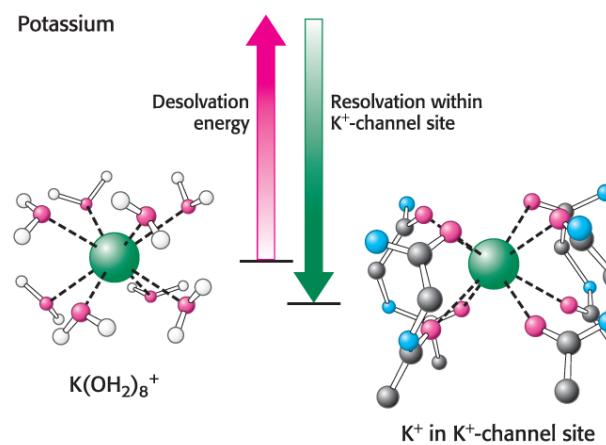
Ion Channels Response Fast and are Specific



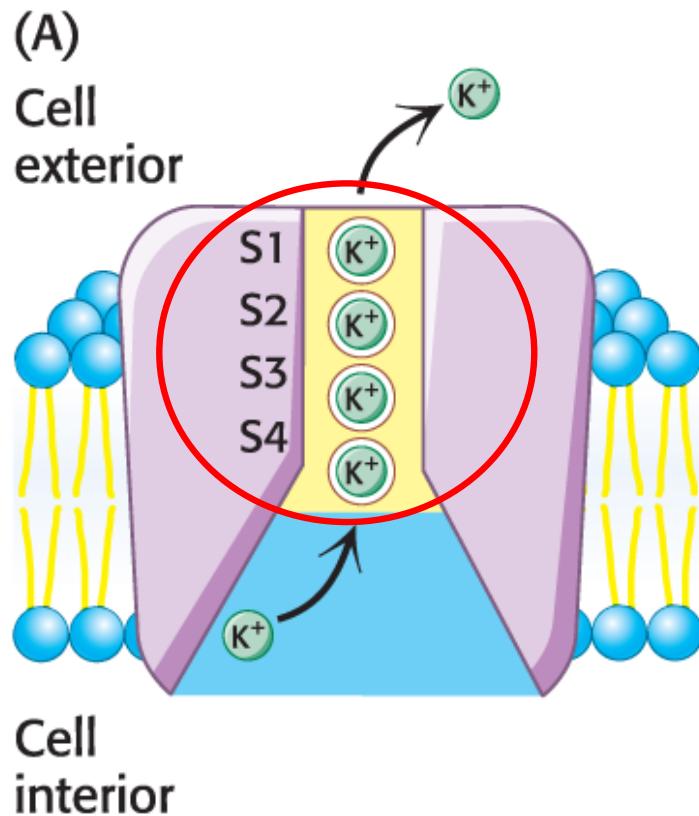
- Has a selectivity filter where potassium ions can interact with the carbonyl groups of the selectivity filter
- Na⁺ ions are too small to form optimal interactions



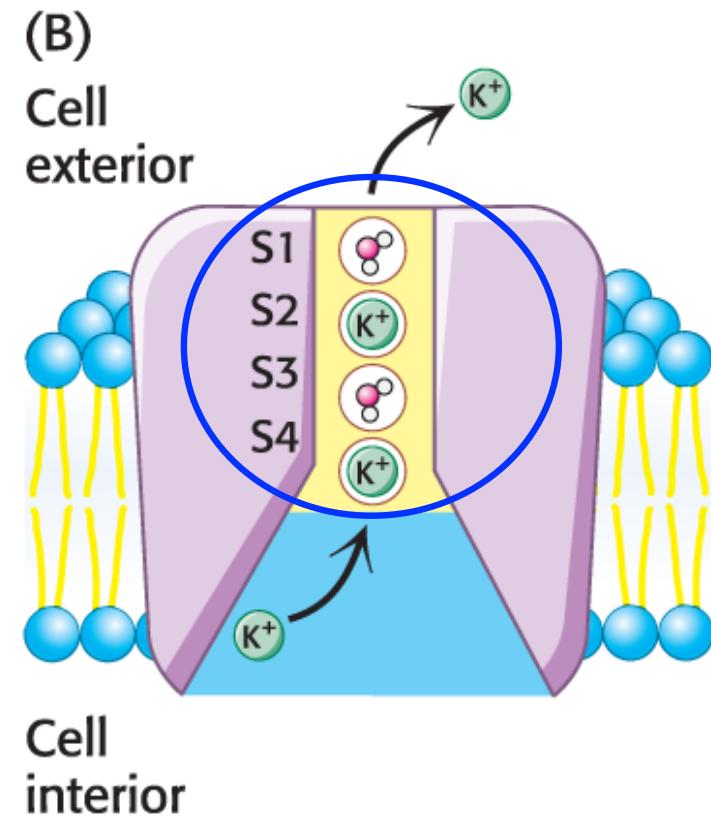
A Sodium ion encased in its solvation shell



Ion Channels Response Fast and are Specific

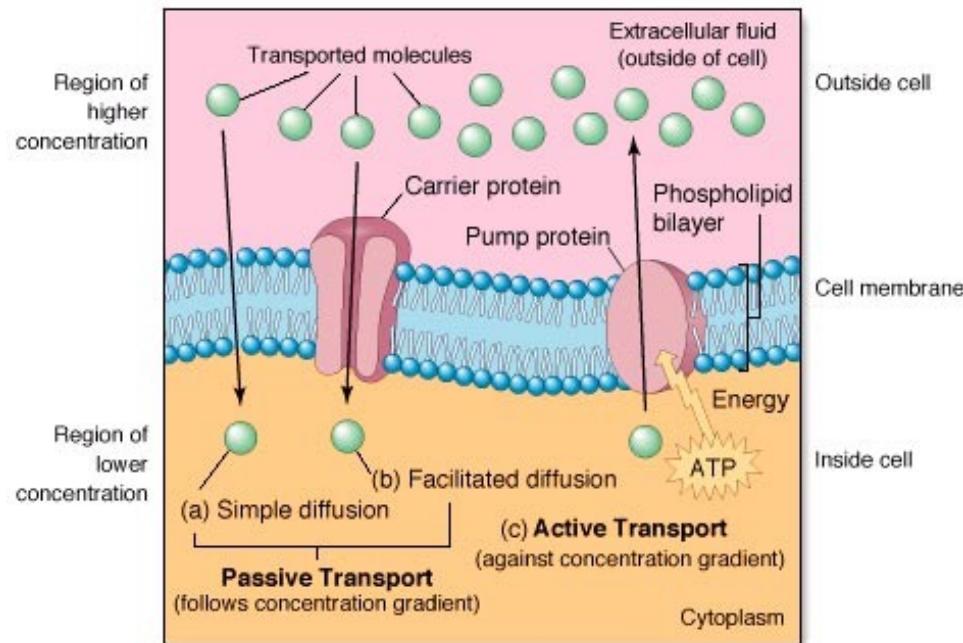


Hard-Knock Model



Knock-On Model

Membrane Proteins As Transporters



Transporters (pumps or channels) facilitate movement of molecules across a membrane.

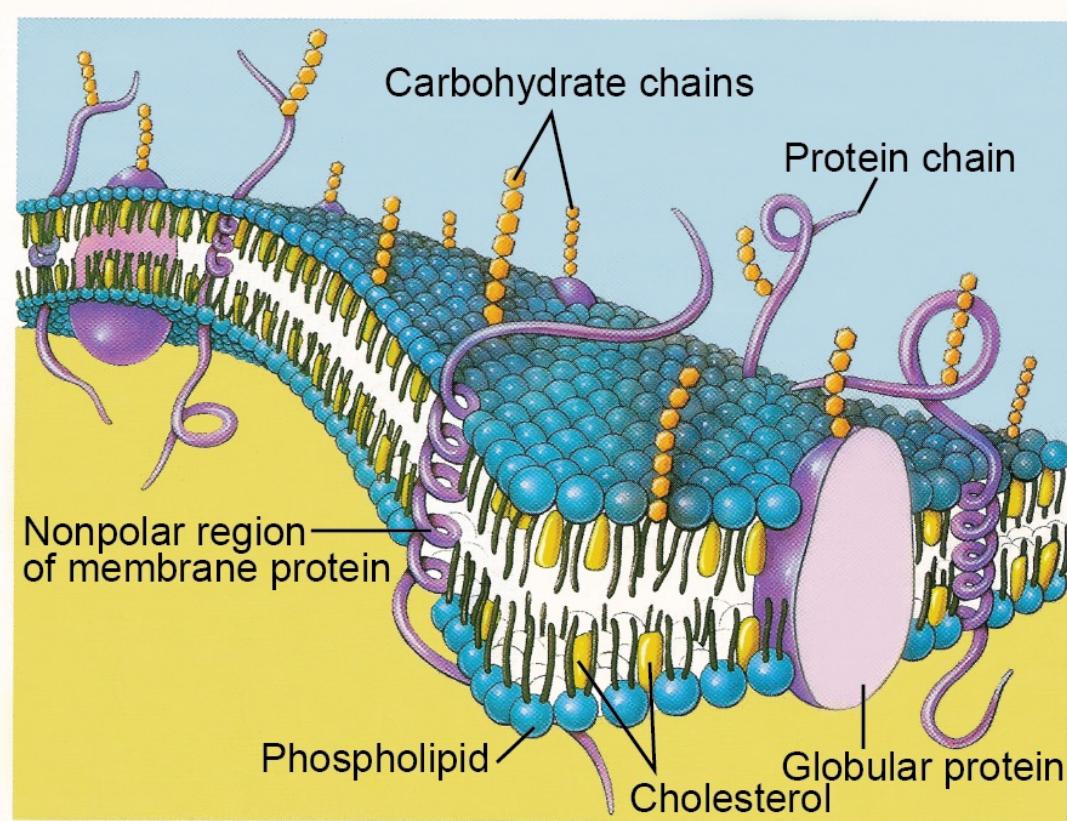
- A small molecule will spontaneously cross a membrane if two conditions are met:
 - 1. concentration of the molecule is higher on one side of the membrane than the other (**simple diffusion**).
 - 2. molecule is **lipophilic** or soluble in nonpolar solutions.
- Molecules meeting these criteria can simply diffuse across the cell membrane.
- **Polar molecules** can diffuse across a membrane down their concentration gradient only with the assistance of a particular protein called a channel. Such movement is called **facilitated diffusion** or **passive transport**.
- Movement of molecules against a concentration gradient requires a source of energy and is called **active transport**.

Quick Quiz 3

Which of the following is always true of ligand-gated ion channels?

- A. They are always in an open conformation.
- B. They undergo a conformational change during their action.
- C. They respond to ion concentration changes to allow ligands to cross the membrane.
- D. They are inhibited by the pufferfish chemical tetrodotoxin.
- E. When an appropriate ligand is bound, the channel changes to the closed conformation.

The Fluid Mosaic Model



- **Fluid Mosaic Model:**
Membranes are 2D solutions of oriented lipids and globular proteins.
- Lipid bilayer has dual roles: acts as a solvent for integral membrane proteins and as a permeability barrier.
- Membrane proteins are free to diffuse unless anchored by special interactions.

Quick Quiz 2

Which of the following is **NOT** involved in lipid bilayer formation?

- A. A decrease in ΔG
- B. The hydrophobic effect
- C. A decrease in entropy
- D. Van der Waals interactions
- E. Electrostatic interactions

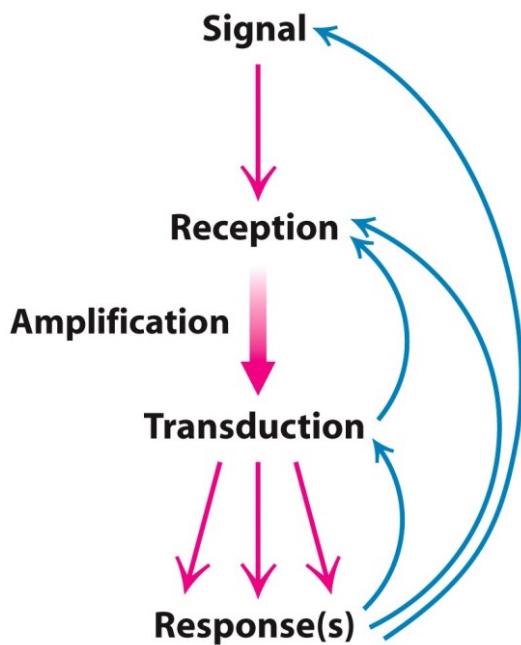
Signal Transduction

environmental cue → biochemical response

**light/smell/blood-glucose concentration →
changes in ion-channel activity/enzyme activity/gene expression**

Signal Transduction Depends on Molecular Circuits

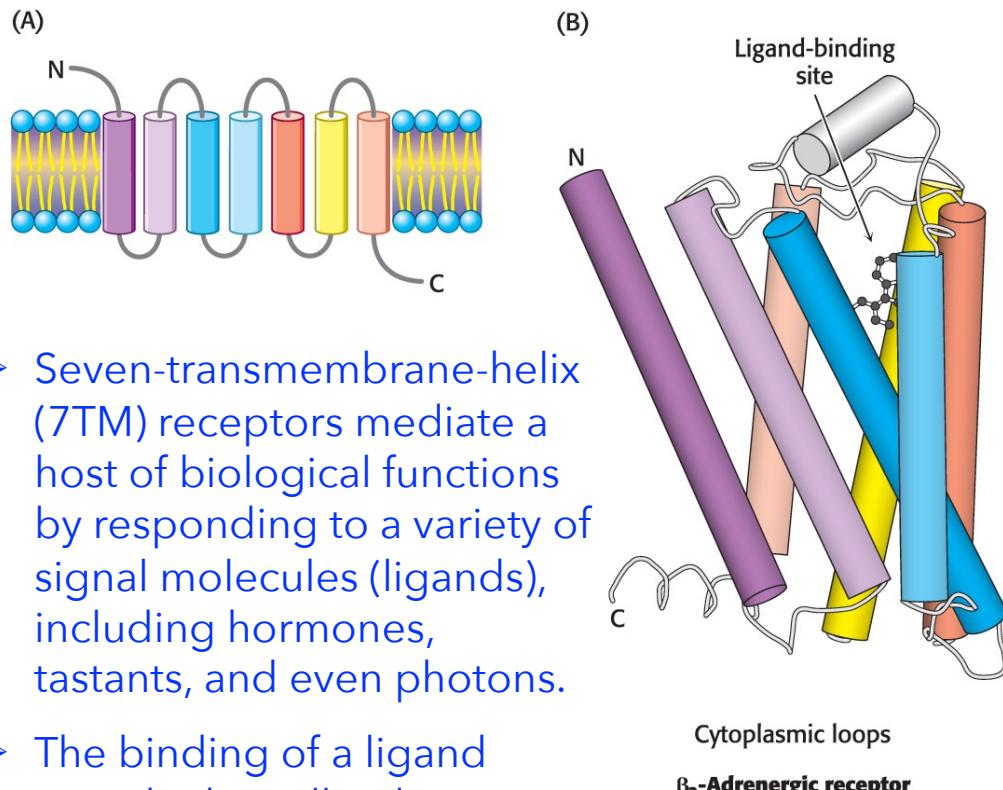
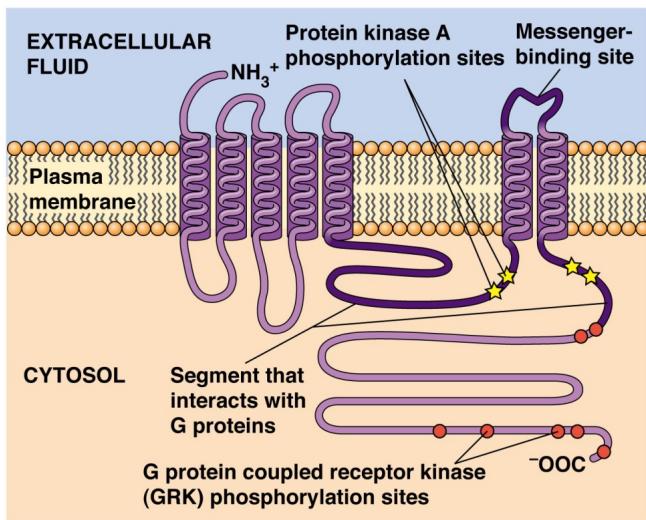
- Signal transduction mechanisms by which extracellular signals are received, amplified and converted to a cellular response.



- Signal transduction cascades have many components in common:
 1. **Release of a primary message** as a response to a physiological circumstance.
 2. **Reception of the primary message** by a receptor, usually an integral membrane protein.
 3. **Relay of the detection of the primary message** to the cell interior by the generation of an intracellular second message.
 4. **Activation of effector molecules** by the second messenger that result in a physiological response.
 5. **Termination of the signal** cascade.

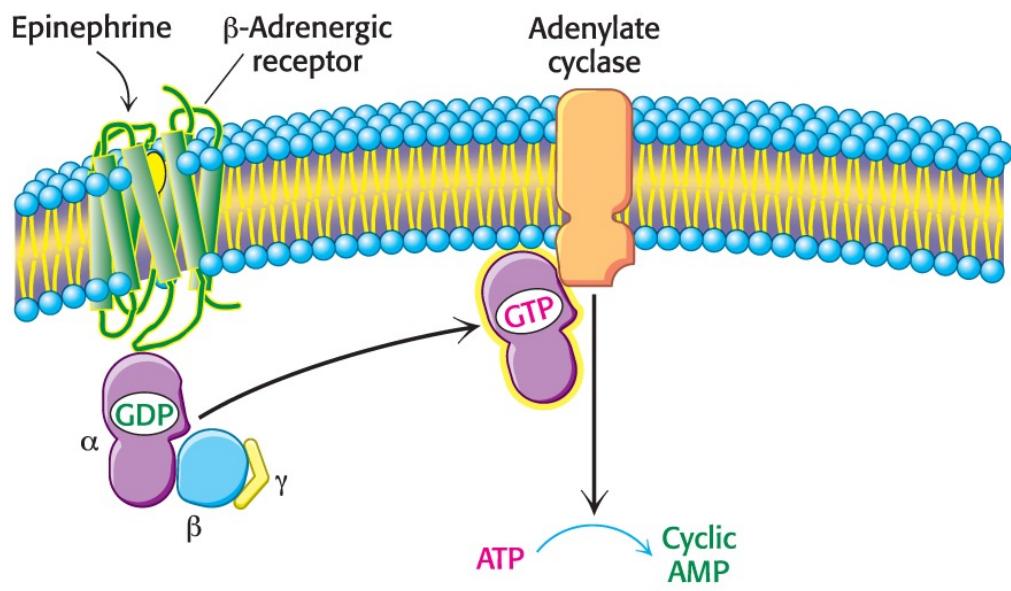
Receptor Proteins Transmit Information into the Cell

- There are three major classes of membrane receptors:
 1. Seven transmembrane receptors associated with heterotrimeric G-proteins.
 2. Dimeric membrane receptors that recruit protein kinases.
 3. Dimeric protein receptors that are protein kinases.



- Seven-transmembrane-helix (7TM) receptors mediate a host of biological functions by responding to a variety of signal molecules (ligands), including hormones, tastants, and even photons.
- The binding of a ligand outside the cell induces a structural change in the receptor that can be detected inside the cell.

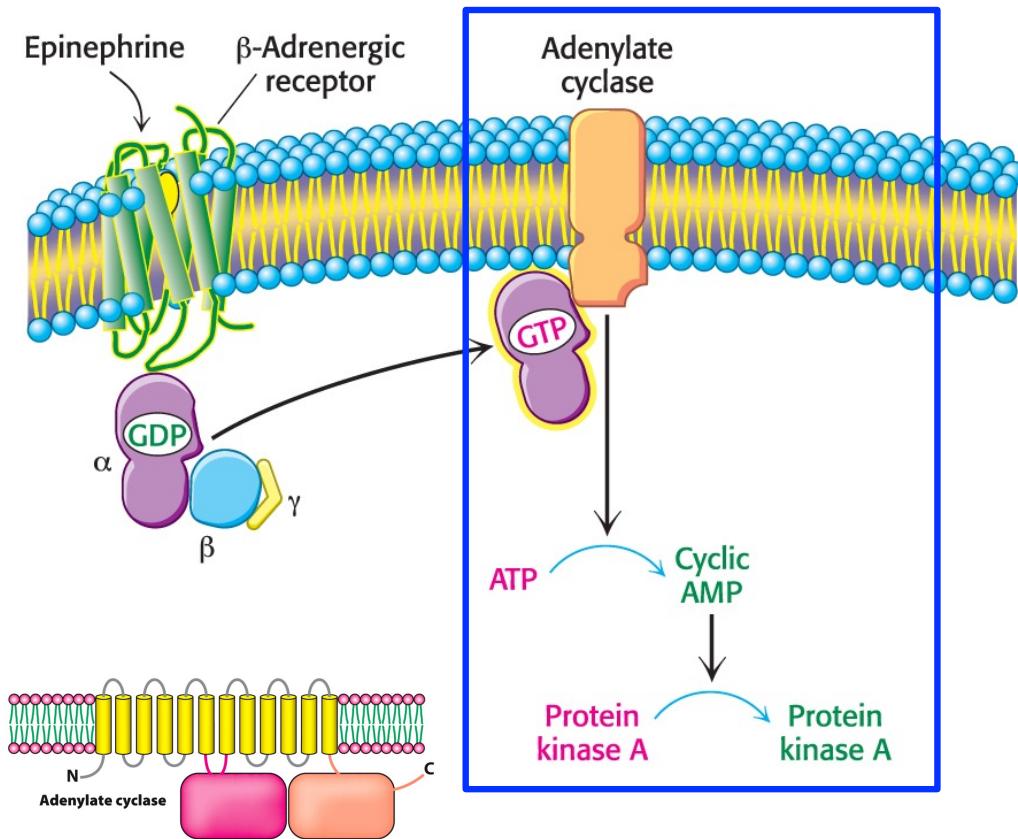
Ligand binding leads to activation of G proteins



- Ligand binding to 7 TM receptors leads to the activation of **G proteins**.
- Because **7TM receptors** are always associated with G proteins, they are often called **G protein coupled receptors** (GPCR).

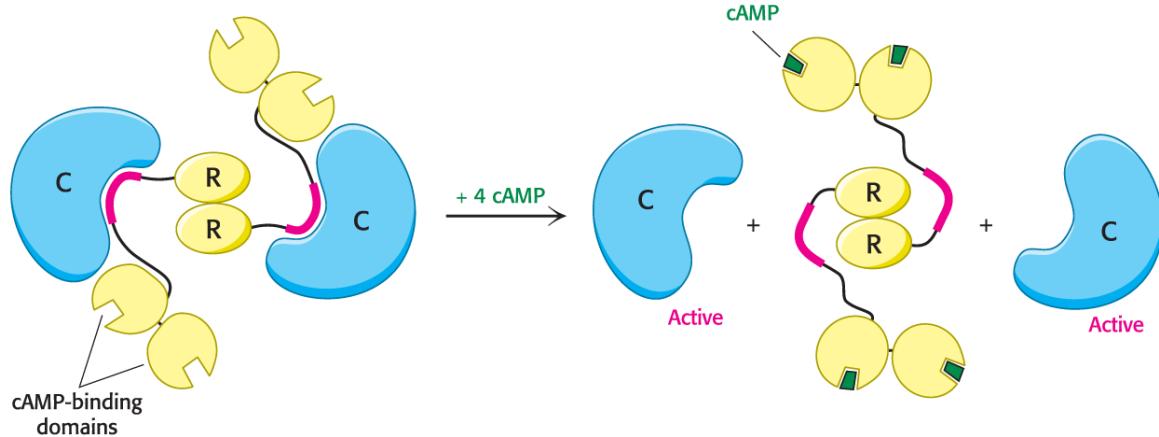
- The **β-adrenergic receptor** is activated by binding to epinephrine, also called adrenaline.
- Upon binding of epinephrine, the cytoplasmic aspect to the β-adrenergic receptor activates a heterotrimeric G-protein.
- The inactivated G-protein is a heterotrimer consisting of an α subunit, bound to GDP, and β and γ subunits.
- Upon activation by the receptor, the α subunit dissociates from the βγ dimer and exchanges GDP for GTP.
- The GTP bound α-subunit transmits the signal to other cellular components.
- Note on amplified response.

Activated G proteins transmit signals by binding to other proteins



- In the case of the β-adrenergic receptor signal transduction pathway, the activated G protein, termed Gas, stimulates the integral membrane enzyme, **adenylate cyclase**.
- Activation of the cyclase leads to the synthesis of the second messenger, cyclic adenosine monophosphate (cAMP).
- Cyclic AMP stimulates the phosphorylation of many target proteins by activating protein kinase A.

cAMP → activates Protein Kinase A → phosphorylation

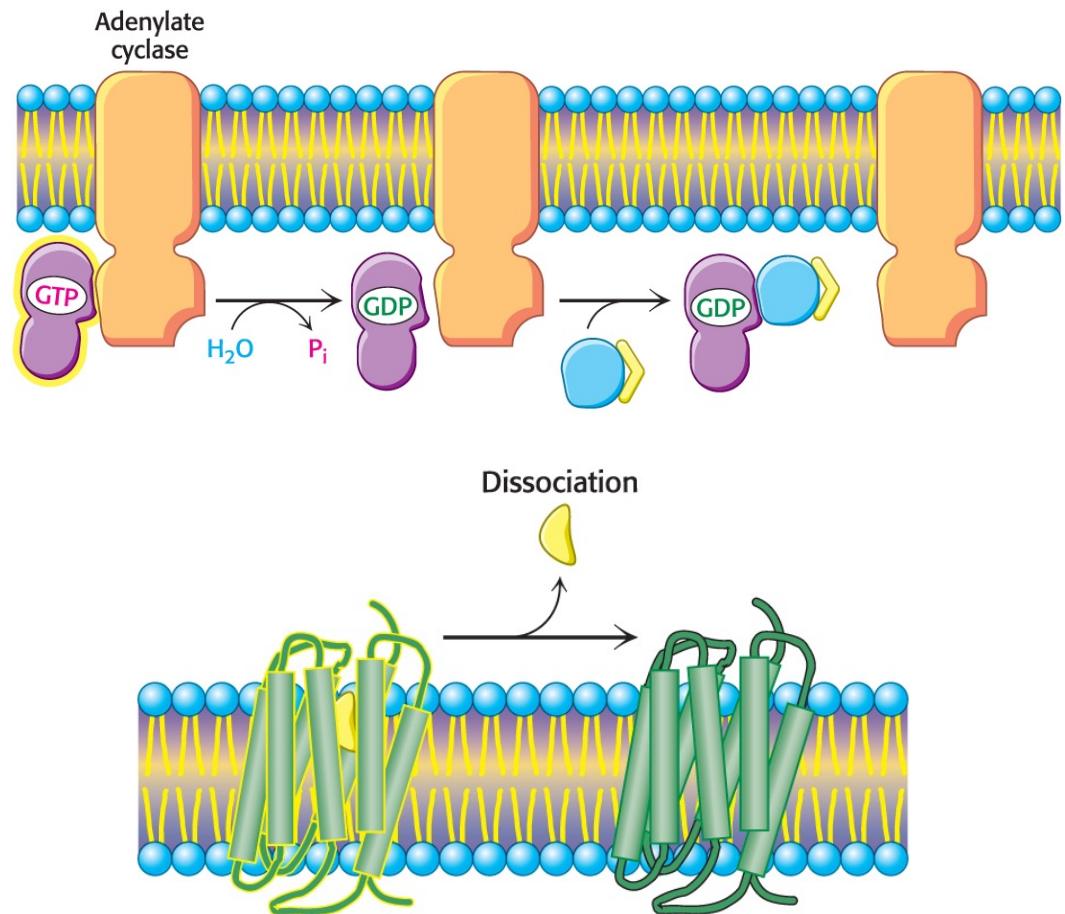


- Cyclic AMP activates **protein kinase A**. Protein kinase A consists of two pairs of subunits, 2 catalytic (C) subunits and 2 regulatory (R) subunits.
- Binding of cAMP by the regulatory subunits dissociates these subunits from the complex, resulting in activation of the 2 C subunits.

- The activated C subunits continue the epinephrine signal transduction pathway by phosphorylating protein targets that alter physiological functions of the cell.
- Increased [cAMP] → affects so many cellular processes
 - Secretion of acid in stomach lining
 - Aggregation of blood platelets
 - Opening of chloride ions in the pancreas.
- Cascade terminated by an enzyme that converts cAMP to AMP → does not activate PKA

Signal Termination

- G proteins spontaneously reset themselves through GTP hydrolysis. The epinephrine-imitated pathway is shut down in a variety of ways:
 1. G_a has inherent GTPase activity that cleaves the bound GTP to GDP. The G_a bound to GDP spontaneously reassociates with the $\beta\gamma$ subunits, terminating the activity of the G protein ([note on hydrolysis rate](#)).
 2. Cyclic AMP phosphodiesterase converts cAMP to AMP, which does not activate protein kinase A.
 3. Epinephrine- β -adrenergic receptor interaction is reversible. Once the concentration of epinephrine falls, the receptor will no longer be active.



Clinical Insight

- Cholera and whooping cough are due to altered G-protein activity.
- Cholera is an acute bacterial disease that produces life-threatening diarrhea.
- *Choleragen*, the bacterial toxin, modifies a G_{as} protein such that it is trapped in the active GTP-bound form. The net result is a loss of NaCl and water into the intestine.
- *Pertussis toxin*, the cause of whooping cough, also modifies a G protein. In the case of pertussis toxin, the G protein, G_{ai} , is trapped in the inactive form. G_{ai} , which normally inhibits a host of biochemical targets, is thus rendered inactive.

How cholera affects the body

Cholera is an acute intestinal infection that causes severe diarrhea, dehydration and, if not treated promptly, death.

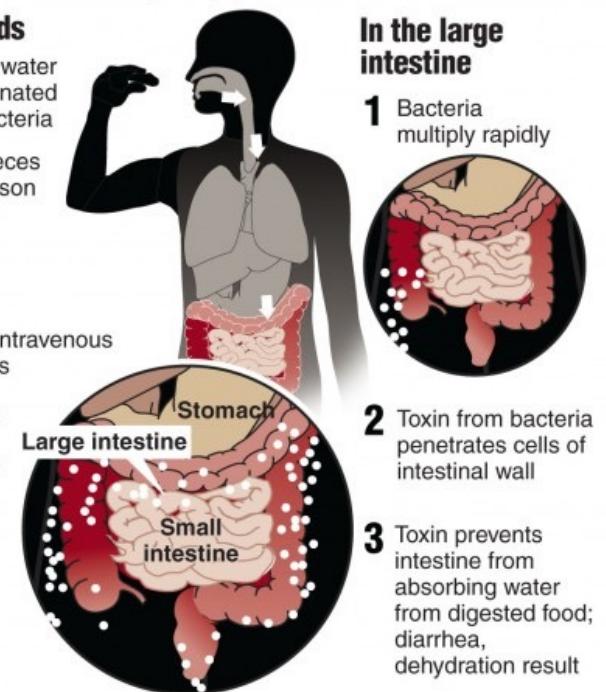
How it spreads

- People ingest water or food contaminated with cholera bacteria
- In epidemic, feces of diseased person is source of contamination

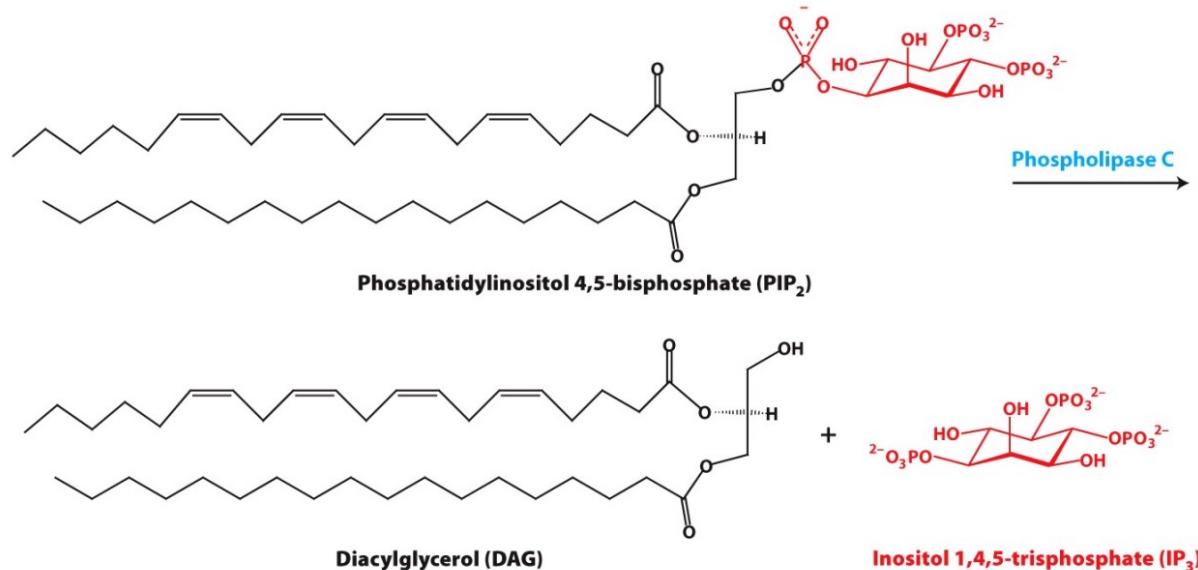
Treatment

- Salt solution, intravenous fluids, antibiotics
- In unprepared communities, death rates can be as high as 50 percent

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Source: World Health Organization

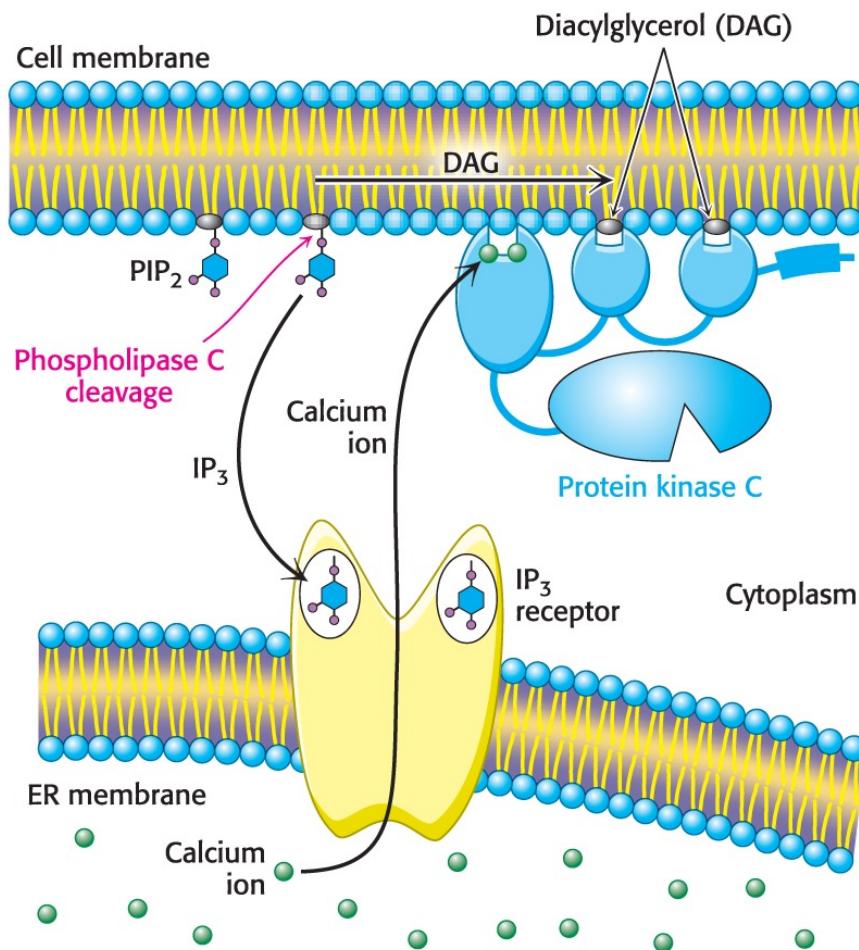


Phospholipase C generates two second messengers



- Some G-protein-coupled receptors activate the **phosphoinositide pathway**. This pathway involves the G_{aq} protein as a component of the trimeric G protein complex.
- G_{aq} activates phospholipase C, which cleaves the membrane lipid phosphatidylinositol bisphosphate into two second messengers: **inositol 1, 4, 5-trisphosphate (IP₃)** and **diacylglycerol (DAG)**.
- hydrolysis of phosphatidylinositol bisphosphate by Phospholipase C → generates two second messengers

The Phosphoinositide Cascade



- IP₃ binds to the IP₃-gated channel (IP₃ receptor) in the endoplasmic reticulum, allowing an influx of Ca^{2+} ions into the cytoplasm. **The Ca^{2+} ions regulate a host of cellular functions.**
 - Smooth-muscle contraction
 - Vesicle release
 - Glycogen breakdown
- DAG, in conjunction with Ca^{2+} , activates protein kinase C → **phosphorylates serine/threonine residues in many target proteins**

Quick Quiz 4

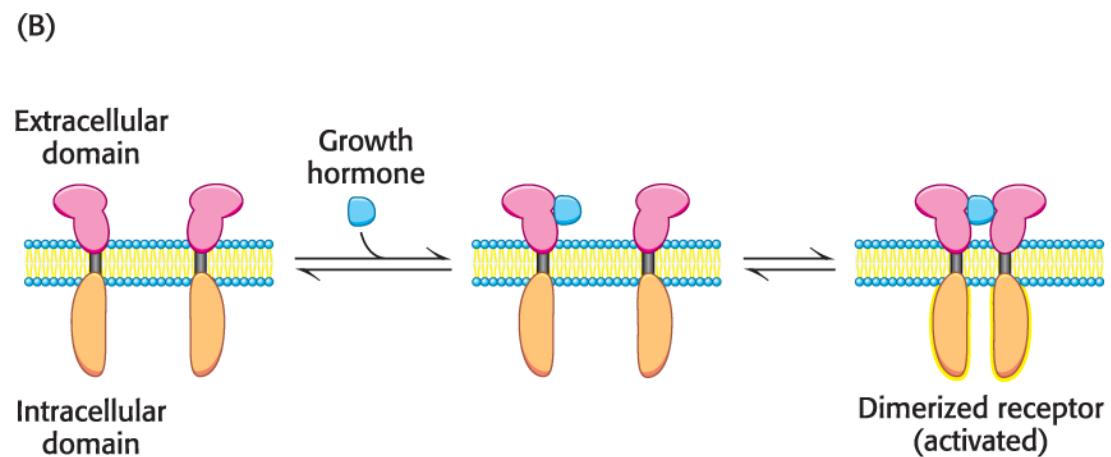
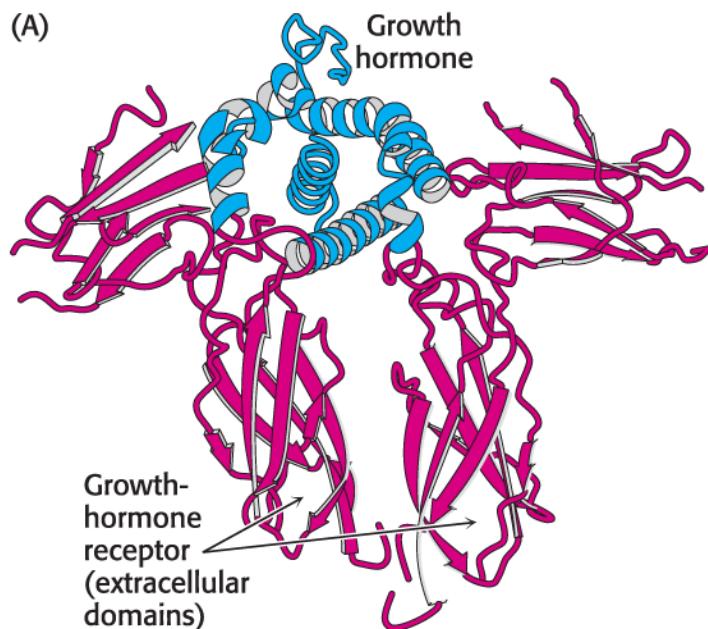
Which of the following is not common in the majority of signal transduction pathways?

- A. Specialized protein domains that mediate specific interactions.
- B. Use of covalent modification.
- C. Involvement of proteases
- D. Use of second messengers.
- E. Involvement of kinases.

Receptor Dimerization

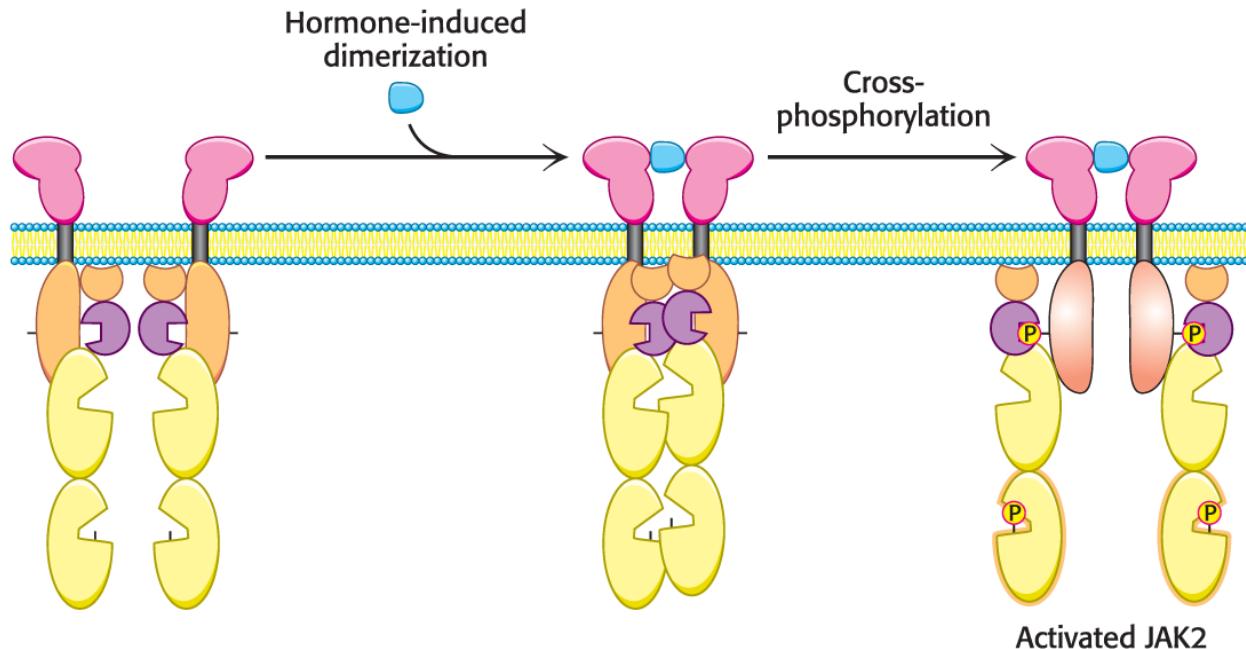
Receptor dimerization may result in tyrosine kinase recruitment.

- *Human growth hormone receptor* is a monomeric integral membrane protein with an extracellular and an intracellular domain joined by an intramembrane α -helix.
- Upon hormone binding, the receptor dimerizes.



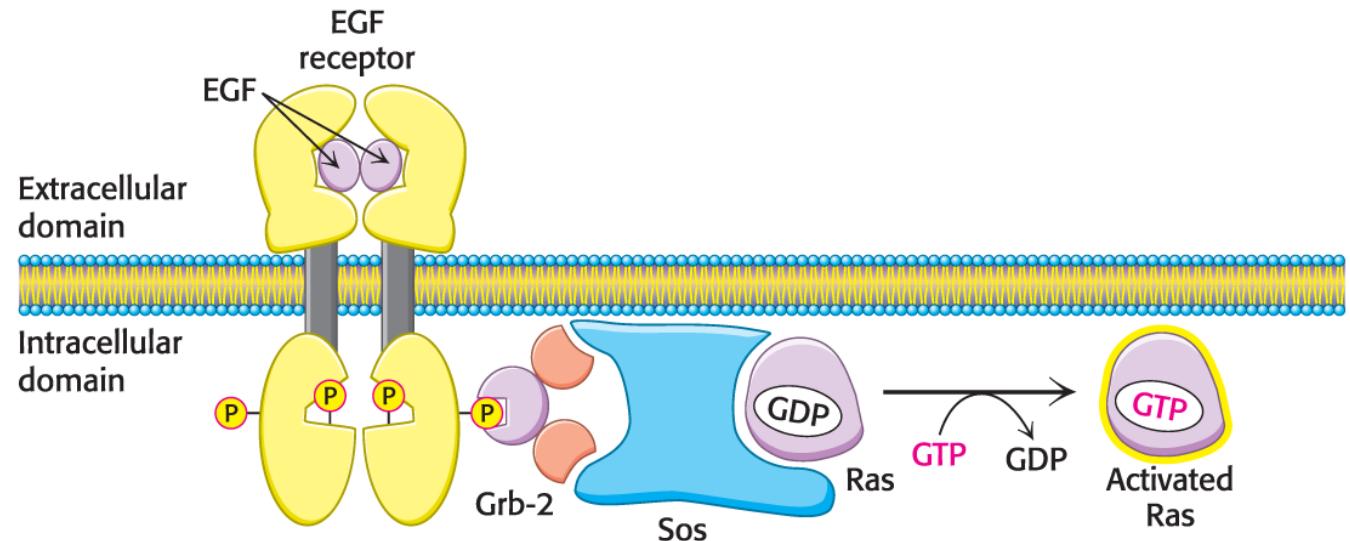
Receptor Dimerization

- Receptor dimerization may result in tyrosine kinase recruitment.
 - Dimerization of the extracellular domains of the receptor brings together the intracellular domains, which are associated with Janus kinase 2 (JAK2).
 - Each JAK phosphorylates its partner on a tyrosine residue, activating the two kinases.



Receptor Dimerization

- Some receptors contain tyrosine kinase domains within their covalent structures.
- Some growth factors and hormone receptors, such as the epidermal growth factor (EGF) and insulin, bind to receptors that are tyrosine kinases, called receptor tyrosine kinases (RTK). Upon growth factor or hormone binding, these receptor form dimers.
- Receptor dimerization leads to cross-phosphorylation and activation of the two intracellular kinase domains.
- The phosphorylated kinases form docking platforms for other components of the signal transduction pathway.



Ras Superfamily of GTPases

| Subfamily | Function |
|------------------|--|
| Ras | Regulates cell growth through serine or threonine protein kinases |
| Rho | Reorganizes cytoskeleton through serine or threonine protein kinases |
| Arf | Activates the ADP-ribosyltransferase of the cholera toxin A subunit; regulates vesicular trafficking pathways; activates phospholipase D |
| Rab | Plays a key role in secretory and endocytotic pathways |
| Ran | Functions in the transport of RNA and protein into and out of the nucleus |

Quick Quiz 5

Which of the following does not occur upon the binding of epidermal growth factor to the epidermal growth factor receptor?

- A. The extracellular domains interact.
- B. The intracellular domains interact.
- C. The intracellular domains interact with adenylate cyclase.
- D. The receptor is activated.
- E. All of the above occur.

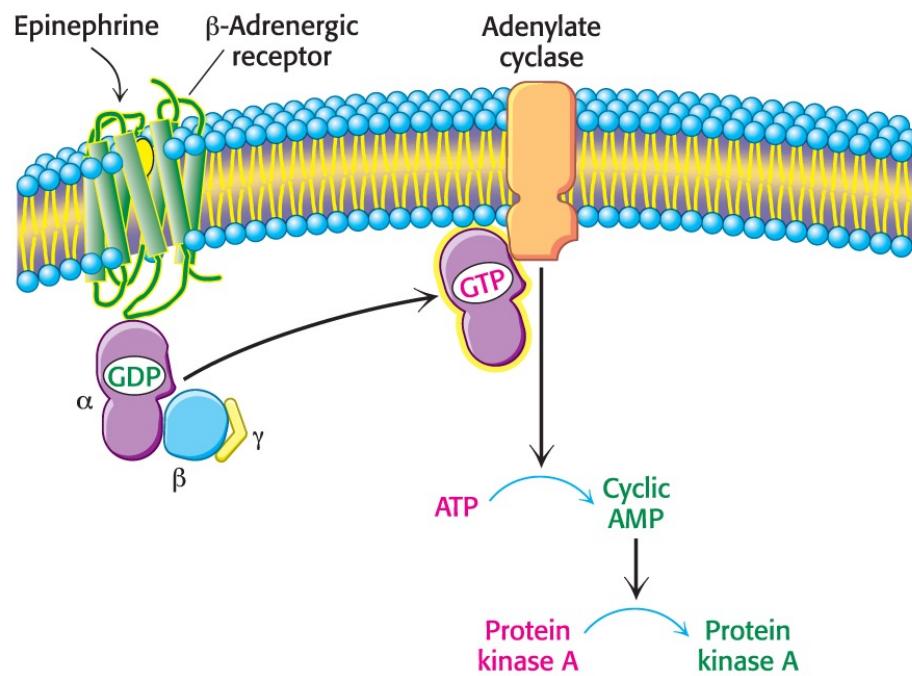
Why are membrane receptor proteins often used to transfer information from the cell's environment to its interior?

- The molecular signal is not soluble in the interior of the cell.
- The signal molecule is transported into the cell by the receptor.
- The signal molecule is too large or too polar to pass through the cell membrane.
- The molecular signal would overstimulate the signaling pathway if it were internalized.

Odorant receptors and β -adrenergic receptors are 7TM receptors that initiate a signal cascade through G proteins.

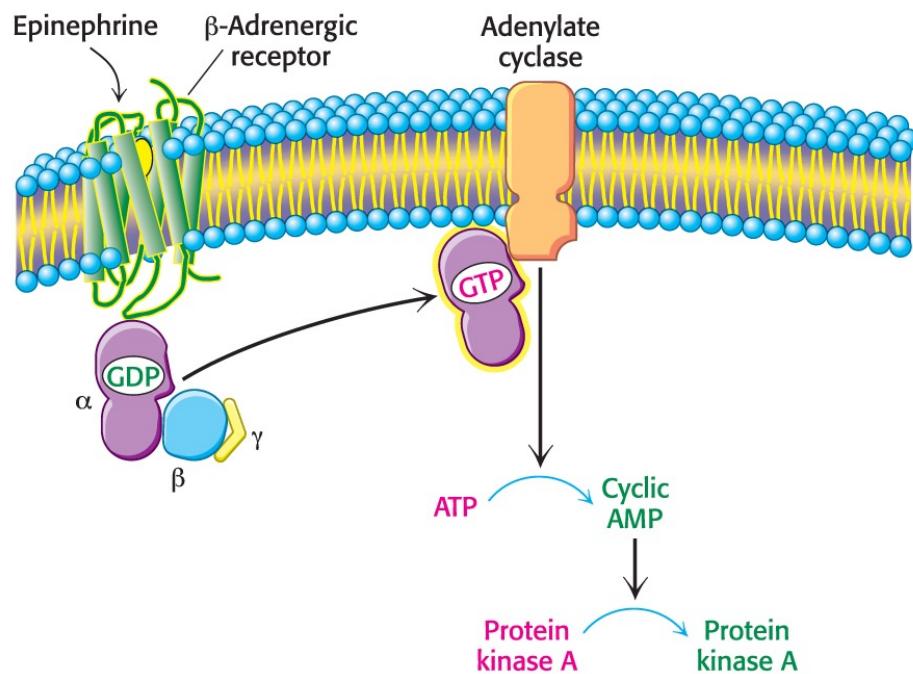
Which of the following steps is common between the signal-transduction cascade mediated by the odorant receptor and the signal-transduction cascade mediated by the β -adrenergic receptor?

- an increase in intracellular levels of cAMP
- an increase in intracellular levels of IP₃
- activation of protein kinase A
- an influx of cations into the cell



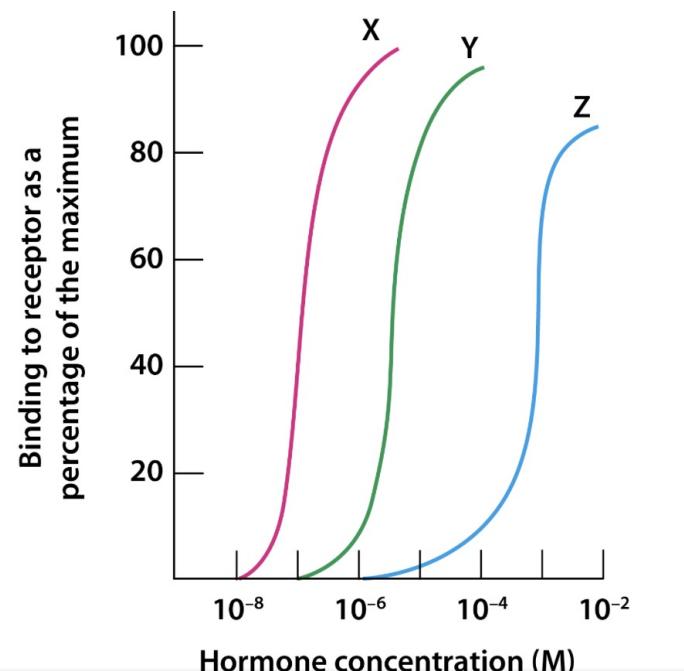
Which step occurs immediately after epinephrine binds to the β -adrenergic receptor?

- G_{αs} diffuses to adenylate cyclase.
- cAMP binds to protein kinase A.
- GTP displaces GDP in G_{αs}.
- β -arrestin binds to the receptor.
- G_{αs} diffuses away from G_{βγ}.



The graph shows the hormone-binding specificity of a hypothetical membrane receptor. The results are for three different hormones, X, Y, and Z. The graph plots the percentage binding capacity of the receptor as a function of hormone concentration for each hormone.

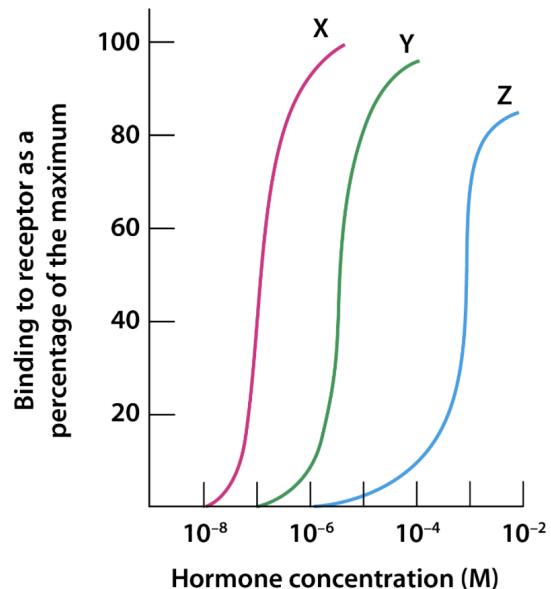
Using the graph of percentage binding versus hormone concentration, give the estimated molar (M) concentration for each hormone that yields 50% of maximal binding.



Based on the concentration that yields 50% maximal binding, which hormone shows the highest binding affinity for the receptor?

- X
- Y
- Z
- X, Y, and Z have the same affinity

Measuring adenylate cyclase activity as a function of hormone concentration reveals whether the hormone–receptor complex stimulates the adenylate cyclase cascade. The results of this experiment are shown in the graph that plots percentage adenylate cyclase activity against hormone concentration.



Considering the relative binding affinities and adenylate cyclase activity as a function of hormone concentration, what can you conclude about the mechanism of action of the hormone–receptor complexes?

- All of the hormone–receptor complexes for X, Y, or Z lead to adenylate cyclase stimulation.
- None of the hormone–receptor complexes for X, Y, or Z lead to adenylate cyclase stimulation.
- Only the hormone–receptor complex for X leads to adenylate cyclase stimulation.
- Unlike that of X and Y, the hormone–receptor complex for Z does not stimulate adenylate cyclase.

The hydrolysis of phosphatidylinositol bisphosphate (PIP_2) by phospholipase C generates what two secondary messengers?

- diacylglycerol and inositol 1,4,5-triphosphate
- diacylglycerol phosphate and inositol 4,5-diphosphate
- free fatty acids and a molecule in which inositol 4,5-diphosphate is linked via a phosphate to glycerol
- diacylglycerol and inositol 4,5-bisphosphate
- phosphatidylinositol 3,4,5-triphosphate and cAMP

Why does calmodulin bound with calcium interact with target proteins, whereas free calmodulin does not?

- Calcium ions serve to bridge negatively charged groups on calmodulin and the target protein.
- Calcium ion binding neutralizes negative charges on calmodulin such that electrostatic repulsion between it and negative charges on the target protein do not occur.
- Calcium binding results in a conformational change in calmodulin, producing a structure that can bind to target proteins.
- Calcium binding to regulatory subunits results in the release of the active catalytic subunits.
- Calcium binding results in a conformational change in calmodulin, producing a structure that can be activated by protein kinase A-dependent phosphorylation.

Metabolism in Context: Insulin Signaling Regulates Metabolism

- The polypeptide hormone insulin is secreted when the blood is rich in glucose.
- Insulin is the biochemical signal for the fed state.
- Insulin consists of two polypeptide chains linked by disulfide bonds.
- The insulin receptor is a receptor **tyrosine kinase class** of membrane proteins.
- Receptor dimers form on insulin binding, leading to cross-phosphorylation and activation of the kinase domains.

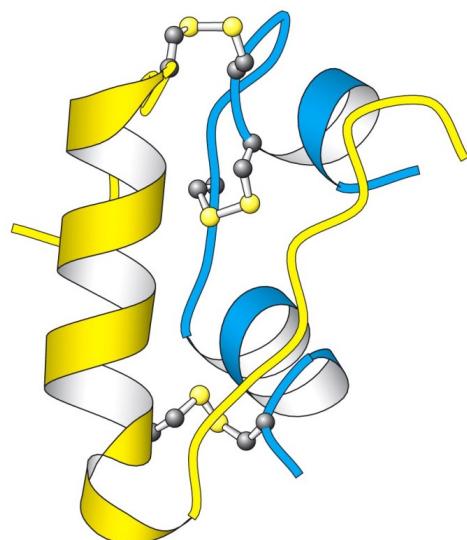


Figure 13.17
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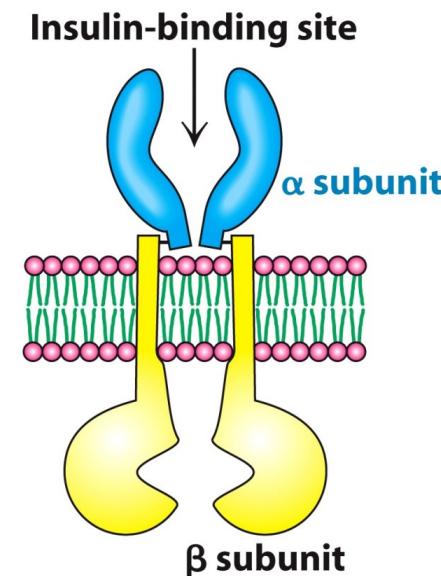


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Metabolism in Context: Insulin Signaling Regulates Metabolism

- The activated kinase of the insulin receptor phosphorylates **insulin-receptor substrates (IRSs)**.
- The phosphorylated IRSs are adaptor proteins to convey the insulin signal.
- Phosphoinositide-3 kinase binds IRS and then phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP₂) to form phosphatidylinositol 3,4,5-trisphosphate (PIP₃).
- PIP₃ activates PIP₃-dependent kinase, which in turn, phosphorylates and activates the kinase AKT.
- AKT phosphorylates glucose transporter (GLUT4), increasing glucose uptake by the cells, as well as enzymes that convert glucose into glycogen.

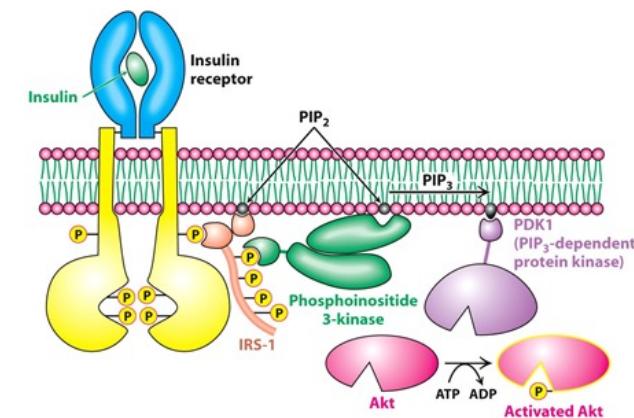


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Metabolism in Context: Insulin Signaling Regulates Metabolism

- Protein phosphatases remove phosphates from the activated proteins in the insulin signal transduction pathway, terminating the insulin signal.
- Lipid phosphatases contribute to signal termination by converting PIP₃ into PIP₂.

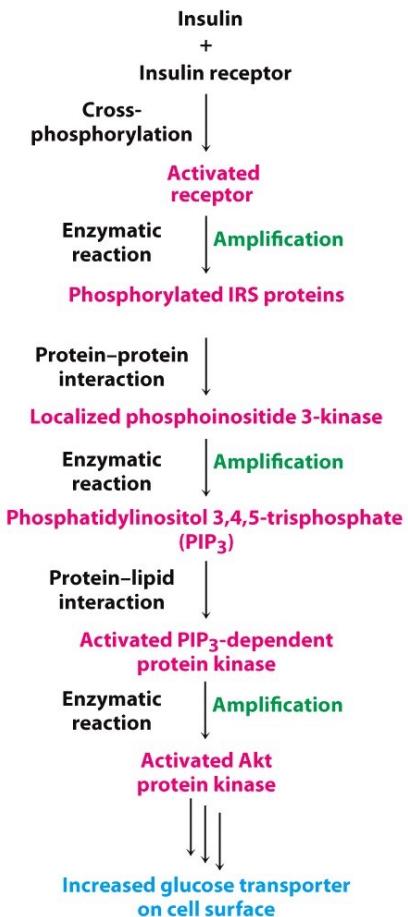


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Calcium Ion Is a Ubiquitous Cytoplasmic Messenger

- Ca^{2+} is an important second messenger in eukaryotic signal transduction pathways.
- The protein **calmodulin (CaM)** is a common Ca^{2+} sensor.
- Calmodulin, with four Ca^{2+} binding sites called EF hands, is activated upon binding Ca^{2+} .
- The Ca^{2+} -calmodulin complex activates a variety of biochemical targets, including pumps, such as the plasma membrane Ca^{2+} ATPase, and the calmodulin-dependent protein kinase (CaM kinase).
- Recall the Ca^{2+} also plays a role in the phosphoinositide cascade.

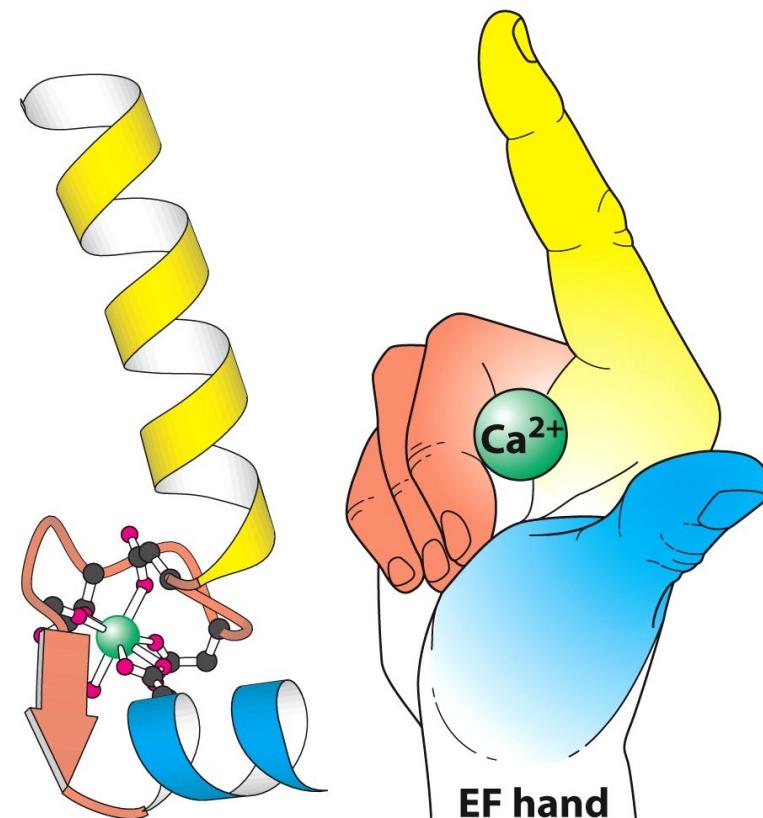


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Quick Quiz 6

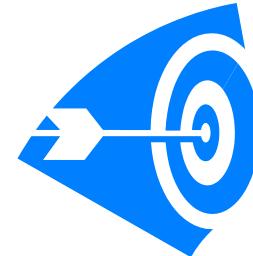
The insulin receptor is an example of _____.

- A. a seven-transmembrane receptor
- B. a receptor threonine kinase
- C. a receptor phosphatase
- D. a membrane channel
- E. a receptor tyrosine kinase.

Answer:

E

Assigned Problems



| Chapter | Tymochko, Berg, Stryer, Biochemistry, 2 nd Edition, | Chapter | Tymochko, Berg, Stryer, Biochemistry, 2 nd Edition, |
|----------------|--|----------------|--|
| 12 | 3, 4, 6, 8, 9, 13, 15, 19, 23, 24, 25, 29, 30. | 13 | 1, 6, 8, 9, 13, 15, 20, 22, 23, 25, 27. |
| Chapter | Tymochko, Berg, Stryer, Biochemistry, 3 rd Edition, 4 th Edition (second line) | Chapter | Tymochko, Berg, Stryer, Biochemistry, 3 rd Edition, 4 th Edition (second line) |
| 12 | 3, 4, 6, 8, 9, 13, 15, 19, 23, 24, 25, 29, 30. 3, 4, 6, 8, 9, 13, 15, 19, 23, 24, 25, 29, 30. | 13 | 1, 6, 8, 9, 13, 15, 20, 22, 23, 25, 27. 1, 6, 8, 9, 13, 15, 20, 22, 23, 25, 27. |