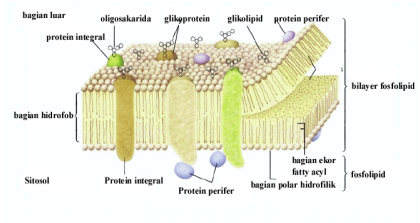
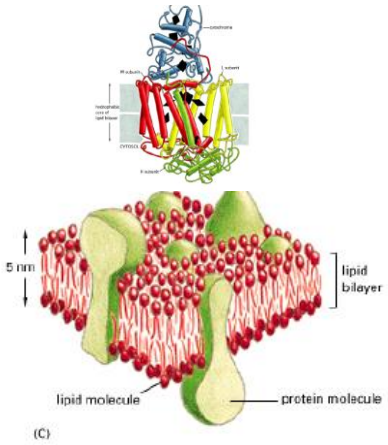
CELL MEMBRANE
Cell Biology and Its Application
BI-1202





Function of cell membrane:

- **Boundary**

Continuous, encloses the cell, nucleus, organelles

- **Selective permeable barrier**

Avoid molecules exchange from one side to the other side.
Avoid the entrance of certain molecules to the cytoplasm

- **Movement of soluble molecules**

Make the entrance of certain substances to cytoplasm from outside cell possible

- **Responding to extracellular stimuli**

→ Signal Transduction → receptor + ligand.
Different type of cell, different receptor molecule

- **Inter-celullar interaction**

Plasma membrane mediates cell interaction in multicellular organism → cell communication

- **Place for biochemical activities**

- **Energy transduction**

Involved in the process of energy transformation

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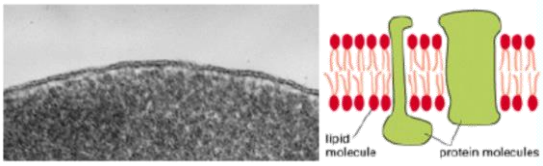
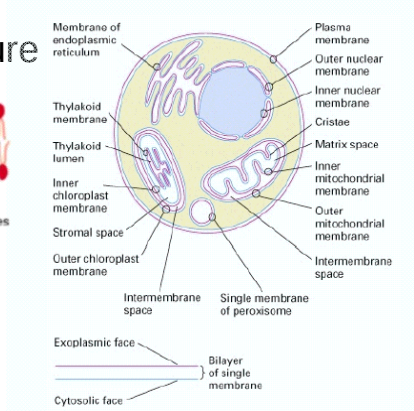
Membrane structure





lipid bilayer :

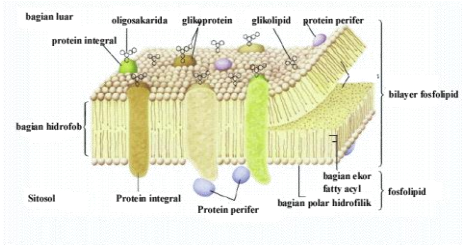
- Polar molecules (hydrophilic) face to the outer part
- hydrophobic part (fatty acyl chain) protected from water environment → amphipathic .

Protein

- Trans-membrane Molecules or attached in lipid layer

Carbohydrate

- biomarker in the cell surface



Fluid mosaic model
(Jonathan Singer & Garth Nicolson, 1960)

Table 8.1 Components of the Cell Membrane

Component	Composition	Function	How It Works	Example
Phospholipid molecules	Phospholipid bilayer	Provides permeability barrier, matrix for proteins	Excludes water-soluble molecules from nonpolar interior of bilayer	Bilayer of cell is impermeable to water-soluble molecules, like glucose
Transmembrane proteins	Carriers	Transport molecules across membrane against gradient	"Escort" molecules through the membrane in a series of conformational changes	Glycophorin carrier for sugar transport
	Channels	Passively transport molecules across membrane	Create a tunnel that acts as a passage through membrane	Sodium and potassium channels in nerve cells
	Receptors	Transmit information into cell	Signal molecules bind to cell-surface portion of the receptor protein; this alters the portion of the receptor protein within the cell, inducing activity	Specific receptors bind peptide hormones and neurotransmitters
Interior protein network	Spectrins	Determine shape of cell	Form supporting scaffold beneath membrane, anchored to both membrane and cytoskeleton	Red blood cell
	Clathrins	Anchor certain proteins to specific sites, especially on the exterior cell membrane in receptor-mediated endocytosis	Proteins line coated pits and facilitate binding to specific molecules	Localization of low-density lipoprotein receptor within coated pits
Cell surface markers	Glycoproteins	"Self"-recognition	Create a protein/carbohydrate chain shape characteristic of individual	Major histocompatibility complex protein recognized by immune system
	Glycolipid	Tissue recognition	Create a lipid/carbohydrate chain shape characteristic of tissue	A, B, O blood group markers

The Lipid Bilayer

Amphipathic molecules → spontaneously forms bilayer

- **hydrophilic/ polar end & hydrophobic/ non polar end**
- **most abundant membrane lipids → phospholipids: polar head group & 2 hydrophobic hydrocarbon tails**

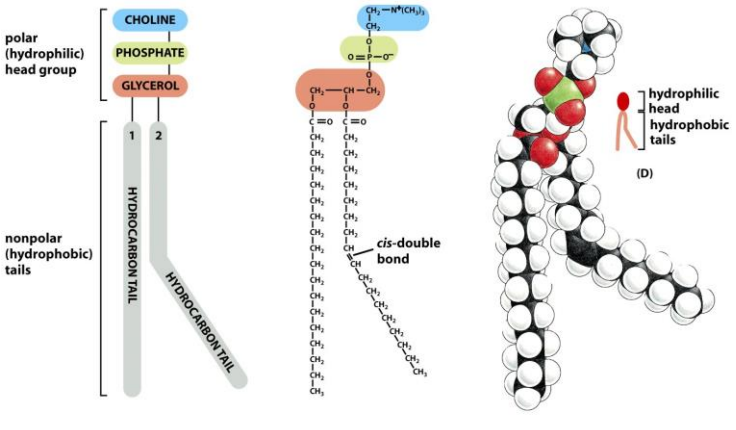


Figure 10-2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

4 types of phospholipids in the mammalian plasma membranes

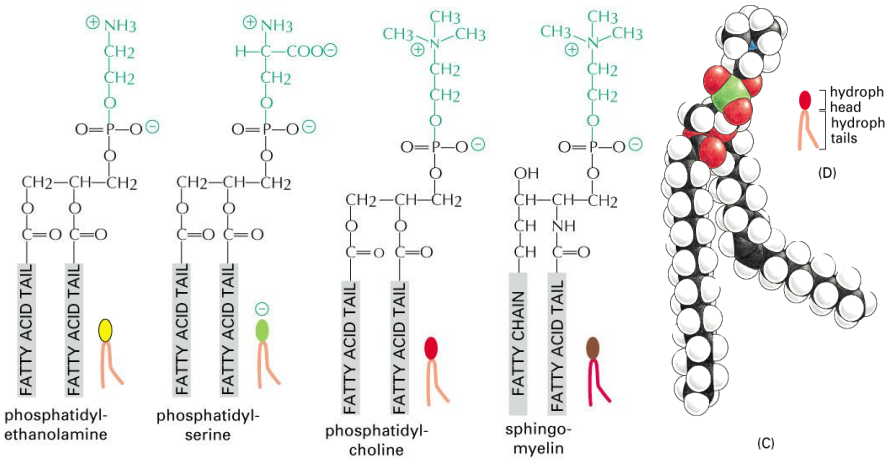


Figure 10–12. Molecular Biology of the Cell, 4th Edition.

Figure 10–2 part 3 of 3. Molecular Biology of the

Four major phospholipids in mammalian plasma membrane (different head group). All lipid molecules are derived from phosphoglycerides, except for sphingomyelin, which is derived from sphingosine

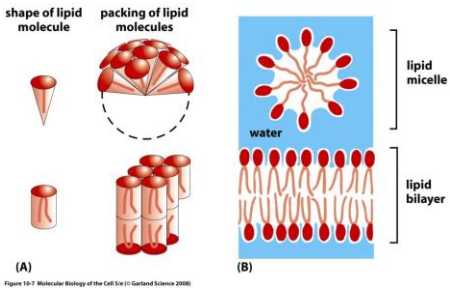
Lipid membrane components:

- Phosphoglycerides
- Sphingolipid
- cholesterol

Table 10–1 Approximate Lipid Compositions of Different Cell Membranes

LIPID	PERCENTAGE OF TOTAL LIPID BY WEIGHT					
	LIVER CELL PLASMA MEMBRANE	RED BLOOD CELL PLASMA MEMBRANE	MYELIN	MITOCHONDRION (INNER AND OUTER MEMBRANES)	ENDOPLASMIC RETICULUM	*E. COLI* BACTERIUM
Cholesterol	17	23	22	3	6	0
Phosphatidylethanolamine	7	18	15	28	17	70
Phosphatidylserine	4	7	9	2	5	trace
Phosphatidylcholine	24	17	10	44	40	0
Sphingomyelin	19	18	8	0	5	0
Glycolipids	7	3	28	trace	trace	0
Others	22	13	8	23	27	30

Table 10-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)



Packaging arrangement of lipid molecules in an aqueous environment:
wedge-shaped molecules → form micelles;
cylinder-shaped phosholipid molecules → form bilayers

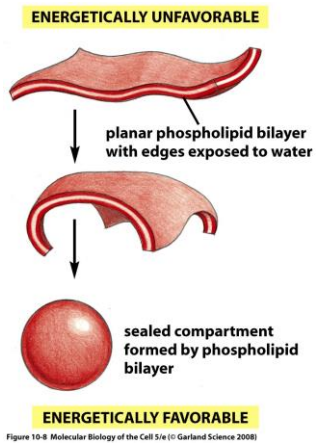


Figure 10-8 Molecular Biology of the Cell 5/e (© Garland Science 2008)

The spontaneous closure of a phospholipid bilayer to form a sealed compartment.
The closed structure is stable because it avoids the exposure of the hydrophobic hydrocarbon tails to water, which would be energetically unfavorable

Lipid and membrane fluidity

- Fluidity → viscosity
- Mobility → structure
- interaction → intercellular junction.
- Formation in certain structure: cell division, movement, endocytosis, secretion

Singer and Garth Nicolson :
lipid bilayer → lateral movement inside the membrane → dynamic structure → rapid interaction or semipermanent interaction

Flip flop → flippase enzyme
→ passive transmembrane movement

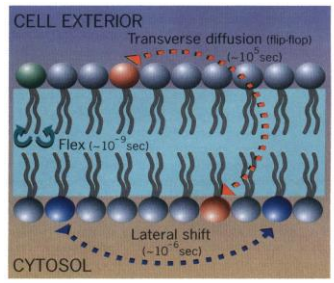
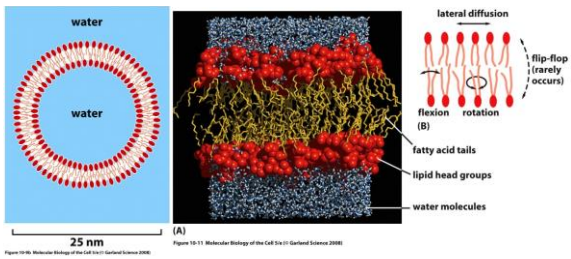
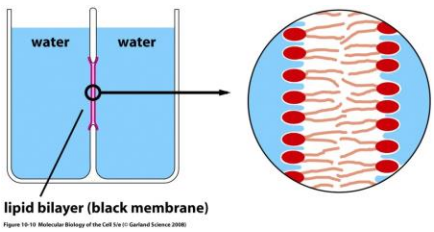


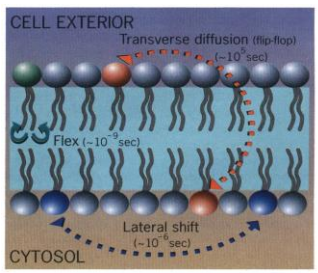
Figure 4.27 The possible movements of phospholipids in a membrane. The types of movements in which membrane phospholipids can engage and the approximate time scales over which they occur. Whereas phospholipids move from one leaflet to another (called flip-flop) at a very slow rate, phospholipids diffuse laterally within a leaflet rapidly.



Liposome



A cross-sectional view of black membrane, a synthetic lipid bilayer



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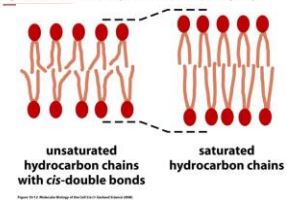


The influence of cis-double bonds in hydrocarbon chains. Double bonds make it more difficult to pack the chain together, thereby making the lipid bilayer difficult to freeze. Fatty acid chain of unsaturated → thinner than saturated fatty acid

The fluidity of a lipid bilayer

Depends on:
- Composition
- Temperature

The lipid bilayer is not composed exclusively of phospholipids, also contains: cholesterol & glycolipids

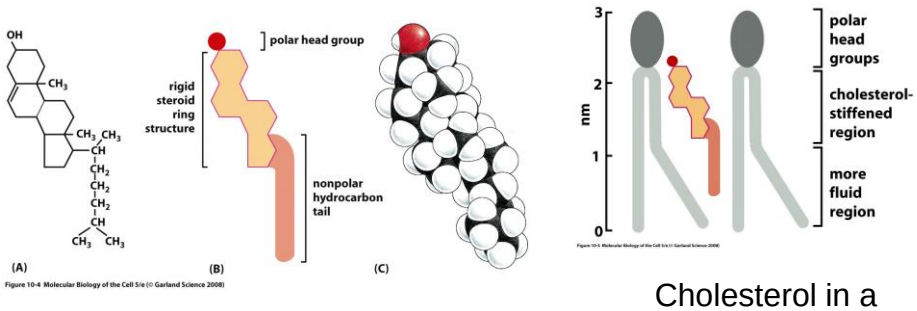


Figure 10-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cholesterol in a lipid bilayer

The asymmetry of the lipid bilayer

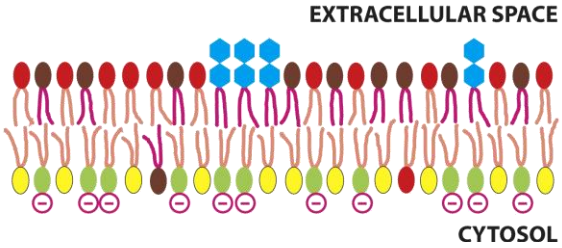


Figure 10-11. The asymmetrical distribution of phospholipids and glycolipids in the lipid bilayer of human red blood cells. The symbols used for the phospholipids are those introduced in Figure 10-10. In addition, glycolipids are drawn with hexagonal polar head groups (*blue*). Cholesterol (not shown) is thought to be distributed about equally in both monolayers.

Lipid asymmetry is functionally important → many cytosolic proteins bind to specific lipid head groups found in the cytosolic monolayer of the lipid bilayer:
- protein kinase C (PKC): is activated in response to various extracellular signals; it binds to cytosolic face where phosphatidylserine is concentrated and requires this negatively charged phospholipid for its activity
- Phosphatidylinositol : PI-3-kinase (lipid kinase)
- Phospholipase C

Membrane Proteins

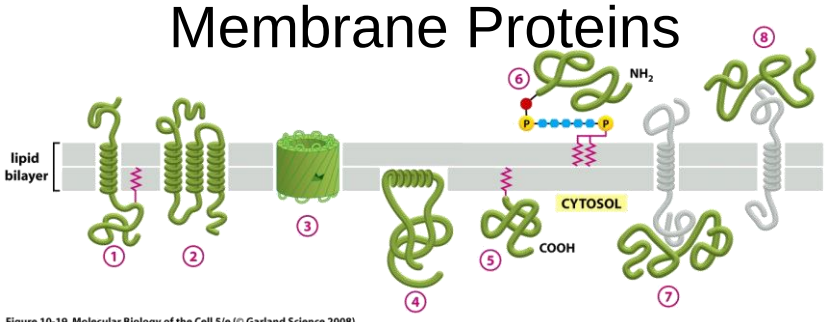


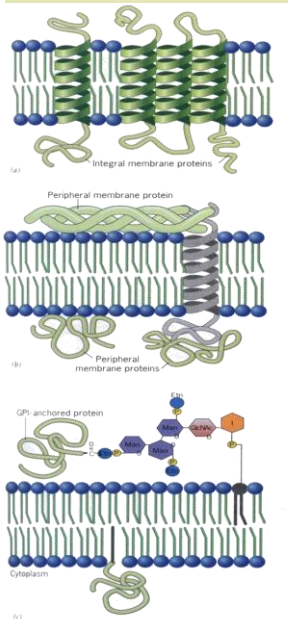
Figure 10-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)

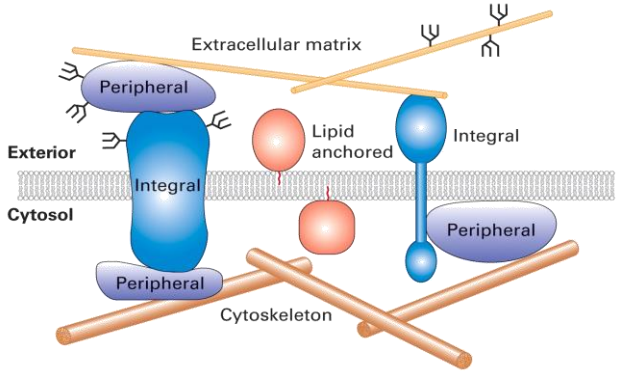
Membrane proteins can be associated with the lipid bilayer in various ways:

1. trans-membrane proteins are thought to extend across the bilayer as a single α helix
2. As multiple α helices
3. As a rolled-up β sheet (a β barrel)
4. Anchored to the cytosolic surface by an amphipatic α helix that partitions into the cytosolic monolayer of the lipid bilayer through the hydrophobic face of the helix
5. Attached to the bilayer solely by a covalently attached lipid chain (fatty acid / prenyl group) in the cytosolic monolayer
6. Via an oligosaccharide linker to phosphatidylinositol in noncytosolic monolayer

7 & 8. Attached to the membrane by noncovalent interactions with other proteins

Membrane protein :





- trans-membrane → integral → amphiphatic
- peripheral protein binds to membrane surface : non-covalent bond
- bind to lipid outside the lipid membrane in the extracellular or in the cytoplasmic

Structure of trans-membran protein

The spectrin-based cytoskeleton on the cytosolic side of the human red blood cell plasma membrane

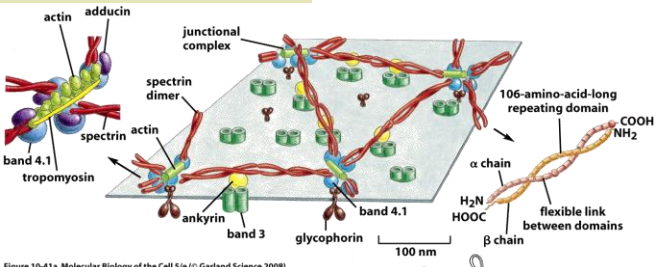
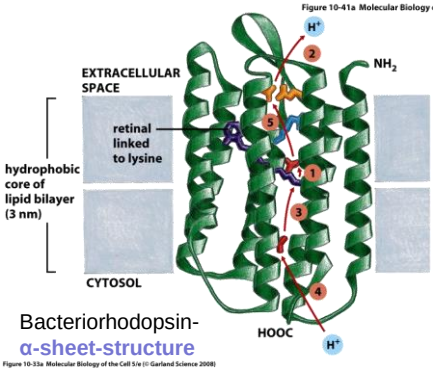
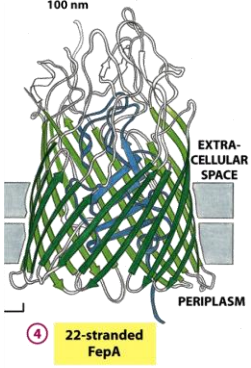


Figure 10-41a Molecular Biology of the Cell 5/e (© Garland Science 2008)



Bacteriorhodopsin-
α-sheet-structure

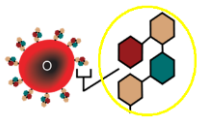
Figure 10-33a Molecular Biology of the Cell 5/e (© Garland Science 2008)

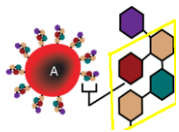


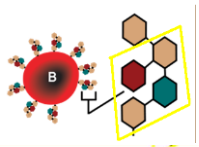
E coli FepA Protein transports iron ion
β-Barrel structure

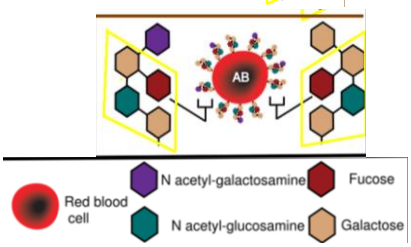
The difference between blood type: O, A, B, and AB

- O → H-determinant is not modified. Everyone has enzyme to synthesis antigen.
- A → plus N-acethylgalactosamin by GalNAc transferase.
- B → H-determinant plus D-Galactose by Gal transferase.
- AB → has 2 transferase and synthesize antigen A and B









The relevance between donor and resipient

Resipient \ Donor	O	A (has GalNAc transferase)	B (has Gal transferase)	AB (has Gal and GalNAc transferase)
0	√			
A	√	√		
B	√		√	
AB	√	√	√	√

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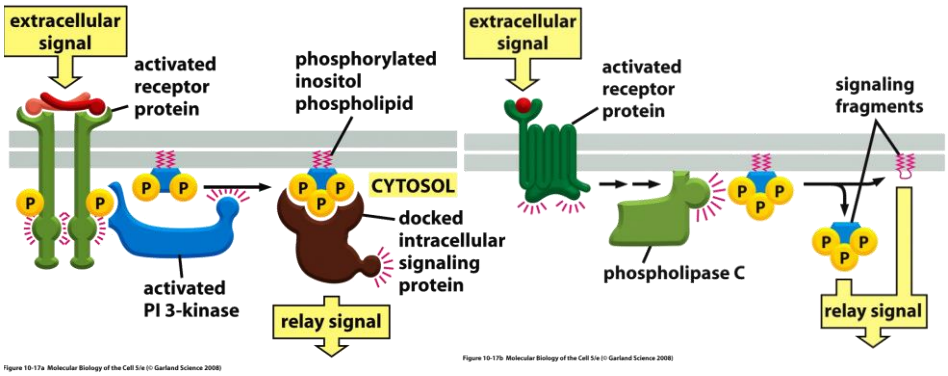

Some functions of membrane phospholipids in cell signaling:

A. Extracellular signals can activate PI 3-kinase, which phosphorylates inositol phospholipids in the plasma membrane. Various intracellular signaling molecules then bind to these phosphorylated lipids and are thus recruited to the membrane where they can interact and help relay the signal into the cell

B. Other extracellular signals activate phospholipases that cleave phospholipid. The lipid fragments then act as signaling molecules to relay the signal into the cell

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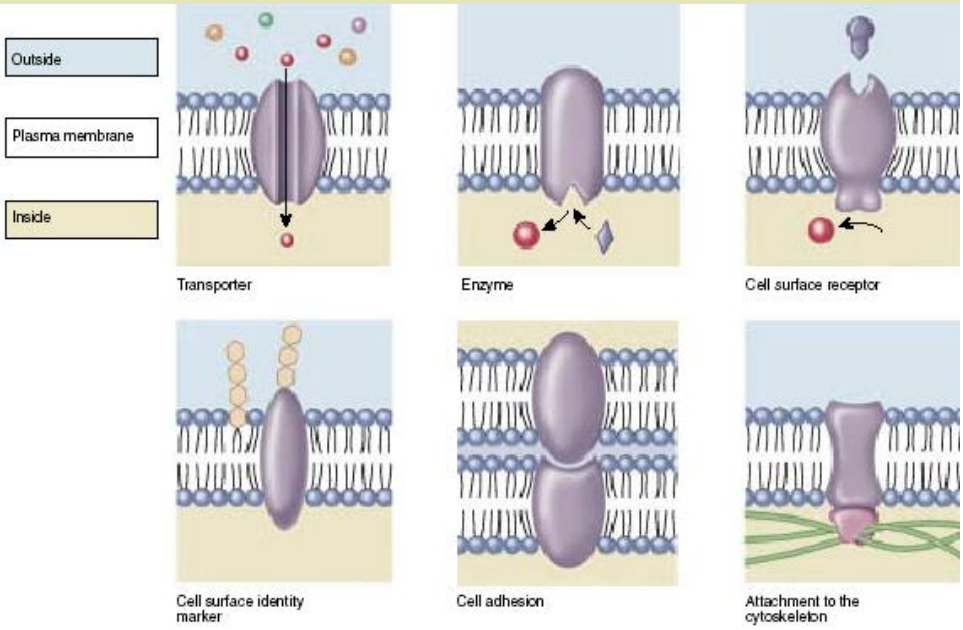
Function of Protein Membrane:



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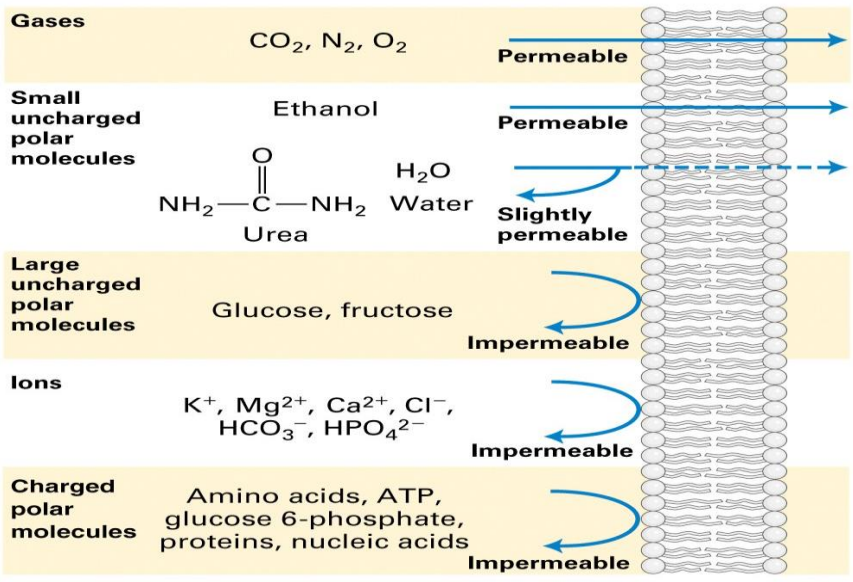
Relative Permeability of phospholipid bilayer



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Movement of substance through the membrane

1. **Passive (by diffusion)** : spontanenous movements from high concentration to the lower concentration
2. **Active:** use the energy

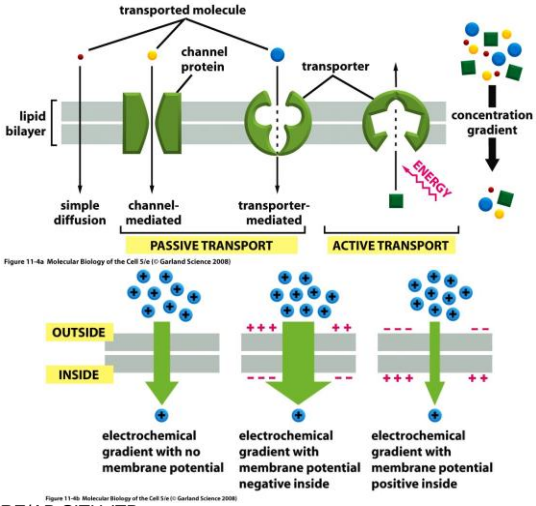

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TABLE 7-1 Mechanisms for Transporting Ions and Small Molecules Across Cell Membranes

	Transport Mechanism			
Property	Passive Diffusion	Facilitated Diffusion	Active Transport	Cotransport*
Requires specific protein	−	+	+	+
Solute transported against its gradient	−	−	+	+
Coupled to ATP hydrolysis	−	−	+	−
Driven by movement of a cotransported ion down its gradient	−	−	−	+
Examples of molecules transported	O_2, CO_2, steroid hormones, many drugs	Glucose and amino acids (uniporters); ions and water (channels)	Ions, small hydrophilic molecules, lipids (ATP-powered pumps)	Glucose and amino acids (symporters); various ions and sucrose (antiporters)

*Also called *secondary active transport*.

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Diffusion through the membrane

Non-electrolite substance passively diffuse trough the membrane if:

- Concentration of one compound is higher than the other
- The membrane should be permeable to that compound
  - The compound can pass trough the membrane
  - Can pass trough aqueous pores (aquaporin : water)

Determinant factor for penetration speed of solutes/ compound:

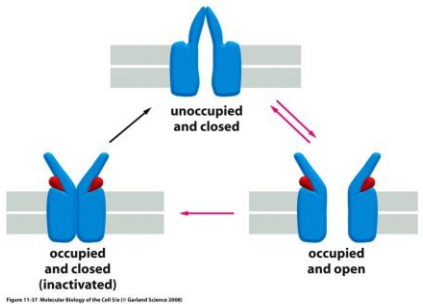
- Solubility in nonpolar solvent
- Size

Diffusion of water trough the membrane → osmosis

- Semi-permeable membrane
  Water molecule moves faster trough cell membrane compared to soluble ions or polar compound
- Water moves trough semi-permeable membrane from high concentration to low concentration

Ion diffusion trough the membrane

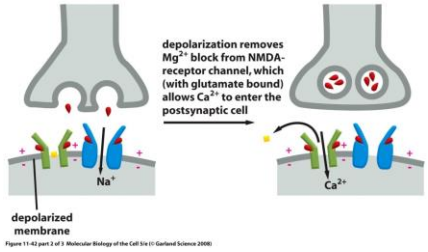
1. The membrane is very impermeable against charged molecules, including small ion .
2. Cell membrane has ion channel that is permeable for a certain ion



Ion channel opens and closes trough:

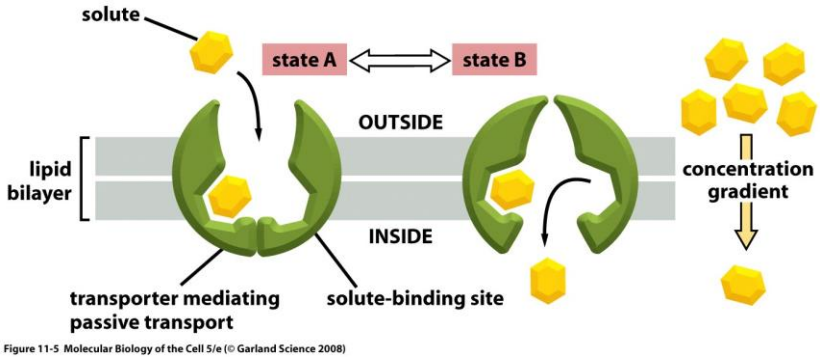
1. voltage-gated channels → depends on the difference in ion charge in both sides of membrane, example: K-ion channel

2. ligand-gated channels →change in molecule conformation by the presence of bound molecule to this channel, e.g acetylcholine



***Facilitated* difussion**

diffusion of compound from high concentration to low concentration. The compound binds to facilitative transporter (integral protein) → as a diffusion fasilitator on cell membrane



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Active Transport : against concentration gradient

a) needs energy

b) involve integral protein →pump

1. Binds to hydrolize ATP : Na+/K+-ATP-ase (natrium-kalium pump)→ type-P pump
   - Ca2+-ATP-ase Ca transport from ER to extracellular part or inside ER
   - H+/K+-ATP-ase in epithelial cell in digestive system

2. Co-transport : bind to ion gradient
   - Transfer of glucosa : Na ion – epithelial
   - Sucrosa – H+ ion (in plants)

→ simport

→ antiport

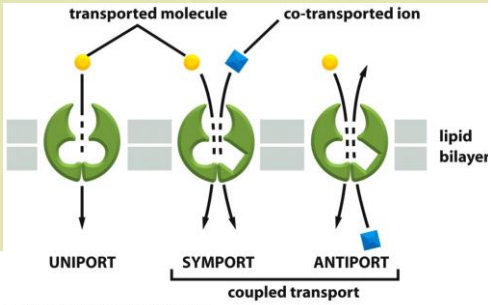

Figure 11-8 Molecular Biology of the Cell 5/e (© Garland Science 2008)

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Animation: Na – K with hydrolised ATPase

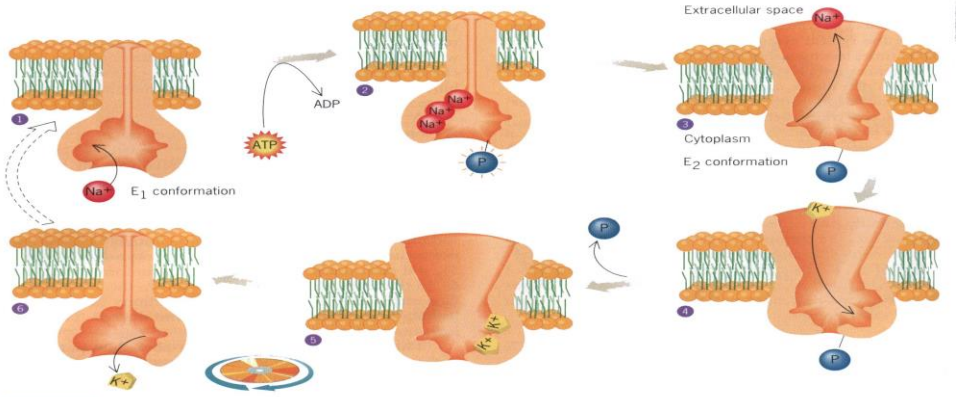
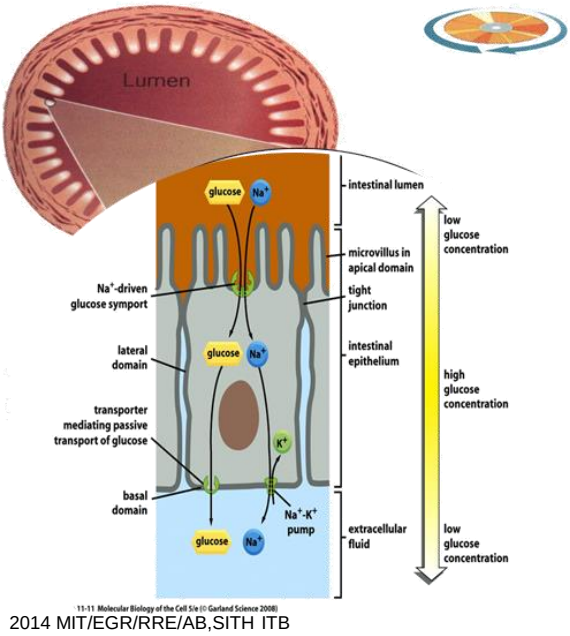


Figure 4.44 Schematic concept of the Na^+/K^+-ATPase transport cycle. Sodium ions (1) bind to the protein on the inside of the membrane. ATP is hydrolyzed, and the phosphate is transferred to the protein (2), changing its conformation (3) and allowing sodium ions to be expelled to the external space. Potassium ions then bind to the protein (4), and then the phosphate group is removed (5), which causes the protein to snap back to its original conformation, moving the potassium ions to the inside of the cell (6). Unlike facilitated diffusion, the changes in the shape of the protein are driven by energy from ATP hydrolysis, which allows the transport system to move these ions against their electrochemical gradients. Note that the actual Na^+/K^+-ATPase is a tetramer consisting of two different membrane-spanning subunits: a larger α subunit, which carries out the transport activity, and a smaller β subunit, which functions primarily in the maturation and assembly of the pump within the membrane.

Co-transport : animation



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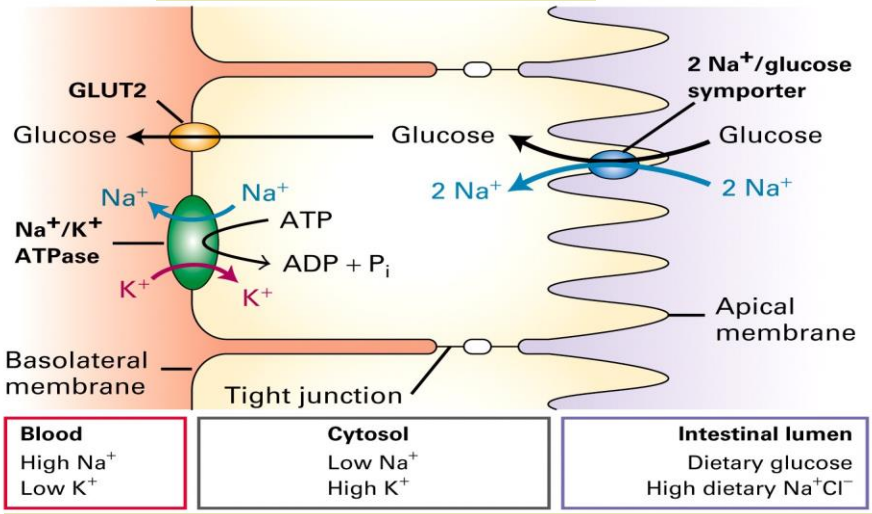
example : Oralit - Pocari



Oralit & pocari contains sugar and Na+ that can avoid the body from dehydration → because always induce water uptake

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Oral Rehydration Salts and Ionic Drinks

- General composition of ionic drinks: water, sugar, Sodium chloride (Na^+ dan Cl^-) , Kalium (K^+)
- Our body needs ions: (Na^+), (K^+), (Ca^{2+}), (Mg^{2+}), (Cl^-), (HPO_4^{2-}), dan (HCO_3^-)
- Ions cannot be produced by our body

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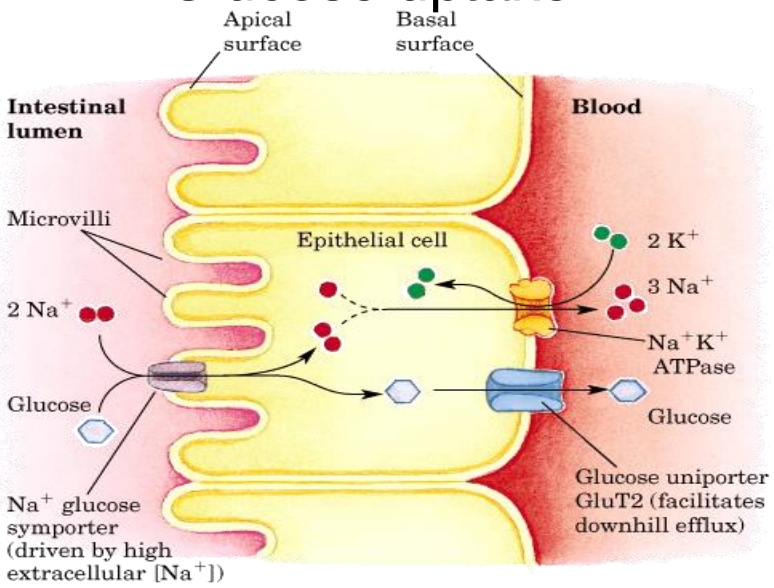
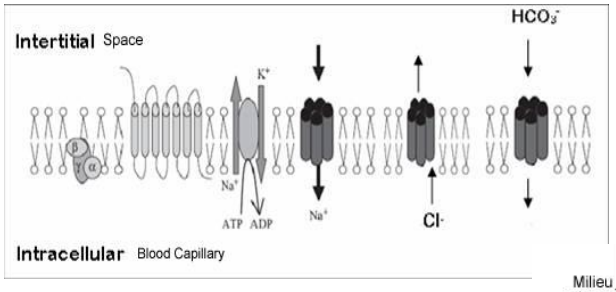
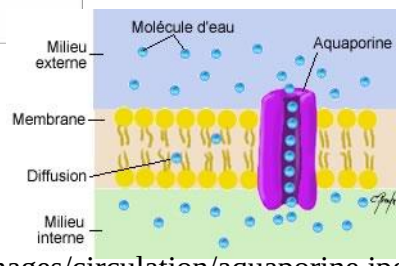
Glucose uptake



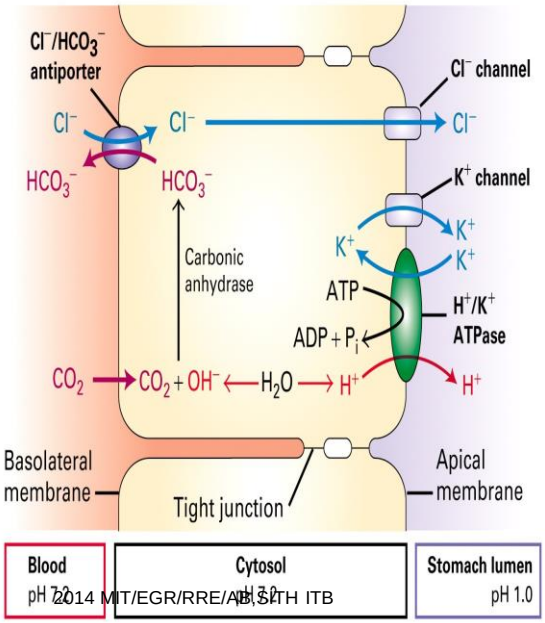
Mechanism in membrane Transport: intravenous



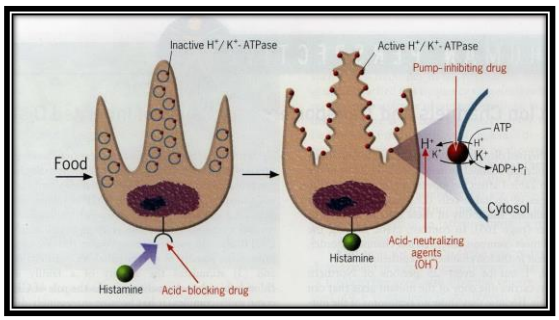


http://www.colfir.net/rof/chantal.proulx/images/circulation/aquaporine.jpg

Mechanism HCl Secretion



- Hydrogen ions are formed from the dissociation of water molecules.
- Carbonic anhydrase converts CO_2 and water to HCO_3^- and H^+.
- HCO_3^- is exchanged for Cl^- on the basal side of the cell and HCO_3^- diffuses into the blood.
- K^+ and Cl^- ions diffuse into the canaliculi.
- Hydrogen ions are pumped out of the cell into the canaliculi in exchange for K^+, via the H+/K+ ATPase



- Competitive inhibitor of histamine at parietal cell H_2 receptor.
- Suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid.

H2 Reseptor Antagonist

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Acid Controlling Agent

Antacid

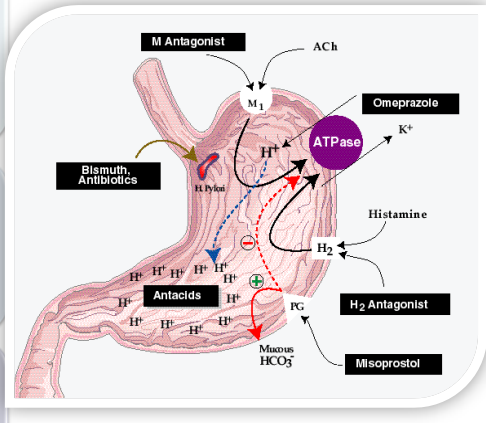
- Antacids *neutralize* the acid once it's in the stomach
- Example : Aluminium hydroxide (Amphojel, AlternaGEL)

Proton Pump Inhibitor (PPI)

- Binds covalently to the H^+/K^+-ATPase acid-pump, completely blocking acid secretion, until more pumps are made
- Example : Omeprazole

H_2 Receptor Antagonist

- The H_2 antagonists are competitive inhibitors of histamine at the parietal cell H_2 receptor
- Example : cimetidine (Tagamet), Famotidine (Pepcid)



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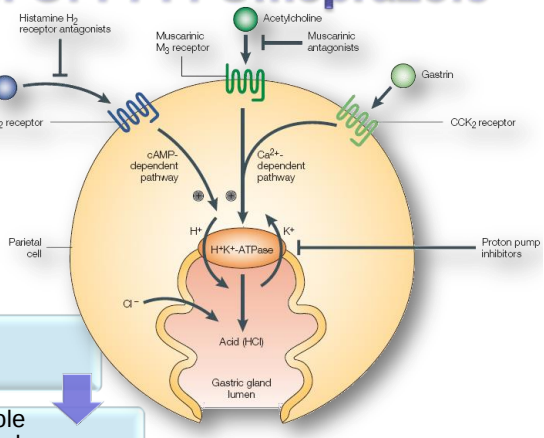
Mechanism Of PPI : Omeprazole



Omeprazole is not an active inhibitor of the H^+/K^+ ATPase.

Acid decomposition of Omeprazole revealed an intermediate compound a sulphenamide

Sulphenamide bind covalently to the cystein residues of H^+/K^+ ATPase.

Inhibition H^+/K^+ ATPase

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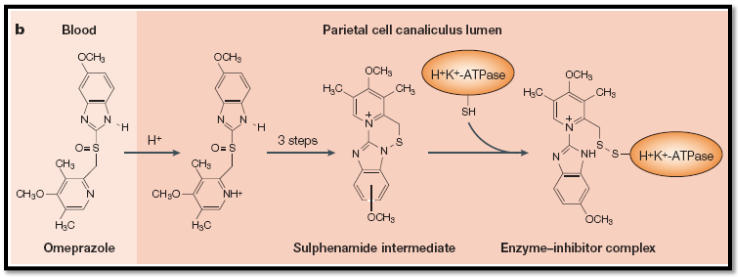
Biotransformation : Omeprazol



Omeprazole is weak base activated by a proton catalysed process to sulphenamide intermediate that covalently bind with sulphydryl group of cystein residue of H+/K+ ATPase → inhibiting its activity

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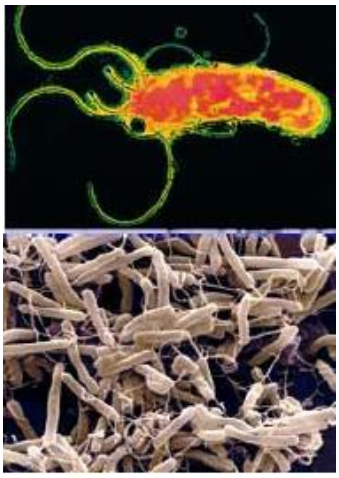
Pathology



- **NSAIDs** cause ulcers by interfering with the stomach's ability to protect itself from acidic stomach juices
- Normally the stomach secrete mucus that coats the stomach lining and shields it from stomach acid which is stimulated by prostaglandin
- NSAIDs block function of cyclooxigenase that essential for the production of prostaglandin.

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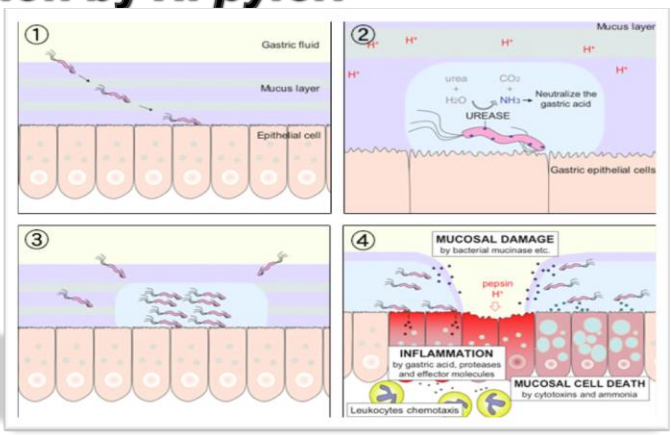
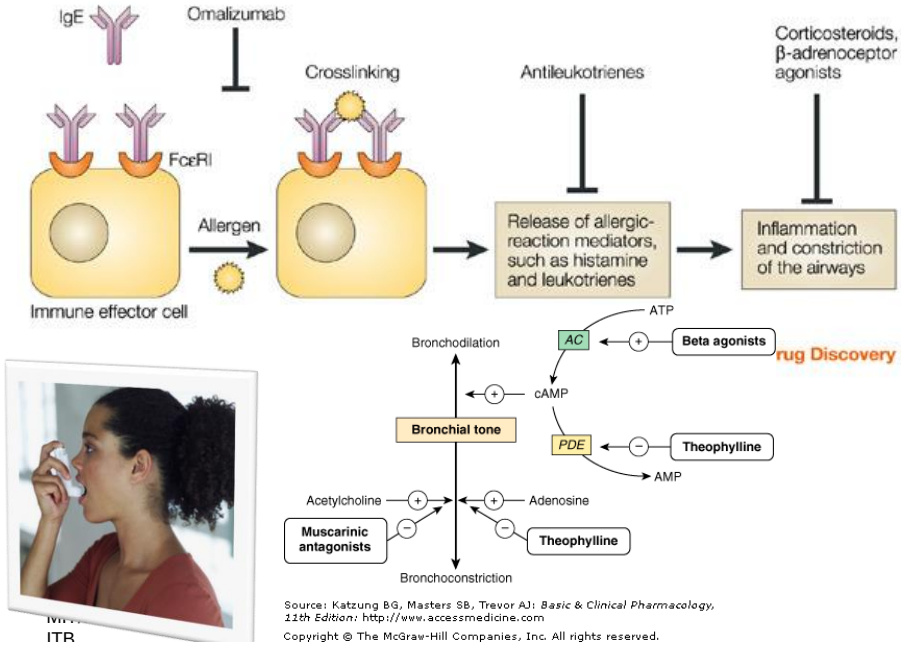
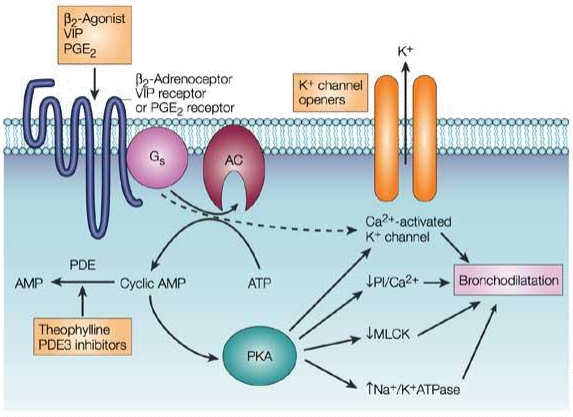
Infection by *H. pylori*



- H. pylori penetrate the mucus layer of host stomach and adhere the surface of gastric mucosal epithelial cells.
- Produce ammonia from urea by the urease, and the ammonia neutralize the gastric acid to escape from elimination.
- Proliferate, migrate, and finally form the infectious focus.
- The gastric ulcer is developed by destruction of mucosa, inflammation and mucosal cell death.

Mechanism action of asthmatic drugs





Nature Reviews | Drug Discovery

Activation of $_2$ adrenoceptors, vasoactive intestinal peptide (VIP) and prostaglandin E_2 (PGE_2) receptors results in activation of adenylyl cyclase (AC) via a stimulatory G-protein (G_s) and an increase in cAMP concentration. This activates protein kinase A (PKA), which then phosphorylates several target proteins, resulting in the opening of calcium-activated potassium channels (K_{Ca}) or maxi-K channels, decreased phosphoinositide (PI) hydrolysis, increased Na^+/K^+ ATPase and decreased myosin light chain kinase (MLCK) activity, which leads to relaxation of airway smooth muscle. In addition, $_2$-adrenoceptors can be coupled directly via G_s to K_{Ca}. cAMP is broken down by phosphodiesterases (PDE), which are inhibited by theophylline and selective PDE3 inhibitors, and which could therefore be potential asthma therapies.

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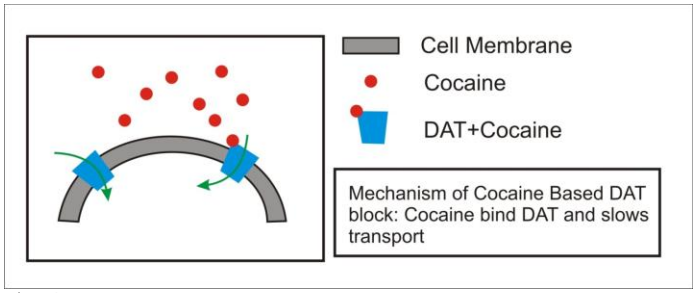
Various Anesthetic Drugs (and its mechanism)

Example: Cocaine

A stimulant of a central nervous system and appetite suppressant.

This drug binds to dopamine transporter protein → pre-synaptic neuron can't reuptake the dopamine from post-synaptic neuron → pre-synaptic neuron will in polarization state.



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Example: gas across the membrane: Viagra →NO → plasma membrane of blood vessel → relaxation of blood vessel

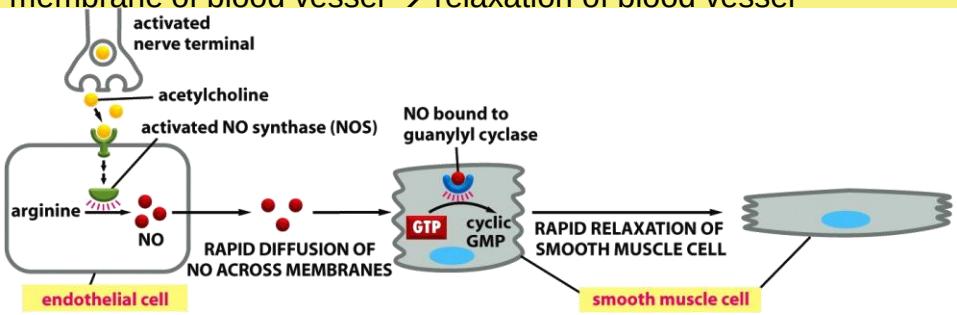
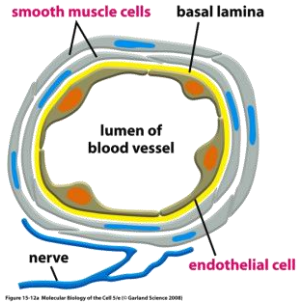
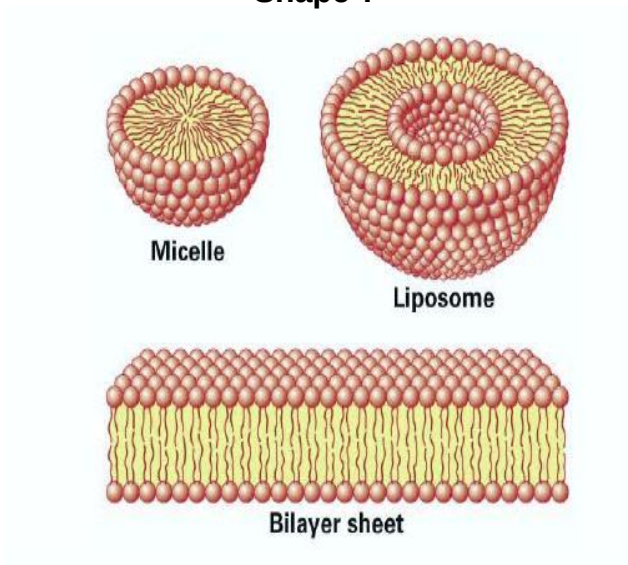


Figure 15-12b Molecular Biology of the Cell 5/e (© Garland Science 2008)

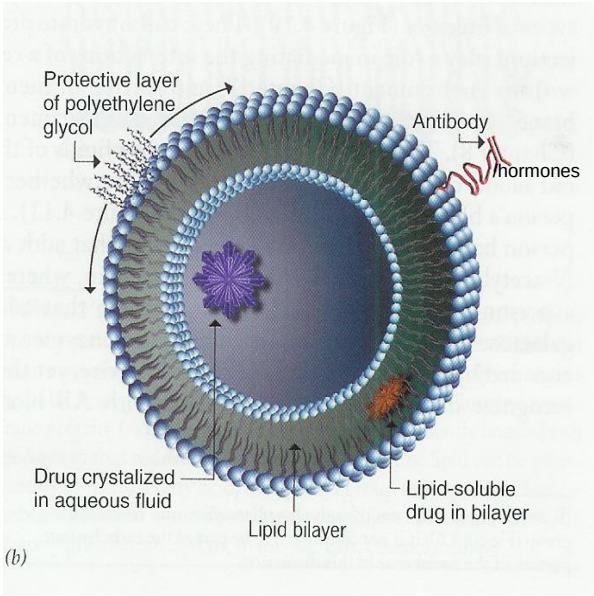


Shape ?



Application → liposome, drug delivery

Application of Lipid membrane : liposome vesicle with diameter 40 – 100 nm, contains i.e. : anti-cancer drug(doxorubicin-sulfat), DNA



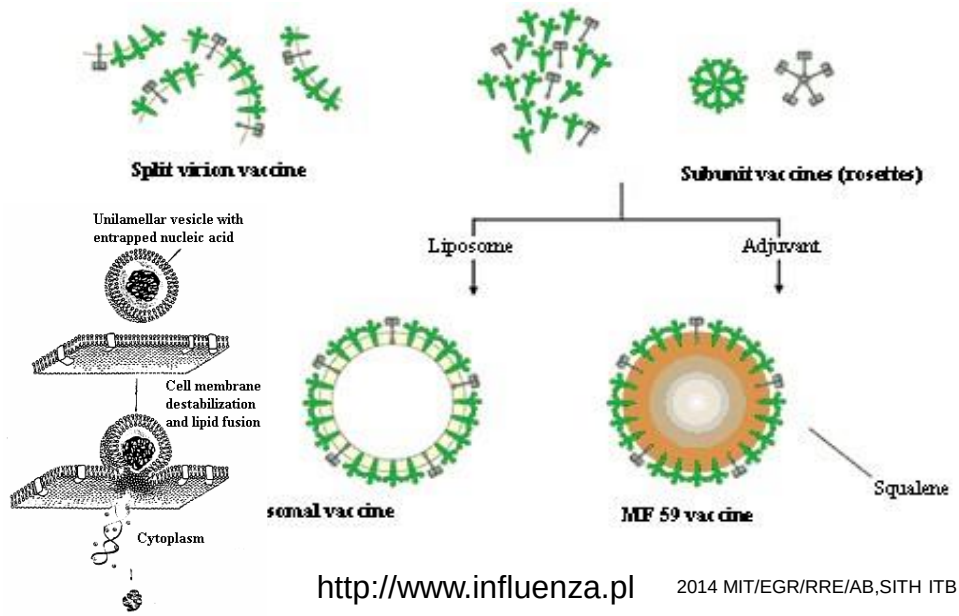
Liposomes can be formulated and processed to differ in size, composition, charge, and lamellarity and accordingly, a wide range of compounds may be incorporated into either the lipid or trapped aqueous space

The biodegradable and non-toxic nature of phospholipid vesicles proposes that these formulations are amenable to administration without serious side effects

Liposomes can alter the biodistribution of entrapped substances and protect the enclosed materials from inactivation by the host defense mechanisms.11 Therefore, liposomes can be used as vehicles to achieve specific delivery of therapeutic drugs to target organs. In addition, liposomes can reduce toxicity of antimicrobial, antiviral, and chemotherapeutic agents, and they have demonstrated the ability to modulate or potentiate the immunogenicity of antigenic substances

To enhance tissue targeting, liposome surface has been modified with antibodies or ligands recognized by specific cell types. To enhance the efficiency of gene delivery by the introduction of molecules directly into cells, virosomes have been developed by combining liposomes with fusiogenic viral envelope proteins. Liposomes are now being used in the treatment of intractable human diseases such as cancer and monogenic disorders

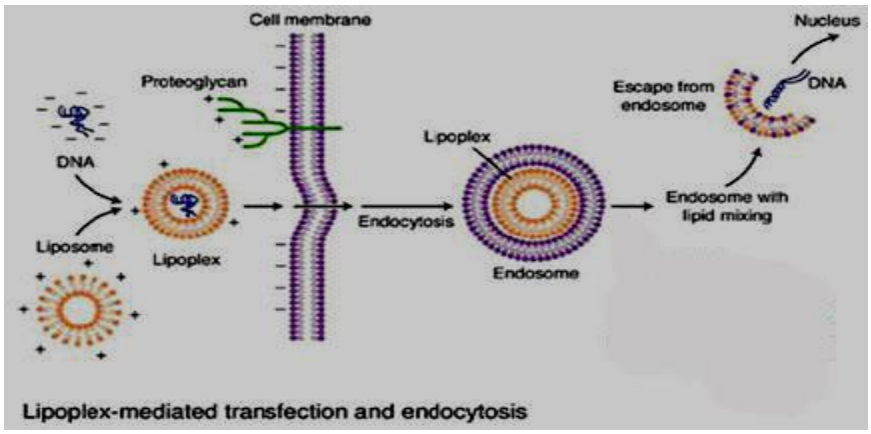
Delivery of vaccine using liposom



http://www.influenza.pl

Gene therapy and oral drug

- Cationic lipid Lipid and cationic polymer could improve delivery of plasmid DNA



http://www.acceleratingfuture.com/michael/blog/images/Gene_therapy.jpg

CYTOPLASMIC MEMBRANE SYSTEM

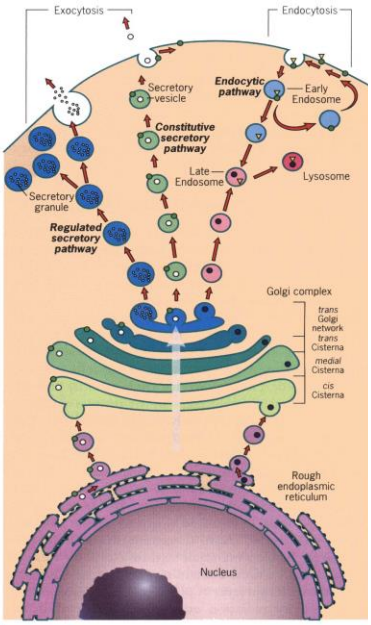
organelles → dynamics → the membrane forms an integrated network

Organelle materials → vesicles transport, formation of vesicles from previous organelles - Biosynthesis/ secretory pathway: protein synthesis in RE →modified in Golgi → transported to the destination - Opposite pathway: endolitic pathway→ lysosom, endosom

2 secretory activities :

1)Constitutive : the materials are transported inside secretory vesicles and excreted out, and reach its destiny – signal peptida

2)Regulative: The materials were secreted out and store inside vesicles and will be secreted only receives the stimulus



Lysosom

- Organelle that “eat”
- Contains 50 hydrolitic enzymes, formed in rough ER and stored in lysosome.
- Lysosomal enzymes→ hydrolised every biological molecules degradation results → excreted trough cytoplasmic→ Hydrolase enzyme
- Size: 25-50 nm - 1μm.
- Lysosome
  - In Kupffer cell (liver) → destroy certain substance inside cell that comes from the environment .
  - Macrophage and neutrophil phagocyte foreign substance by pH inactivation i.e: bacteria
  - spermatozoa: acrosome
- Lysosome functions in self destruction (organelles) autophagus → exocytosis or as lipofuchsin granules

Uptake particles and macromolecules by cell : phagocytosis, endocytosis: pinocytosis, receptor-mediated

Phagocytosis

- uptake large particles(> 0.5μm) from environment→ phagosome~ autophage
- Phagosome with lysosome functions as→ phagolysosome

Examples, cells: macrophage, neutrophil

- phagocytosis → opsonization certain microbes/ substance → destroyed by lysosomal enzymes or oxygenated free radicals in the phagosome.
- Actin helps phagocytosis

Pinocytosis :

→ liquid, soluble molecules or suspended macromolecule

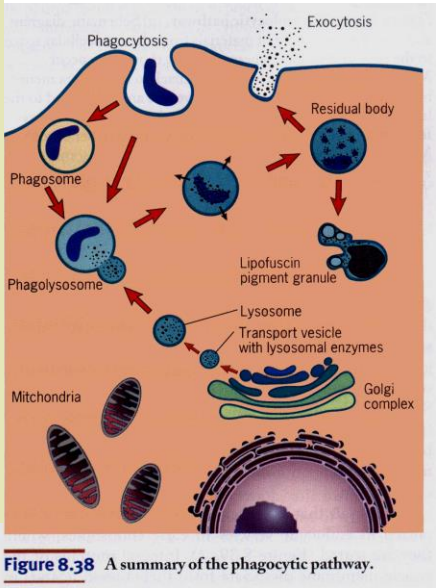
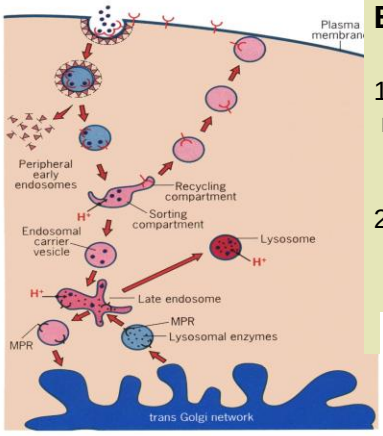


Figure 8.38 A summary of the phagocytic pathway.



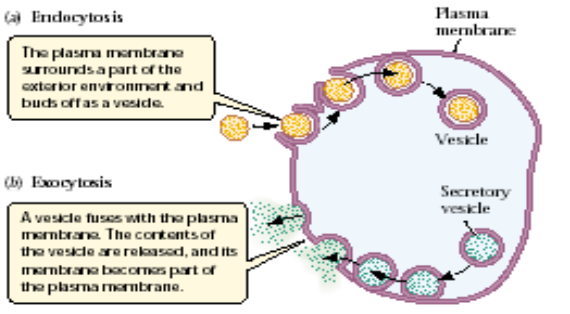
(a)

Figure 8.39 **The endocytic pathway.** (*a*) Schematic diagram showing the movement of materials from the extracellular spac to the early endosomes, where sorting is thought to occur. Membrane receptors are usually sent back to the plasma membrane, whereas materials within the vesicle are transferred to th late endosomes. Materials (and hydrolytic enzymes) are transferred from late endosomes to lysosomes by a number of routes Mannose 6-phosphate receptors (MPRs) carry lysosomal enzymes to late endosomes and are then shuttled back to the TGN for further transport duties. (*b,c*) Experimental demonstration of the movement of materials from early endosomes to late endosomes. The cell depicted in *b* had been incubated for

Endocytosis :

1)bulk-phase endocytosis :
non specific; occurs all the time – secretory cell membrane

2)receptor-mediated endocytosis : binding certain substance to the receptor in membrane plasma. : LDL, artery sclerosis



5.15 Endocytosis and Exocytosis Endocytosis and exocytosis are used by all eukaryotic cells to take up substances from and release substances to the outside environment.