Plasma Membrane

Ultra structure and composition of Plasma membrane

Like all other cellular membranes, the plasma membrane consists of both lipids and proteins.

The Lipid Bilayer

Phospholipids present in cells spontaneously form shee tlike phospholipid bilayers, which are two molecules thick. The hydrocarbon chains of the phospholipids in each layer, or leaflet, form a hydrophobic core that is 3–4 nm thick in most biomembranes. A cross section of all single membranes stained with osmium tetroxide looks like a railroad track: two thin dark lines (the stain– head group complexes) with a uniform light space of about 2 nm (the hydrophobic tails) between them. The lipid bilayer has two important properties. First, the hydrophobic core is an impermeable barrier that prevents the diffusion of water-soluble (hydrophilic) solutes across the membrane. The second property of the bilayer is its stability. The bilayer structure is maintained by hydrophobic and van der Waals interactions between the lipid chains.

A typical biomembrane is assembled from phosphoglycerides, sphingolipids, and steroids. All three classes of lipids are amphipathic molecules having a polar (hydrophilic) head group and hydrophobic tail. The hydrophobic effect and van der Waals interactions, cause the tail groups to self-associate into a bilayer with the polar head groups oriented toward water.

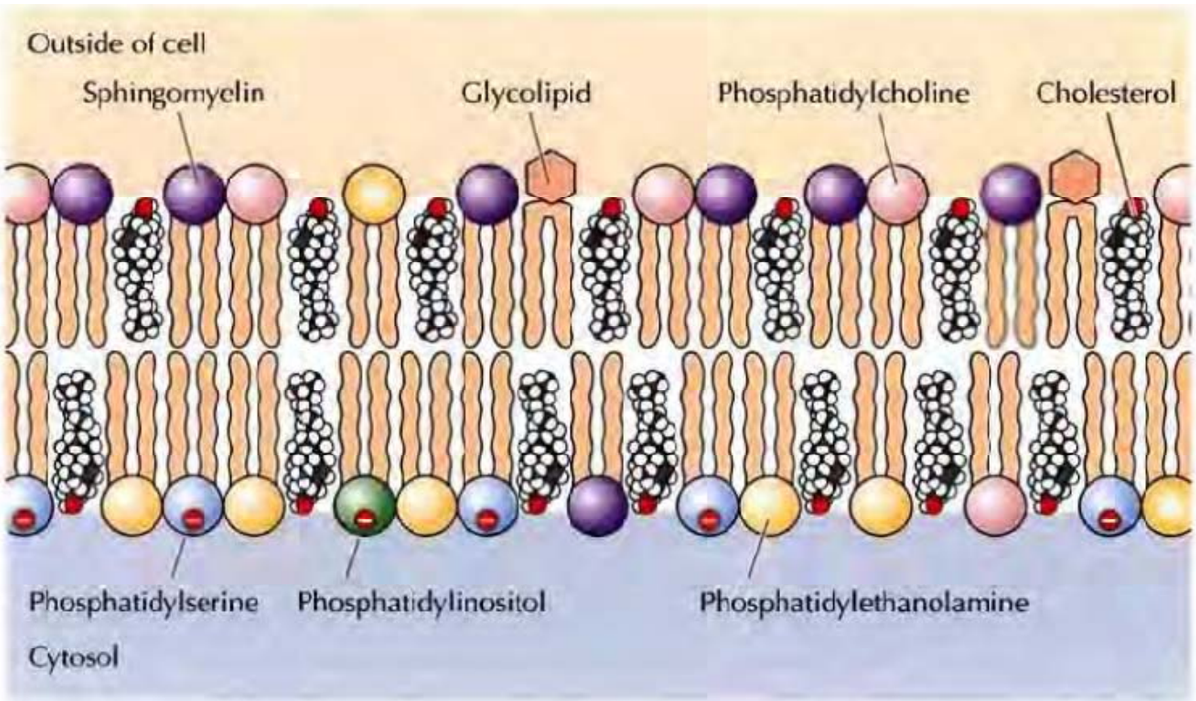

Figure.1. Lipid Components of the Plasma Membrane

Phosphoglycerides: The most abundant class of lipids in most membranes, are derivatives of glycerol 3-phosphate (Figure 1). A typical phosphoglyceride molecule consists of a hydrophobic tail composed of two fatty acyl chains esterified to the two hydroxyl groups in glycerol phosphate and a polar head group attached to the phosphate group. The two fatty acyl chains may differ in the number of carbons that they contain (commonly 16 or 18) and their degree of saturation (0, 1, or 2 double bonds). A phosphogyceride is classified according to the nature of its head group. In phosphatidylcholines, the most abundant phospholipids in the plasma membrane, the head group consists of choline, a positively charged alcohol, esterified to the negatively charged phosphate. In other phosphoglycerides, an OH-containing molecule such as ethanolamine, serine, and the sugar derivative inositol is linked to the phosphate group. The negatively charged phosphate group and the positively charged groups or the hydroxyl groups on the head group interact strongly with water.

The plasmalogens are a group of phosphoglycerides that contain one fatty acyl chain, attached to glycerol by an ester linkage, and one long hydrocarbon chain, attached to glycerol by an ether linkage (COOOC). These molecules constitute about 20 percent of the total phosphoglyceride content in humans. Their abundance varies among tissues and species but is especially high in human brain and heart tissue.

Sphingolipids: All of these compounds are derived from sphingosine, an amino alcohol with a long hydrocarbon chain, and contain a long-chain fatty acid attached to the sphingosine amino group. Sphingomyelin is the most abundant sphingolipid and its overall structure is quite similar to that of phosphatidylcholine. Other sphingolipids are amphipathic glycolipids whose polar head groups are sugars. Glucosylcerebroside, the simplest glycosphingolipid, contains a single glucose unit attached to sphingosine. Glycolipids constitute 2–10 percent of the total lipid in plasma membranes; they are most abundant in nervous tissue.

Cholesterol: Cholesterol and its derivatives constitute the third important class of membrane lipids, the steroids. The basic structure of steroids is a four-ring hydrocarbon. Cholesterol, the major steroidal constituent of animal tissues, has a hydroxyl substituent on one ring. Cholesterol is especially abundant in the plasma membranes of mammalian cells but is absent from most prokaryotic cells.

Membrane Proteins

While lipids are the fundamental structural elements of membranes, proteins are responsible for carrying out specific membrane functions. Most plasma membranes consist of approximately 50% lipid and 50% protein by weight, with the carbohydrate portions of glycolipids and glycoproteins constituting 5 to 10% of the membrane mass. There about one protein molecule

per every 50 to 100 molecules of lipid. In 1972 Jonathan Singer and Garth Nicolson proposed the fluid mosaic model (Figure 2) of membrane. In this model, membranes are viewed as two-dimensional fluids in which proteins are inserted into lipid bilayers. There are two classes of proteins, namely, peripheral and integral membrane proteins. Peripheral membrane proteins dissociate from the membrane following treatments with polar reagents, such as solutions of extreme pH or high salt concentration that do not disrupt the phospholipid bilayer. These proteins are not inserted into the hydrophobic interior of the lipid bilayer. Instead, they are indirectly associated with membranes through protein-protein interactions like include ionic bonds, which are disrupted by extreme pH or high salt.

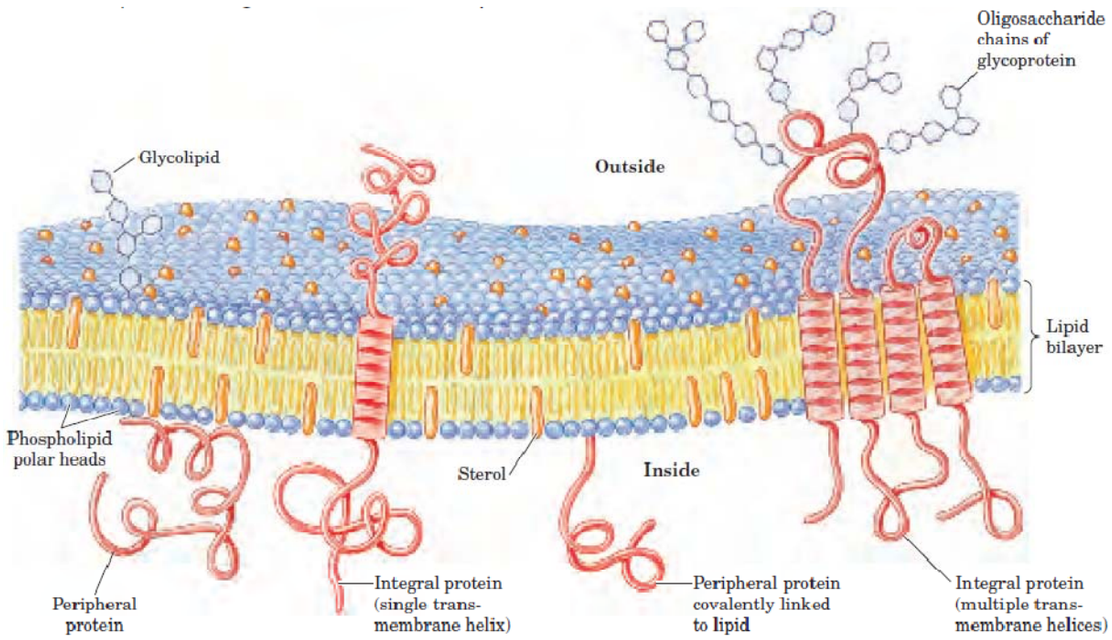

Figure.2. Fluid mosaic model of Plasma Membrane

Integral membrane proteins can be released only by treatments that disrupt the phospholipid bilayer. Portions of these integral membrane proteins are inserted into the lipid bilayer, so they can be dissociated only by reagents like detergent that disrupt hydrophobic interactions. Many integral proteins are transmembrane proteins, which span the lipid bilayer with portions exposed on both sides of the membrane. These proteins can be visualized in electron micrographs of plasma membranes prepared by the freeze-fracture technique. In these specimens, the membrane is split and separated into its two leaflets. The membrane-spanning portions of transmembrane proteins are usually *a*-helices of 20 to 25 hydrophobic amino acids that are inserted into the membrane of the endoplasmic reticulum during synthesis of the polypeptide chain. Carbohydrate groups are added to the polypeptide chains in both the endoplasmic reticulum and Golgi

apparatus, so most transmembrane proteins of the plasma membrane are glycoproteins with their oligosaccharides exposed on the surface of the cell.

Another third class of protein known as lipid-anchored membrane proteins are bound covalently to one or more lipid molecules. The hydrophobic carbon chain of the attached lipid is embedded in one leaflet of the membrane and anchors the protein to the membrane. The polypeptide chain itself does not enter the phospholipid bilayer (Figure 3).

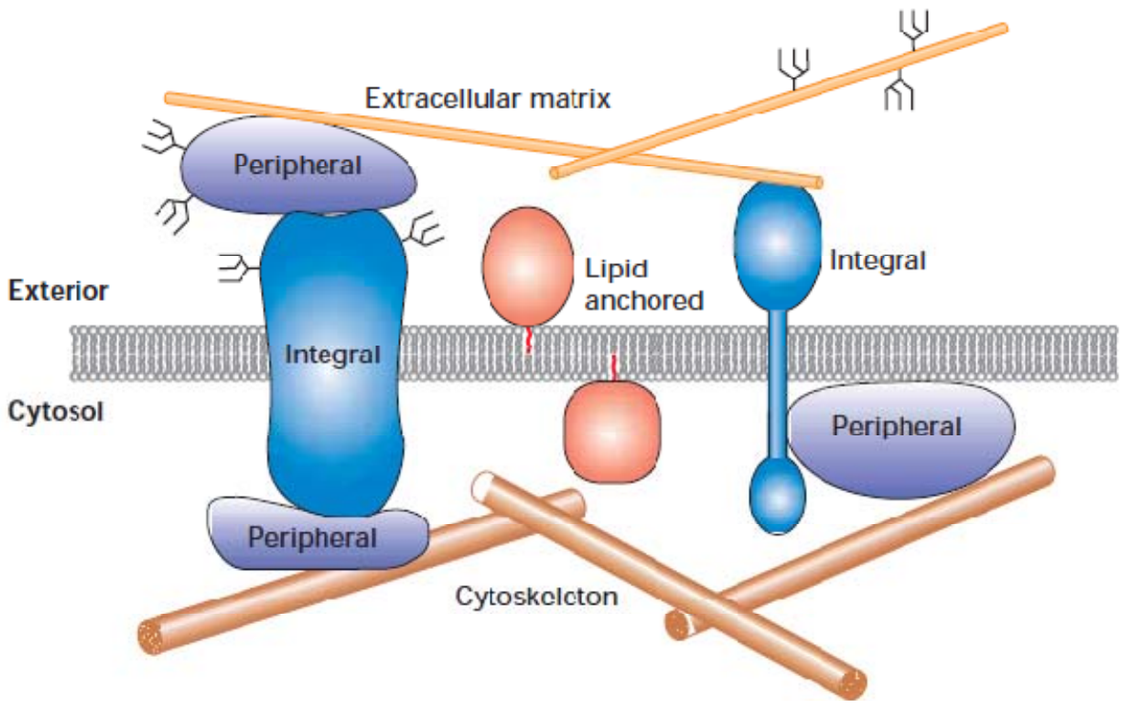

Figure.3. Various types of membrane proteins

In addition to these proteins, which are closely associated with the bilayer, cytoskeletal filaments are more loosely associated with the cytosolic face, usually through one or more peripheral (adapter) proteins. Such associations with the cytoskeleton provide support for various cellular membrane; they also play a role in the two-way communication between the cell interior and the cell exterior. Finally, peripheral proteins on the outer surface of the plasma membrane and the exoplasmic domains of integral membrane proteins are often attached to components of the extracellular matrix or to the cell wall surrounding bacterial and plant cells.

Transport across membrane

1. Passive Diffusion

The simplest mechanism by which molecules can cross the plasma membrane is passive diffusion. During passive diffusion, a molecule simply dissolves in the phospholipid bilayer, diffuses across it, and then dissolves in the aqueous solution at the other side of the membrane.

No membrane proteins are involved and the direction of transport is determined simply by the relative concentrations of the molecule inside and outside of the cell. The net flow of molecules is always down their concentration gradient-from a compartment with a high concentration to one with a lower concentration of the molecule.

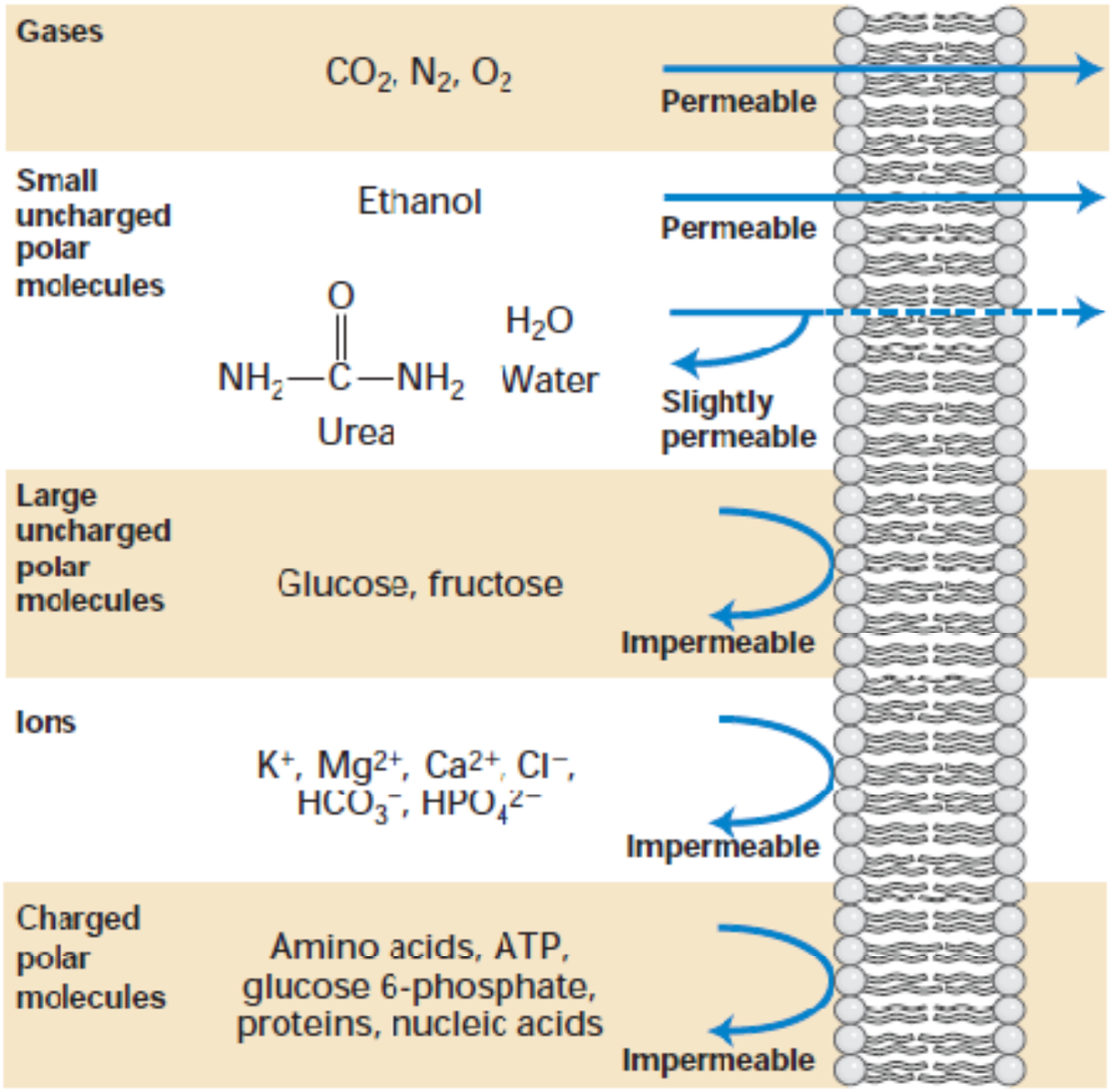

Figure.4. Relative permeability of a pure phospholipid bilayer to various molecules

Passive diffusion is thus a nonselective process by which any Leukocyte molecule able to dissolve in the phospholipid bilayer is able to cross the plasma membrane and equilibrate between the inside and outside of the cell. Importantly, only small, relatively hydrophobic molecules are able to diffuse across a phospholipid bilayer at significant rates (Figure 4). Thus gases (such as O_2 and CO_2), hydrophobic molecules (such as benzene), and small polar but uncharged molecules (such as H_2O and ethanol) are able to passively diffuse across the plasma membrane. Other biological molecules, however, are unable to dissolve in the hydrophobic

interior of the phospholipid bilayer. Consequently, larger uncharged polar molecules such as glucose are unable to cross the plasma membrane by passive diffusion, as are charged molecules of any size (including small ions such as H^+, Na^+, K^+, and Cl^-). The passage of these molecules across the membrane instead requires the activity of specific transport and channel proteins, which therefore control the traffic of most biological molecules into and out of the cell.

2. Facilitated transport or facilitated diffusion

Facilitated diffusion, like passive diffusion, involves the movement of molecules in the direction determined by their relative concentrations inside and outside of the cell. No external source of energy is provided, so molecules travel across the membrane in the direction determined by their concentration gradients and, in the case of charged molecules, by the electric potential across the membrane. However, facilitated diffusion differs from passive diffusion in that the transported molecules do not dissolve in the phospholipid bilayer. Instead, their passage is mediated by proteins that enable the transported molecules to cross the membrane without directly interacting with its hydrophobic interior. Facilitated diffusion therefore allows polar and charged molecules, such as carbohydrates, amino acids, nucleosides, and ions, to cross the plasma membrane.

Two classes of proteins that mediate facilitated diffusion have generally been distinguished: carrier proteins and channel proteins.

A) Carrier proteins

Carrier proteins bind specific molecules to be transported on one side of the membrane. They then undergo conformational changes that allow the molecule to pass through the membrane and be released on the other side. The type of carrier proteins involved in facilitated diffusion is uniporters which transport a single type of molecule down its concentration gradient. Carrier proteins are responsible for the facilitated diffusion of sugars, amino acids, and nucleosides across the plasma membranes of most cells. The glucose transporter provides a well-studied example of a carrier protein.

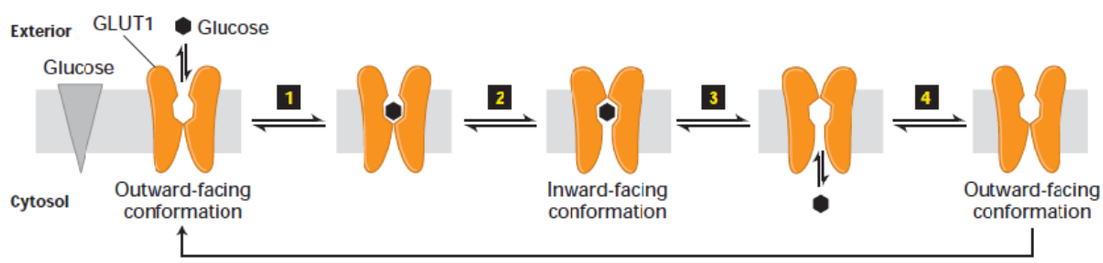

Figure. 5. Facilitated diffusion by uniporter GLUT1

Most mammalian cells use blood glucose as the major source of cellular energy and express GLUT1 Uniporter. Since the glucose concentration usually is higher in the extracellular medium (blood in the case of erythrocytes) than in the cell, GLUT1 generally catalyzes the net import of

glucose from the extracellular medium into the cell. Under this condition, Vmax is achieved at high external glucose concentrations. Like other uniporters, GLUT1 alternates between two conformational states. In one conformation, the glucose-binding site faces outward; in the other, the binding site faces inward. Binding of glucose to the outward-facing site (step 1) triggers a conformational change in the transporter as a result the binding site is now facing inward toward the cytosol (step 2). Glucose then is released to the inside of the cell (step 3). Finally, the transporter undergoes the reverse conformational change, regenerating the outward-facing binding site (step 4). If the concentration of glucose is higher inside the cell than outside, the cycle will work in reverse (step 4 n step 1), resulting in net movement of glucose from inside to out. The actual conformational changes are probably smaller than those depicted here. Figure 5 depicts the sequence of events occurring during the unidirectional transport of glucose from the cell exterior inward to the cytosol. GLUT1 also can catalyze the net export of glucose from the cytosol to the extracellular medium exterior when the glucose concentration is higher inside the cell than outside.

B) Channel proteins

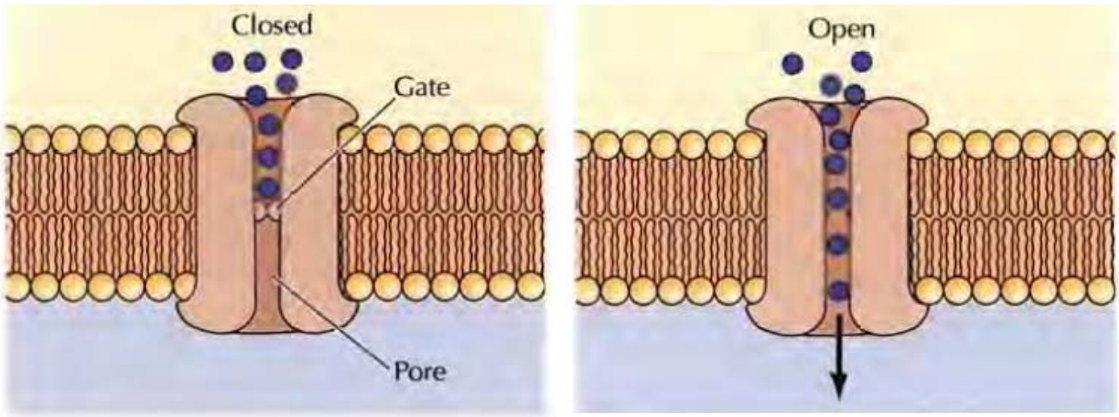

Figure.6. Model of an ion channel

In contrast to carrier proteins, channel proteins form open pores in the membrane, allowing small molecules of the appropriate size and charge to pass freely through the lipid bilayer. The best characterized channel proteins are the ion channels, which mediate the passage of ions across plasma membranes. Three properties of ion channels are central to their function (Figure 6). First, transport through channels is extremely rapid. More than a million ions per second flow through open channels- a flow rate approximately a thousand times greater than the rate of transport by carrier proteins. Second, ion channels are highly selective because narrow pores in the channel restrict passage to ions of the appropriate size and charge. Thus specific channel proteins allow the passage of Na^+, K^+, Ca^{2+} and CI^- across the membrane. Third, most ion channels are not permanently open. Instead, the opening of ion channels is regulated by "gates"

that transiently open in response to specific stimuli. Some channels (called ligand-gated channels) open in response to the binding of neurotransmitters or other signaling molecules; others (voltage-gated channels) open in response to changes in electric potential across the plasma membrane.

3. Active Transport

The net flow of molecules by facilitated diffusion, through either carrier proteins or channel proteins, is always energetically downhill in the direction determined by electrochemical gradients across the membrane. In many cases, however, the cell must transport molecules against their concentration gradients which accomplished by active transport. Active transport is thermodynamically unfavorable (endergonic) and takes place only when coupled (directly or indirectly) to an exergonic process such as the absorption of sunlight, an oxidation reaction, the breakdown of ATP, or the concomitant flow of some other chemical species down its electrochemical gradient.

A) Primary active transport

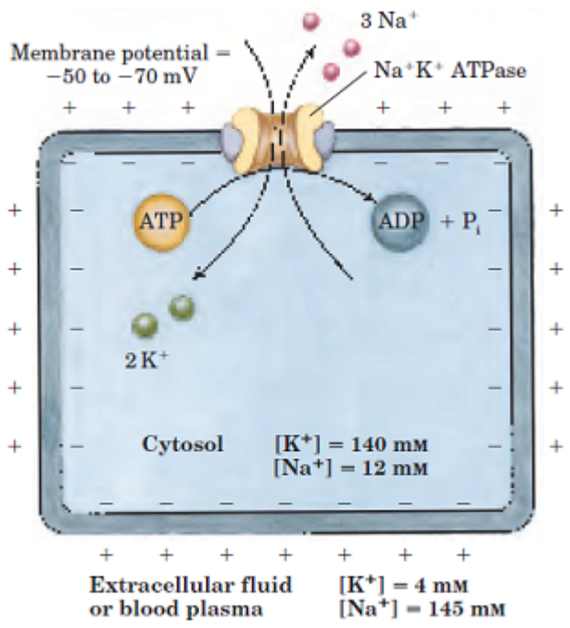

Figure.7. Na+ K+ ATPase

In primary active transport, solute accumulation is coupled directly to an exergonic chemical reaction, such as conversion of ATP to ADP+ Pi. The ion pumps responsible for maintaining gradients of ions across the plasma membrane provide important examples of active transport driven directly by ATP hydrolysis. The concentration of Na^+ is approximately ten times higher outside than inside of cells, whereas the concentration of K^+ is higher inside than out. These ion gradients are maintained by the Na^+- K^+ pump (also called the Na^+ K^+ ATPase) which uses energy derived from ATP hydrolysis to transport Na^+ and K^+ against their electrochemical

gradients. This process is a result of ATP-driven conformational changes in the pump (Figure 7). First, Na^+ ions bind to high-affinity sites inside the cell. This binding stimulates the hydrolysis of ATP and phosphorylation of the pump, inducing a conformational change that exposes the Na^+-binding sites to the outside of the cell and reduces their affinity for Na^+. Consequently, the bound Na^+ is released into the extracellular fluids. At the same time, high-affinity K^+ binding sites are exposed on the cell surface. The binding of extracellular K^+ to these sites then stimulates hydrolysis of the phosphate group bound to the pump, which induces a second conformational change, exposing the K^+ binding sites to the cytosol and lowering their binding affinity so that K^+ is released inside the cell. The pump has three binding sites for Na^+ and two for K^+, so each cycle transports three Na^+ and two K^+ ions across the plasma membrane at the expense of one molecule of ATP. The importance of the Na^+- K^+ pump is indicated by the fact that it is estimated to consume nearly 25% of the ATP utilized by many animal cells.

B) Secondary active transport and ion gradients

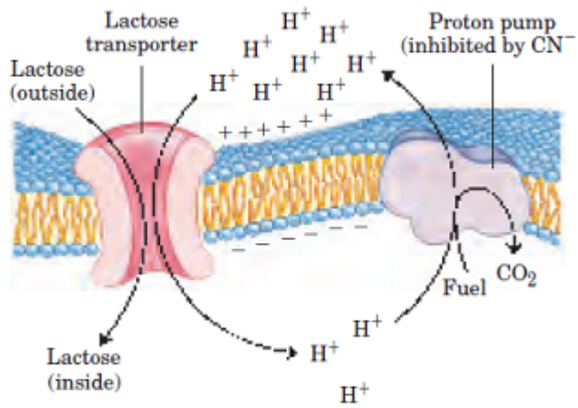

Figure.7. Lactose uptake in *E. coli*

The ion gradients formed by primary transport of Na+ or H+ can in turn provide the driving force for cotransport of other solutes. Many cell types contain transport cell, with the net accumulation of lactose (Figure 7). *E. coli* normally produces a gradient of protons and charge across its plasma membrane by oxidizing fuels and using the energy of oxidation to pump protons outward. The lipid bilayer is impermeable to protons, but the lactose transporter provides a route for proton reentry, and lactose is simultaneously carried into the cell by symport. The endergonic accumulation of lactose is thereby coupled to the exergonic flow of protons into the cell, with a negative overall free-energy change.

Tight junctions

Tight junctions are critically important to the function of epithelial cell sheets as barriers between fluid compartments. For example, the intestinal epithelium separates the Lumen of the

intestine from the underlying connective tissue, which contains blood capillaries. Tight junctions play two roles in allowing epithelia to fulfill such barrier functions. First, tight junctions form seals that prevent the free passage of molecules (including ions) between the cells of epithelial sheets. Second, tight junctions separate the apical and basolateral domains of the plasma membrane by preventing the free diffusion of lipids and membrane proteins between them. Consequently, specialized transport systems in the apical and basolateral domains are able to control the traffic of molecules between distinct extracellular compartments, such as the transport of glucose between the intestinal lumen and the blood supply. While tight junctions are very effective seals of the extracellular space, they provide minimal adhesive strength between the apposing cells, so they are usually associated with adherens junctions and desmosomes in a junctional complex.

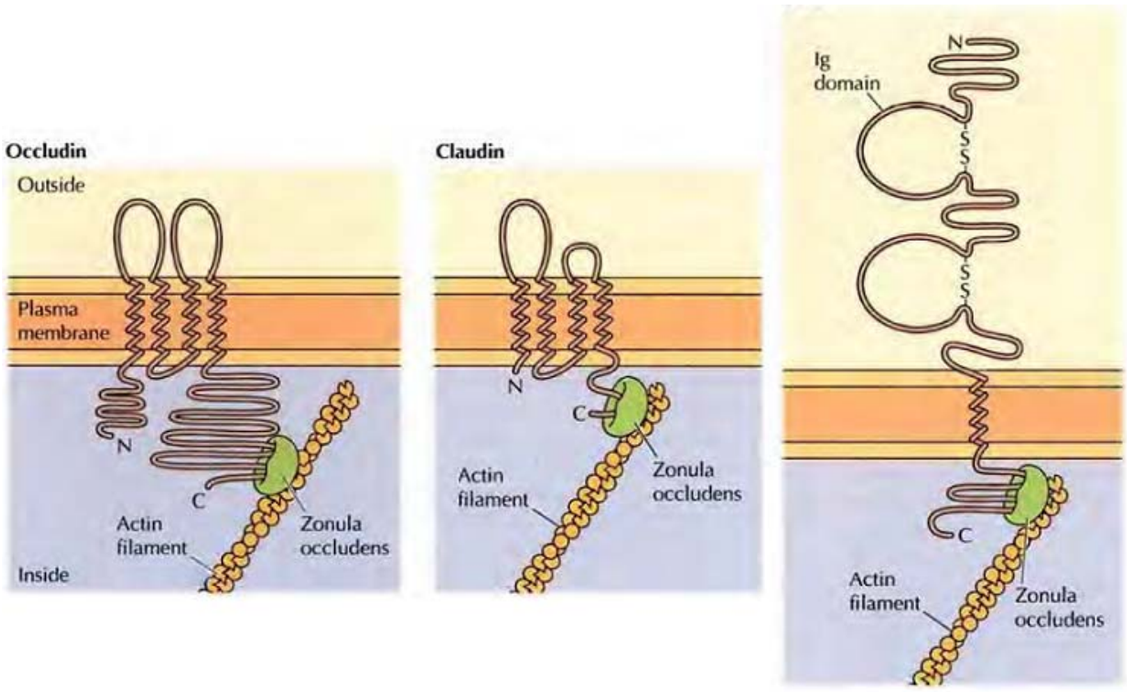

Figure.8. Tight Junction Proteins

Tight junctions are the closest known contacts between adjacent cells. They are formed by a network of protein strands that continues around the entire circumference of the cell. Each strand in these networks is composed of transmembrane proteins of the claudin, occludin, and junctional adhesion molecule (JAM) families. All three of these proteins bind to similar proteins on adjacent cells, thereby sealing the space between their plasma membranes. The cytosolic tails of claudins, occludins, and JAMs are also associated with proteins of the zonula occludens family, which link the tight junction complex to the actin cytoskeleton and hold the tight junction in place on the plasma membrane. Nectins may also be present in tight junctions but

their major role seems to be in recruiting claudins to initiate tight junction formation, analogous to their role in formation of adherens junctions (Figure 8).

Gap Junctions

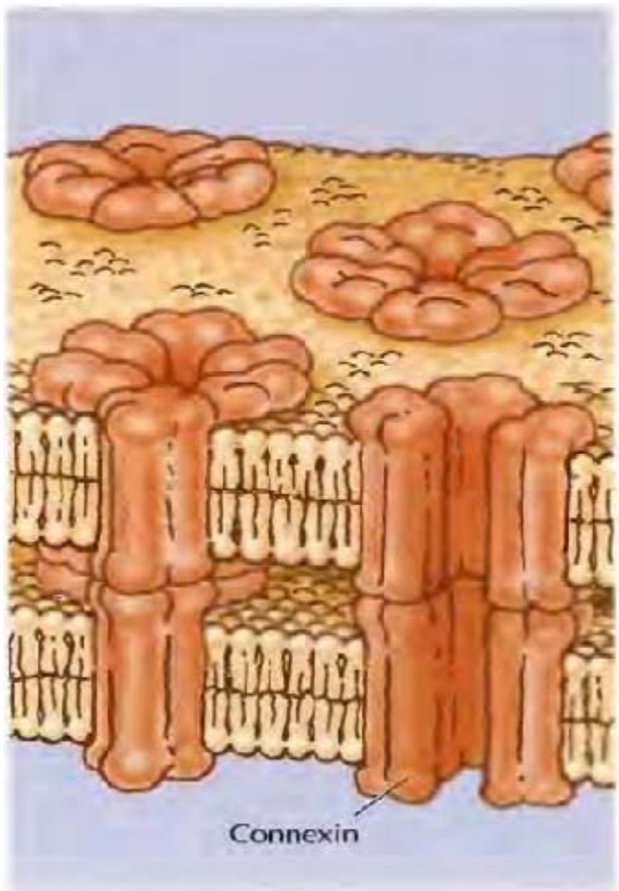

Figure. 9. Gap Junctions

The activities of individual cells in multicellular organisms need to be closely coordinated. This can be accomplished by signaling molecules that are released from one cell and act on another. However, within an individual tissue, such as the liver, cells are often linked by gap junctions, which provide direct connections between the cytoplasms of adjacent cells. Gap junctions are open channels through the plasma membrane, allowing ions and small molecules (less than approximately a thousand daltons) to diffuse freely between neighboring cells, but preventing the passage of proteins and nucleic acids. Consequently, gap junctions couple both the metabolic activities and the electric responses of the cells they connect. Most cells in animal tissues-including epithelial cells, endothelial cells, and the cells of cardiac and smooth muscle communicate by gap junctions. In electrically excitable cells, such as heart muscle cells, the direct passage of ions through gap junctions couples and synchronizes the contractions of neighboring cells. Gap junctions also allow the passage of some intracellular signaling

molecules, such as cAMP and $Ca^{2+,}$ between adjacent cells, potentially coordinating the responses of cells in tissues.

Gap junctions are constructed of transmembrane proteins of the connexin family, which consists of at least 21 different human proteins. Six connexins assemble to form a cylinder with an open aqueous pore in its center. Such an assembly of connexins, a connexon, in the plasma membrane of one cell then aligns with a connexon of an adjacent cell, forming an open channel between the two cytoplasms. The plasma membranes of the two cells are separated by a gap corresponding to the space occupied by the connexin extracellular domains-hence the term "gap junction," which was coined by electron microscopists. Many cells express more than one member of the connexin family, and combinations of different connexin proteins may give rise to gap junctions with varying properties (Figure 9).

Specialized assemblies of gap junctions occur on specific nerve cells in all eukaryotes and form an electrical synapse. The individual connexons within the electrical synapse can be opened or closed in response to several types of signals but, when open, allow the rapid passage of ions between the two nerve cells. The importance of gap junctions- especially in the nervous system- is illustrated by the number of human cliseases associated with connexon mutations.

Desmosomes

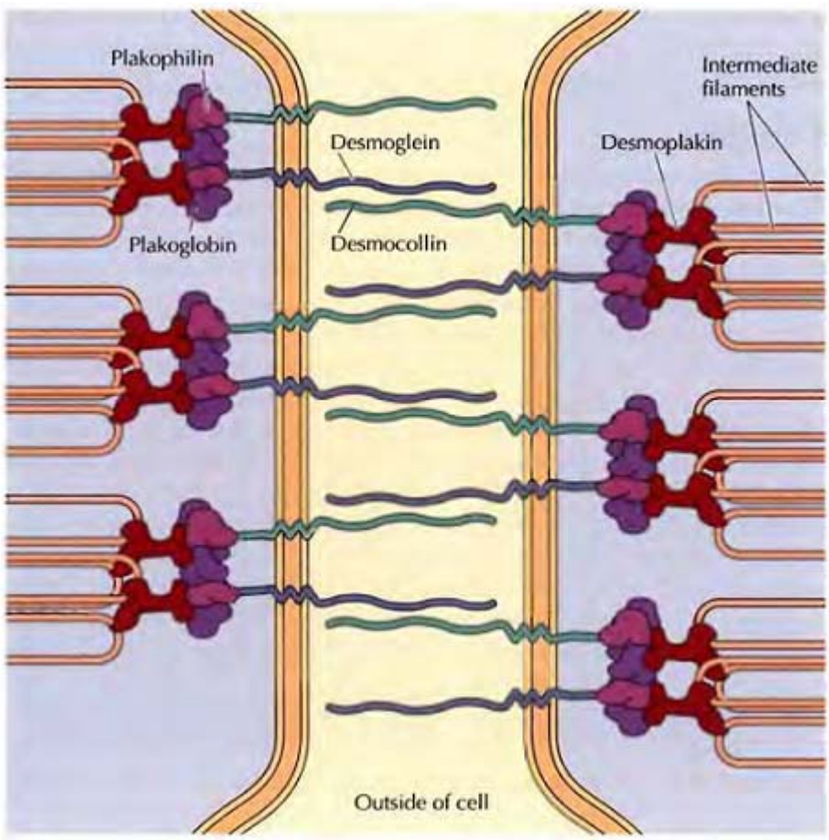

Figure.10. Desmosomes

Desmosomes directly link the intermediate filament cytoskeletons of adjacent cells (Figure). The transmembrane cadherins, desmoglein and desmocollin, bind by heterophilic interactions across the junction. The armadillo family proteins plakoglobin and plakophilin bind to the cytosolic tails of the cadherins and provide a direct link to the intermediate filament binding protein, desmoplakin. Desmoplakin is a member of the plakin family and is related to plectin, which functions analogously at hemidesmosomes. The strength of desmosomallinks between cells is a property of both the intermediate filaments to which they are attached and the multiple interactions between plakoglobin, plakophilin, and desmoplakin that link the intermediate filaments to the cadherins (Figure 10).