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Introduction to Physiology

Med I and Den I students 2023/2024
Outline for Cell Physiology and Transport through biological membranes.

Ref: **Textbook of Medical Physiology. Jordan Edition**, **By Guyton and Hall.**
Pp: 11-14, 47-59.

Plasma membrane as an organelle:

Lipids in plasma membrane:

The plasma membrane is a lipid bilayer in which proteins are impeded. The most abundant of these lipids are phospholipids (P-Choline and P-Ethanol-amine). The molecule of phospholipid has a polar electrical head containing negative charge of phosphate group oriented towards the periphery and two nonpolar fatty acid tails oriented toward the center of the lipid bilayer. The electrical properties of phospholipids permit self assembly in a bilayer structure when found themselves in hydrophilic medium. At the normal body temperature of 37 degrees C the membrane is in fluid state.

Membrane fluidity

The arrangement of the fatty acid tails in phospholipids plays a crucial role in determining the characteristics of the membrane, particularly its fluidity. More unsaturated fatty acids content give more fluidity to membrane and higher cholesterol content prevents extremes in fluidity of plasma membranes.

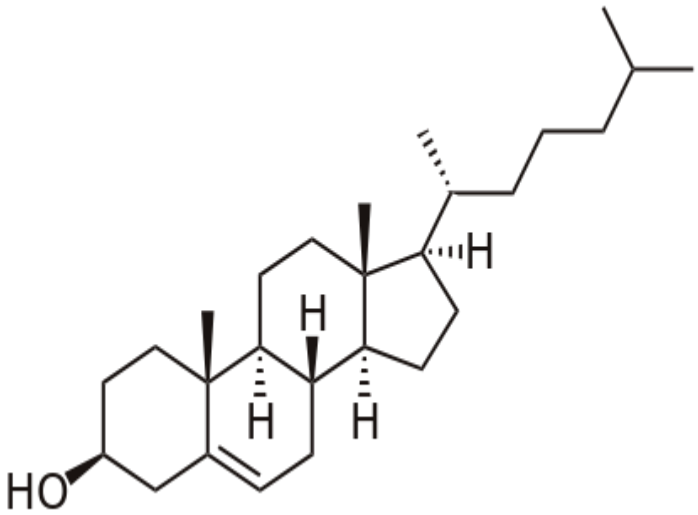
The saturated fatty acids lack double bonds and are therefore straight in shape. On the other hand, unsaturated fatty acids have one or more double bonds, resulting in a bent or kinked structure. The behavior of saturated and unsaturated fatty acid tails in phospholipids differs as the temperature decreases:

- At lower temperatures, the straight tails of saturated fatty acids can tightly pack together, creating a dense and relatively rigid membrane.

- In contrast, phospholipids with unsaturated fatty acid tails cannot pack as tightly due to the bent structure of the tails. As a result, a membrane composed of unsaturated phospholipids remains fluid at lower temperatures compared to one made up of saturated phospholipids.

Most cell membranes consist of a combination of phospholipids, some with two straight (saturated) tails and others with one straight and one bent (unsaturated) tail.

Animals possess an extra membrane constituent, apart from phospholipids, which aids in preserving fluidity. **Cholesterol**, a distinct lipid variety, is intricately interwoven within the phospholipids of the membrane, effectively reducing the impact of temperature fluctuations on fluidity.



The chemical structure of cholesterol is depicted in a diagram, showcasing three hexagonal shaped rings and one pentagon shaped ring. An OH group is connected to the first hexagonal ring, while a hydrocarbon chain is attached to the pentagon shaped ring.

Cholesterol plays a crucial role in regulating the fluidity of phospholipids within a membrane. At lower temperatures, it prevents the phospholipids from tightly packing together, thereby increasing fluidity. Conversely, at higher temperatures, cholesterol reduces fluidity, ensuring that the membrane maintains a functional and healthy level of fluidity. Ultimately, cholesterol broadens the temperature range at which the membrane can effectively function.

This lipid structure prevents water soluble molecules to pass through the bilayer, only lipid soluble substances can diffuse freely through the lipid membrane.

Proteins in plasma membrane:

Many protein structures are found at membrane. Most of these have also a carbohydrate moiety. Some of these proteins are penetrating the whole bilayer structure (integral proteins) others are found at one surface of the membrane (peripheral proteins).

The proteins which are impeded in the plasma membrane serve many functions that include:

- Some proteins that span the membrane form a water filled pathways (**Channels**) which enables water soluble substances to diffuse across the membrane through these structures. These channels are highly selective (Na+ can pass only through sodium channels and K+ can pass only through K+ channels). Not all the time the channel is opened. The activity of these channels is under controlling mechanisms that govern the channels activity. Some of these channels change their activity when the membrane potential is changed (voltage dependent (sensitive) channels). Other channels can open when a specific ligand binds to its receptor and causes opening of channel (chemical gated channels).
- Other proteins serve as **Carrier molecules** which help other molecules to cross biological membrane. These transport proteins are highly selective to substances. They bind to a substance and move it through the interstices to the other side of the membrane.
- Other proteins are **Receptors** for ligands found in the extracellular fluid. The binding of ligand to receptor will initiate cellular events that alter the activity of the cell. (an ex. Activation of Na+ channels in striated muscle after

binding of acetylcholine (Ach) to its receptor on the muscle membrane).

- Other proteins function as **membrane bound enzymes** which control enzymatic reactions either inside or outside the cell.
- Some proteins in the inner surface participate with cytoskeletal proteins to maintain cell shape.
- Some proteins in the outer surface participate with **Carbohydrates** to form adhesion molecules between the cells in tissue structure known as **C**ell **A**dhesion **M**olecules (CAMs). One example of these molecules is cadherin. In addition to the cohesion provided by CAMs and extracellular matrix, some cells are directly linked by specialized junctions. Such as desmosomes (adhering junction), tight junction (impermeable junction), and gap junction (communicating junction).

At the ***adhering junction*** (**desmosome**), filaments of unknown composition extend between the plasma membranes of two closely adjacent cells anchoring them together by maintaining a distance of about 20 nm between the two plasma membranes.

The ***impermeable junction*** (**tight**) is found between epithelial cells, which are joined together to form a sheet, which serve as high selective barrier that separates 2 different compartments. For ex. Epithelial cells that line the digestive tract separate the internal environment from the content of the hollow organs of the digestive system. Cells are held together by tight junctions, which form a tight belt around each cell and prevent passage of any substance between the cells.

The ***communication junctions*** (**gap**) between the cells form small tunnels between adjacent cells which enable neighboring cell to communicate with each other. This tunnel is composed of protein known as connexons. These connexons extend outward from the plasma membrane to join other connexon from the adjacent cell. The tunnel permits small water soluble particles to pass between the connected cells. An example of this type of junction is found in the heart and between smooth muscle cells. This form of communication between neighboring cells has an importance in spreading the electrical activity

(action potential) to adjacent cells and these cells are forming together a functional syncytium. This sort of communication enables synchronizing heart and smooth muscle activity.

Membranes and Transport:

Modalities of transport:

DIFFUSION:

Generally, dissolved particles found in solution are in constant movement. This random motion is due to thermal energy in particles that found themselves at a temperature above the absolute zero (in living systems about 310 degrees K). The random motion in liquids and gases will result in a random collision of particles with each other and with the wall. These haphazard collisions will cause a transfer of kinetic energy from one particle to another and change in the direction of motion. This continuous movement in liquids and gases is known as ***diffusion***.

Diffusion through biological membranes:

Particles can move across biological membrane by diffusion. This type of transport does **not** need consumption of energetic compounds (ATP). It is passive. Because of the lipid constituents of the membrane, only lipid soluble substances can diffuse through the lipid structures. Their diffusion depends on the solubility of particles in the lipid bilayer. Example: O2, CO2, NO and lipid particles can diffuse through the lipid structures.

While water soluble particles cannot pass the bilayer. But, they can be transported across membrane through protein channels. This type of transport is can also be characterized as ***simple diffusion (in some literature is considered as FACILITATD DIFFUSION*** by considering have a protein structure (channel) helped these particles to move across membrane. Also, there are some particles can NOT diffuse through membrane only with the help of a protein structures known as **carriers**. This type of diffusion of particles is known as **facilitated diffusion**.

Factors that influence simple diffusion:

- *Concentration*: More concentration of a substance means more kinetic energy in particles in a given compartment.

Movement of particles across membranes depends on the ***concentration of substances***. Less particles from compartment B where are found in a lower concentration will move to compartment A where are found in a higher concentration.

The Net rate of diffusion (Q) of particles is (diffusion rate from A to B (-) diffusion rate from B to A). One of the factors that influence the rate of net diffusion is *concentration gradient* ($\Delta C = C_A - C_B$), which represents the **Chemical Potential** for movement of particles across membranes.

In addition to concentration gradient, net rate of diffusion (Q) depends also on:

- ***Permeability*** of the membrane to a given substance (P): the higher the permeability for a substance the greater the diffusion rate is through membrane.

- ***Surface area*** of transport (A): diffusion increases by increasing (A). The increase in surface area in biological membranes will result in more protein channels that can be used for diffusion from one compartment to another.

- ***Molecular weight*** (MW): lighter molecules move more quickly than heavier.

-***Membrane thickness*** (X) (distance of movement): the greater the distance the slower the rate of diffusion.

All these factors form the Ficks' law of diffusion:

$J = P.\Delta C$…….(J = Flux, P=Permeability,
ΔC = Concentration gradient)

$P = D.A/\Delta X$ ……. (, A: surface Area, ΔX = membrane Thickness)

$J = D.A.\Delta C/\Delta X$…… (D=Diffusion Coefficient)

In addition to all these factors, diffusion can also be influenced by:

- ***Effect of membrane electrical potential***: mainly influences electrically charged particles.

The presence of a negative potential inside the cell prevents movement of negative (-) charged particles from the extracellular compartment to the intracellular compartment and the positive charged particles from the intracellular to the extracellular compartment.

So, movement of charged particles is governed by an **electro-chemical potential**. This will be discussed in more details later.

- ***Effect of pressure***:

The presence of pressure difference between two compartments

will cause more kinetic energy in particles in the compartment with higher pressure. This will cause movement of more particles from the high pressure side to the low pressure side.

* Factors that influence facilitated diffusion:

This carrier mediated transport also depends on *concentration gradient* of transported substance, with the difference that the rate of transport approaches a maximum called V_{max} . The increase in the rate of net diffusion in simple diffusion is proportional with the ΔC, while in facilitated diffusion when V_{max} is approached no more increase in diffusion will be by increasing ΔC. The limitation is due to the presence of limited number of *carrier molecules* at the membrane.

OSMOSIS:

Not only the particles of solute are transported across membranes, but also water can move across membranes. Under normal circumstances the **net** movement of water across plasma membrane is zero. This keeps the cell volume constant. Under the condition that membrane is NOT permeable to solute particles and there is a concentration difference of particles between the two sides of a membrane. Water can move from the compartment of higher concentration of water (low solute concentration) to the compartment of lower water concentration (high solute concentration). This movement of water is known as **osmosis**.

If a pressure is applied to the side where the concentration of solute is high, this will reduce, stop movement of water molecules to that side. The amount of pressure needed to stop osmosis is known as **osmotic pressure** of that solution.

The osmotic pressure of a solution depends on the concentration of particles in that solution (osmolar concentration). So, one mole of NaCl solution will dissociate in solution to Na+ and Cl- and will have twice osmotic pressure (2 osmolar concentration) as one mole of glucose (one osmolar concentration).

Osmolality = number of osmoles per kg water

Osmolarity = number of osmoles per liter of solution

Tonicity of solution: is osmolarity with regard to the osmolarity of plasma (300 mosmoles). (hypertonic solution has osmolarity higher than plasma. Hypotonic solution has osmolarity lower than plasma. In Isotonic solution, the osmolarity is equal to that of plasma)

ACTIVE TRANSPORT:

As and example: Cells keep more K+ inside. The simple diffusion will cause K+ to move out of the cell. To maintain a constant and high

K+ concentration inside the cell, K+ must be transported inside by other type of transport that can move K+ against a concentration gradient. Movement of particles against their concentration, electrical or pressure gradient is known as active transport. In this type of transport energetic compounds (ATP) are needed. The need for ATP could be by direct breakdown of energetic compounds by the ATP-ase activity of the carrier in ***Primary Active Transport***, or by an indirect use of ATP as in ***Secondary Active Transport***. All active transport systems are equipped with carrier proteins that move transported substances across membranes.

- PRIMARY ACTIVE TRANSPORT:

Examples of Primary active transport:

Na+ - K+ pump: This pump is able to expel 3 molecules of Na+ outside the cell and transport 2 K+ inside by a use of 1 ATP molecule. The carrier protein of this pump has 3 receptive sites for Na+ and 2 receptive sites for K+. Binding of 3 Na+ to the carrier protein in the inside and 2 K+ at the outside will cause activation of ATP-ase that split ATP into ADP and P. The liberated energy will cause conformational change in the carrier protein which results in extruding the 3 Na+ to the outside and transport of 2 K+ to the inside.

The importance of this pump is to maintain concentration difference of Na+ and K+ across plasma and helps in the *regulation of cell volume* by controlling concentration of solutes inside the cell. The presence of high concentration of negatively charged proteins inside tends to attract positive ions. These particles tend to cause osmosis of water to the interior of the cell. If this is not controlled, the cells will swell until they burst. The presence of the pump that expels 3 particles outside for 2 transported inside represents a net loss of ions out of the cell, which controls water osmosis to the cell. In addition to that cell membrane is less permeable to Na+ than K+, which gives Na+ more tendency to remain outside the cell and reduce water osmosis.

By expelling 3 positive ions for 2 transported inside, this pump will create positivity outside the cell and leaving deficit of positive ions inside of about. This *electrogenic* nature of the pump will create a potential difference of about (- 4mv) (if works alone) between the inside and the outside.

Ca++ pump: cells maintain very low Ca++ concentration in their cytosol (10,000 times less of the concentration in ECF). The low Ca++ concentration is maintained by activity of two types of Ca++ pumps. One is found at plasma membrane and expels Ca++ to the ECF. The other is found on membranes of internal vesicular organelles such as sarcoplasmic reticular of muscle cells and mitochondria of most cells. By

reducing Ca++ ions in the sarcoplasm (cytoplasm of muscle cells) by Ca++ pumps this will induce relaxation of muscle cells.

H+ pump: Some cells are specialized in expelling H+, such as parietal cells of gastric mucosa, intercalated cells of the distal tubules and cortical collecting ducts in the kidney. The presence of H+ pumps at the lumenal side of plasma membrane in the gastric mucosa is responsible for decreasing the pH of gastric juice. While H+ of the lower parts of the nephron are responsible for controlling H+ concentration in the body.

- SECONDARY ACTIVE TRANSPORT:

The high Na+ concentration gradient between the cytosol and the extracellular fluid is maintained by the activity of Na+ - K+ ATP-ase pump. Cells are profiting from the tendency of Na+ to diffuse inside the cells and transport other molecules against their concentration gradient along with Na+ in case of secondary active **co-transport** or expelling other particles against their concentration gradient in exchange as in case of secondary active **counter-transport**. In this kind of transport cells are using ATP, but this use is to create a concentration gradient for Na+ (by the activity of Na+ - K+ pump). Then cells can use this concentration gradient to transport certain particles against their concentration gradient across membranes. The use of ATP is NOT direct as in pumps (it's indirect use).

Examples of **co-transport**:

Glucose and aminoacids are transported in the enterocytes (intestinal epithelial cells) during absorption by this mean of secondary active transport. The presence of low Na+ inside the enterocytes by the activity of Na+ - K+ pump at the basolateral membrane will create a driving force for movement of Na+ from intestinal lumen. Carriers at the lumenal membrane will not transport Na+ but only with a particle of glucose or aminoacid. Depends on the type of carrier, many protein carriers have been identified. For aa transport at least 5 types of carriers have been identified. As a result of this transport aminoacids and glucose are transported along with Na+ from the intestinal lumen and these carriers are specific.

Other ions can also be transported by co-transport system, such as Fe++, Cl-, iodine and urate.

Examples of **counter-transport**:

Transport of Ca++ by secondary active transport:

In addition to its active transport by Ca++ pumps, Ca++ can also bind to specialized carrier that can move Na+ inside the cell in exchange with Ca++. This kind of transport is found in most cells including heart muscle.

Transport of H+ by secondary active transport: This kind occurs in proximal tubules where Na+ moves from the lumen to the tubular cells in exchange for H+ which is counter-transported into the lumen.

Other Modalities of Transport:

VESICULAR TRANSPORT:

Large particles can NOT pass membranes. But these particles are packaged and enclosed into vesicles by certain organelles, then these vesicles can fuse with the plasma membrane in case of transport from the intracellular to the extracellular compartment or engulfed into vesicles at plasma membrane, then transported inside. In the second case plasma membrane surround the substance that would be ingested by the cell then pinch off with the engulfed materials and form a vesicle. This mechanism is known as **endocytosis**. Vesicular transport can appear between plasma membrane and the membranes of organelles (such as lysosomes, Endoplasmic reticulum, etc) or between the membranes of organelles. When vesicles are transported through the whole cytoplasm (from one pole to the other pole of plasma membrane) the process is known as (**transcytosis**). If only fluids are transported by vesicular transport from the extracellular compartment, the process is called **pinocytosis.** When large and multimolecular particles are transported by endocytosis, the process is called **phagocytosis**.

The opposite of endocytosis is **exocytosis**. Large synthesized molecules such as enzymes, hormones, neurotransmitters are packaged into vesicles and transported toward plasma membrane. When these vesicles fuse with plasma membrane, their content is released into extracellular fluid. By vesicular transport not only secretory particles are transported toward plasma membrane, but also specific components of the membrane such as channels, receptors, and carriers are added to membrane by fusion of vesicles with plasma membrane.

The release of vesicular content appears to be stimulated event in secretory cells. When the cell is triggered by stimulus, Ca++ increases inside the cytosol, which results in fusion of vesicles and secretion. An example of exocytosis is the release of neurotransmitter at neuromuscular junction. This release of transmitter from the nerve endings appears via Ca++ induced exocytosis.

Intercellular communication and signal transduction mechanisms:

The coordination of cellular activities is critical for maintaining homeostasis and survival of living system as well as control of growth and development of the body as a whole. In addition to cellular communication between cells by gap junctions, control systems that are found in the body, such as endocrine system, nervous system, and paracrine cells release particles (ligands) that can bind to specific receptor at the target cell and change its activity.

Cellular events after ligand binding to receptor:

1. Activation of channels:
   When ligand binds to its receptor this activates membrane bound intermediary protein known as G protein (a protein composed of many subunits). The activation of G protein will induce opening of specific channel such as *chemical gated Na+ channels*. The opening of Na+ or K+ will change the potential difference across membrane, which in turn may cause activation (opening) of other type of channels known as voltage sensitive channels such as opening of *voltage gated Na+ channels or voltage gated Ca++ channels*.

2. Activation of second messenger system:
   Binding of specific ligand to its receptor may result in activation of second messenger that relays order through a series of biochemical events to induce changes in cell activity such as metabolic, secretory, or contractile responses according to cellular function.

c-AMP as second messenger:

Binding of ligand will induce activation of G protein freeing the α subunit of G protein which activates a membrane bound enzyme known as *adenylyl cyclase*. This enzyme converts **ATP** to **c-AMP**. The formed second messenger will activate *c-AMP dependent protein kinase* which phosphorylates particular protein which in turn bring responses inside cell. The process is

amplified inside the cell. Activation of one receptor may result in millions of end products of activated protein kinase enzyme.

Ca++ as second messenger:

Some G proteins activate other type of enzyme. In this pathway *phospholipase C* is activated. This enzyme breaks down **phosphatidyl inositol biphosphate** (PIP2)
(a phospholipid molecule that is anchored to the inner side of plasma membrane). The products of PIP2 breakdown are **diacylglycerol** (DAG) and **inositol triphosphate** (IP3). The IP3 induces release of **Ca++** from endoplasmic reticulum into the cytosol of the cell. Ca++ binds to and activates a protein called calmodulin. The activation of calmodulin triggers Ca++ dependent cellular responses by altering activity of other functional proteins inside target cells.