

Faculty of Medicine 2012

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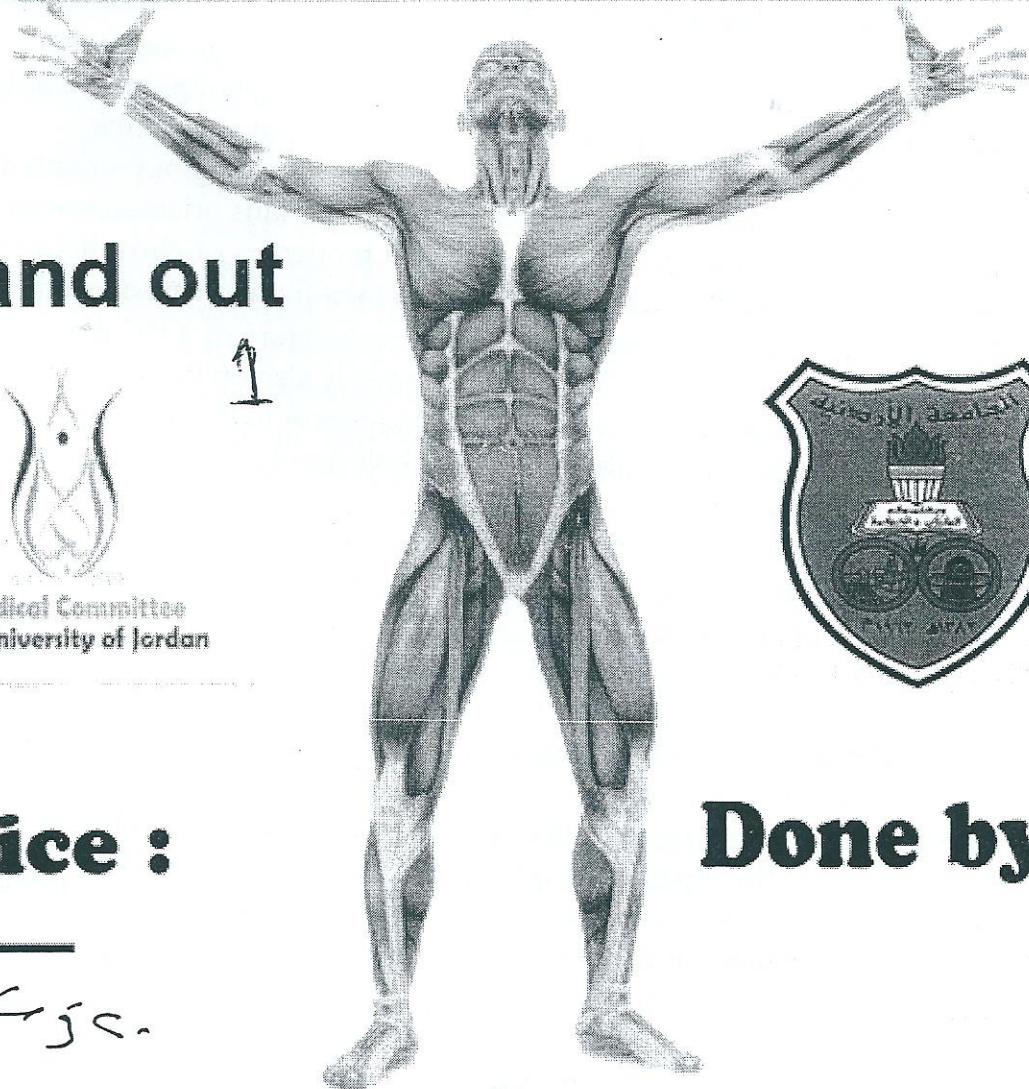
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University of Jordan
Faculty of Medicine
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Medical students, First year 2012/2013
Outline for Cell Membrane and Transport through biological membranes.

Cell Membrane & transport through biological membranes:

Ref.: **Textbook of Medical Physiology**. 12th. Ed. By, Guyton and Hall.

Plasma membrane:

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°C the membrane is in fluid state. The fluidity depends also on the saturation of fatty acid tails and the concentration of cholesterol in the membrane. More unsaturated fatty acids and higher cholesterol content give more fluidity in the membrane.

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:

The protein which is impeded in the plasma membrane serves 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 in the extracellular fluid. The binding of ligand to receptor will initiate cellular events that alter the activity of the cell. 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 Cell Adhesion Molecules (CAMs). One example of these molecules is cadherins. 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 junction (**gap**) between the cells forms 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. ex. this type of junction found in the heart and between smooth muscle cells has an importance in spreading of electrical activity (action potential) to adjacent cells that form together a functional syncytium. This enables synchronizing heart and smooth muscle activity.

Membranes and Transport: (p45-56)

Modalities of transport:

DIFFUSION:

Particle dissolved 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. 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, and NO can diffuse through the lipid structures.

While water soluble particles cannot pass the bilayer. They are transported through protein pore channels. This type of transport is known as *simple diffusion*. Some substances can not diffuse through these channels and can diffuse with the help of proteins known as carriers. This type of diffusion of particles is known as **facilitated diffusion**.

Factors that influence simple diffusion:

-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 diffusion of particles is movement from A to B. One of the factors that influence the rate of net diffusion is *concentration gradient* ($\Delta C = C_A - C_B$), which form 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 substance (P): the higher the permeability for a substance the greater the diffusion 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.

Note: diffusion of **ions** depends also on *membrane electrical potential*:

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*.

Effects 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 or reverse 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 is determined by the number of particles in that solution. So, one mole of NaCl solution will have twice osmotic pressure (2 osmolar concentration) as one mole of glucose (one osmolar concentration). The number of particles in solution of 1 mole of glucose is half the number of particles of dissolved one mole of NaCl.

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 = osmolarity lower than plasma. Isotonic = osmolarity of plasma)

ACTIVE TRANSPORT:

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, which can move K^+ against a concentration gradient. Movement of particles against 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 in case of *primary active transport*. Or by an indirect use of ATP 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^+ 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 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 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 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 more positive potential outside the cell and leaving deficit of positive ions inside. This *electrogenic* nature of the pump will create a potential difference 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 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 and intercalated cells of the distal tubules and cortical collecting ducts in the kidney. The presence of H^+ pumps at the luminal 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 $\text{Na}^+ - \text{K}^+$ ATP-ase pump. Cells are profiting from the tendency of Na^+ to diffuse inside the cells to transport other molecules along with Na^+ in case of secondary active **co-transport** or expelling other particles in exchange 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^+ . Then cells can use this concentration gradient to transport particles 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 transport. The presence of low Na^+ inside the enterocytes by the activity of Na^+ pump at the basolateral membrane will create a driving force for movement of Na^+ from intestinal lumen. Carriers at the luminal 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.

Other ions can also be transported by co-transport system, such as Fe^{++} , iodine, Cl^- , 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 are transported between the intracellular and extracellular fluid not by passing the membrane but enclosed into vesicles that can fuse with membrane in case of transport from the intracellular to the extracellular compartment or engulfed into vesicles of a plasma membrane which transport particles 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 that is transported to the other pole of the cell membrane and expel the content into the extracellular fluid (**transcytosis**) or to lysosomes where they fuse with lysosomal membrane and the content of vesicles is now mixed with the content of lysosomes. This transport from outside into the cell is known as **endocytosis**. If the vesicle contains only fluids, this 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 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 binding of ligand to its receptor:

1. Activation of channels:

When ligand binds to its receptor this activates membrane bound intermediary protein known as G protein. The activation of G protein will induce activation of specific channel such as chemical gated Na^+ channels. The activation of Na^+ or K^+ will change the potential difference across membrane, which in turn may activate other type of channels known as voltage sensitive channels such as opening of Ca^{++} channels.

2. Activation of second messenger system:

Binding of a 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 binds to 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 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 where it 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.