Transport across the cell membrane

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PROGRAMME OUTCOMES

- PO1- Demonstrate comprehensive knowledge and application of the Trisutra concept to explore root causes, identify clinical manifestations of disease to treat ailments and maintain healthy status.
- PO2- Demonstrate knowledge and skills in Ayurveda, acquired through integration of multidisciplinary perspectives and keen observation of clinical and practical experiences.

COURSE OUTCOMES

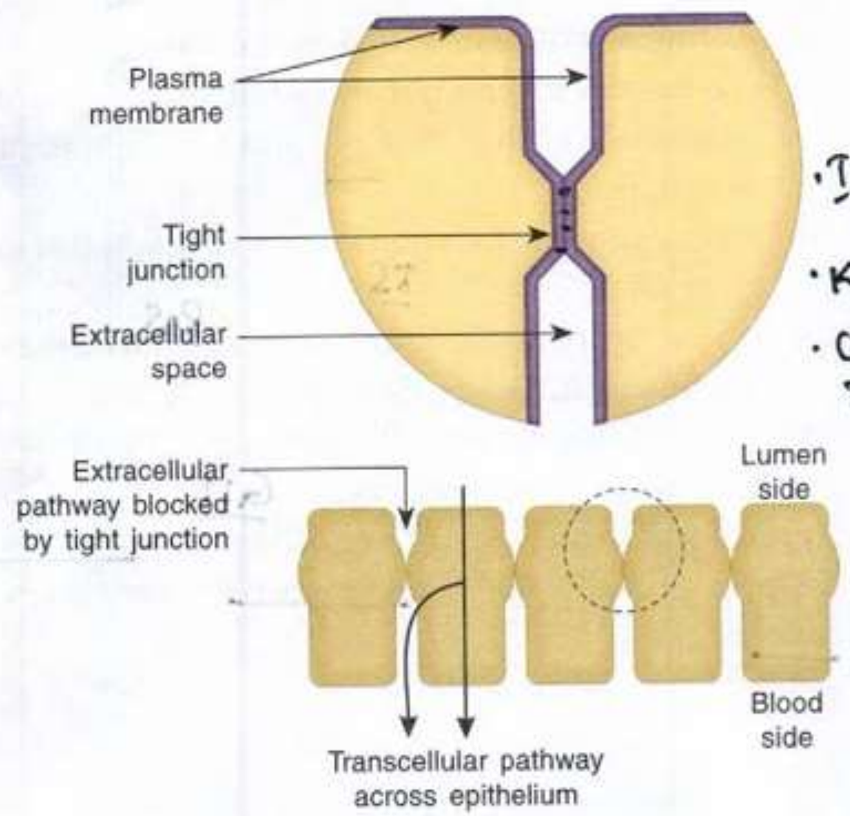
- CO1- Explain all basic principles & concepts of Kriya Sharir along with essentials of contemporary human physiology and biochemistry related to all organ systems.

- **Teaching learning methods-** lecture with power point presentation
  Domain- Cognitive/comprehension
  Must to know / desirable to know / Nice to know- Nice to know
  Millers pyramid- Knows how(applied knowledge)
  Bloom taxonomy- Understand

- **JUNCTIONAL COMPLEXES: CELL JUNCTIONS**
- The cells are associated into tissues by various means :

A. Tight Junction: In this, membranes of two cells become opposed and outer layers of the membranes fuse strongly, thus obliterating the space between the cells.

- This type of junction is characteristically seen along the apical margins of cells in epithelium such as the intestinal mucosa, the walls of the renal tubules, and the choroid plexus.
- Tight junction forms a barrier to the movement of ions and other solutes from one side of the epithelium to the other.

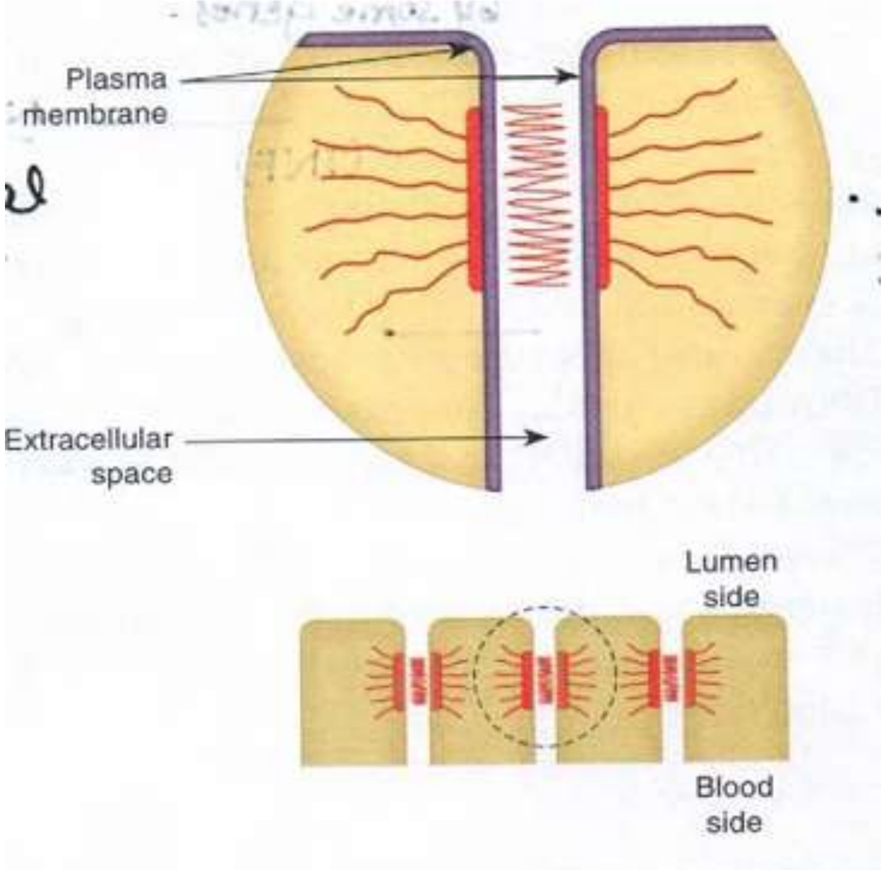


(A) Tight junction

- Intestinal mucosa
- Kidney
- Choroid plexus

B. Desmosomes or Adherens Junction: Here two membranes are separated by a 150-350 A^0 (15-20 nm) space.

- There is dense accumulation of proteins on both the surfaces of the membrane with fibers extending from the cytoplasmic surface of each membrane into the cell.
- This holds adjacent cells firmly together in areas that are subjected· to stretching, such as the skin.

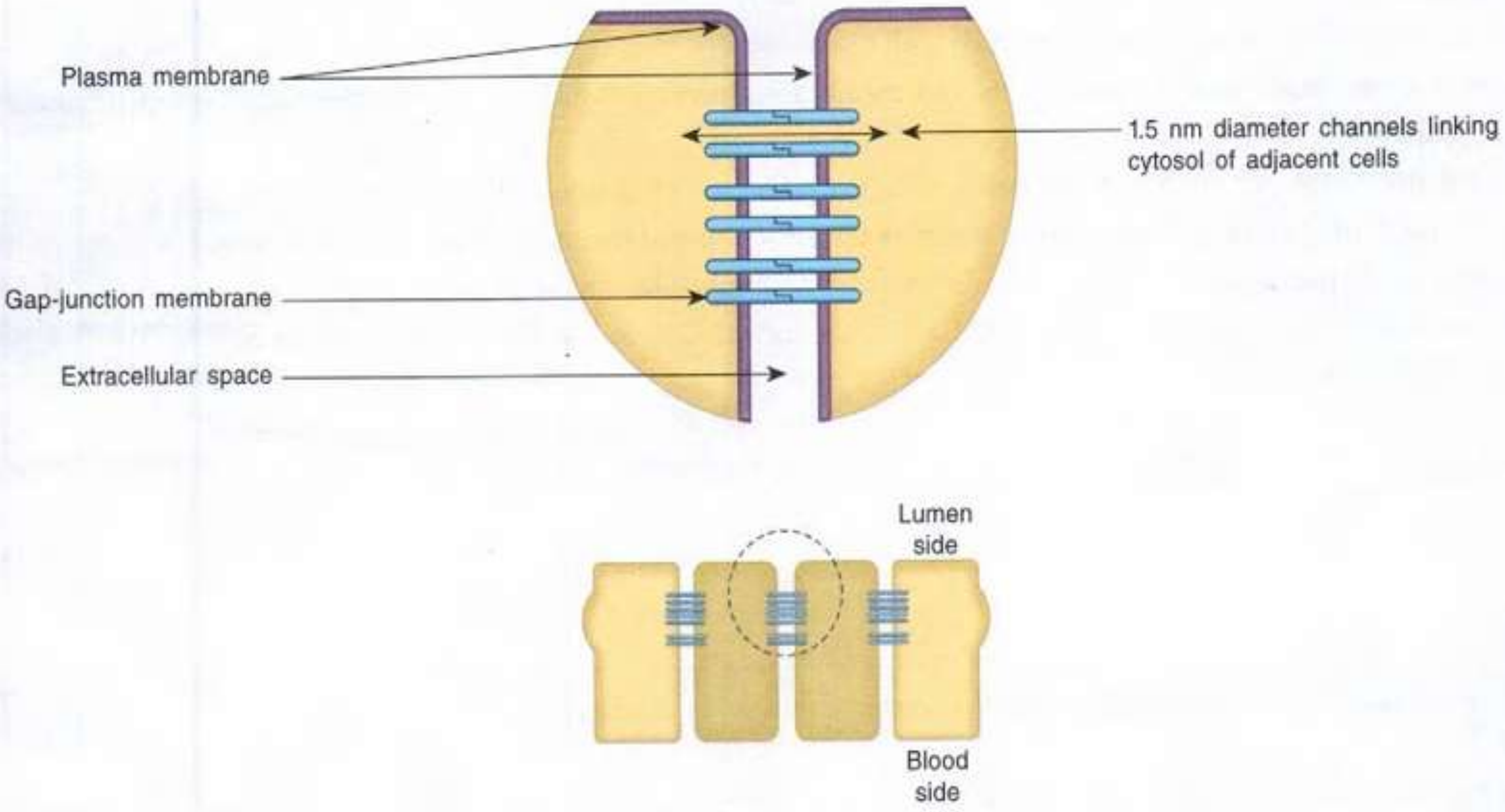


(B) Desmosome or Adherens junction

- **C. Gap Junction or Nexus:** There is 2 nm to 20 nm space between the opposing membranes. This gap is filled with dense packed particles through each of which there appears to be a channel that connects the two cells.
- The diameter of each channel is regulated by intracellular Ca^{2+}, pH and voltage.
- Other advantages of gap junction:

(i) It permits rapid propagation of electrical potential changes from one cell to another, e.g. cardiac and smooth muscle cells.

(ii) It permits the direct transfer of ions and other small molecules up to MW 1000 (e.g. sugars, amino acids) between the cells without traversing the extracellular space.



(C) Gap junction or Nexus

- **APOPTOSIS: PROGRAMMED CELL DEATH**
- It is a Greek word which means loosening or falling. (Apo means 'away' and Ptosis means ‘fall’)

1. Apoptosis is a process of programmed cell death in which body cells die and get absorbed (phagocytosed) under genetic control. Here cell's own gene plays an active role on its death, therefore also called as cell suicide.

- **Mechanism.** Apoptosis may be initiated by:

(i) environmental processes such as inflammation

(ii) internal stimuli

(iii) Fas, a transmembrane protein produced by natural killer cells T-lymphocytes

(iv) Tumour necrosis factor.

- The ultimate pathway initiating apoptosis is activation of group of cysteine proteases inactivate enzymes (together called as, Caspases) within the mitochondria. The activated apoptotic gene causes the cell to undergo DNA fragmentation, condensation of cytoplasm and chromatin; finally the cell break up and remnants are removed by phagocytes.
- **2. Physiological significance.**
- Apoptosis plays an important role during embryonal development and also in adulthood. It removes un-needed cells. For example,

(i) it is responsible for regression of duct system during sex differentiation in the foetus;

(ii) it is responsible for degeneration and regeneration of neurons within the CNS and for the formation of synapse;

(iii) it is responsible for removal of inappropriate clones of immune cells·

(iv) it is responsible for cyclical shedding of endometrium at the time of menstruation; and

(v) it is responsible for cell shed from the tip of the villi in the small intestine.

3. Applied. Abnormal apoptosis occurs in autoimmune diseases, degenerative diseases and cancers.

Transport Across Cell Membranes

- Substances move through the cell membrane by two major processes: passive and active.
- Passive transport requires no energy; active transport on the other hand does consume energy.
- **PASSIVE TRANSPORT PROCESSES**

Here substances move across the cell membrane without any energy expenditure by the cell.

It includes: Diffusion and Osmosis.

A. DIFFUSION

It is a passive process by which molecules move from areas of high concentration to areas of low concentration (down their 'chemical gradient'); and cations (positively charged molecules) move to negatively charged areas whereas anions move to the positively charged areas (down their 'electrical gradient').

- It is of two types:

(1) simple diffusion, and

(2) facilitated diffusion.

1. Simple Diffusion

Characteristic features

(i) It occurs because the heat content of the solution keeps the solvent and the solute particles of the solution in constant motion.

(ii) Net movement stops when the concentration of the molecules is equal everywhere within the solution (diffusional equilibrium).

(iii) Although random movements of the molecules continue after diffusional equilibrium is achieved, the concentration of the molecules throughout the solution remains the same.

(iv) It is the only form of transport that is not carrier mediated.

(v) Factors affecting diffusion. The 'rate at which a material diffuses through a membrane (flux) is given by **Fick's law of diffusion i.e.**

Net rate of diffusion (flux) =

$$- \frac{\text{Diffusion coefficient (D) x Area of the membrane}}{\text{Thickness of membrane (or diffusion distance) (T)}} \times (C_{in} - c_{out})$$

C_{in} and C_{out} = Concentration of the material inside and outside of the membrane. The negative sign indicates that the material is moving down its concentration gradient.

(a) **Distance:** The greater the distance, the longer the time required. In the human body, diffusion distances are usually small as diffusion of substances occurs across the cell membranes of uniform thickness (10nm).

(b) **Size of the gradient:** The larger the concentration gradient, faster the diffusion proceeds.

(c) **Temperature:** The higher the temperature, faster the diffusion rate. At normal body temperature of 37°C diffusion is optimal (maximum).

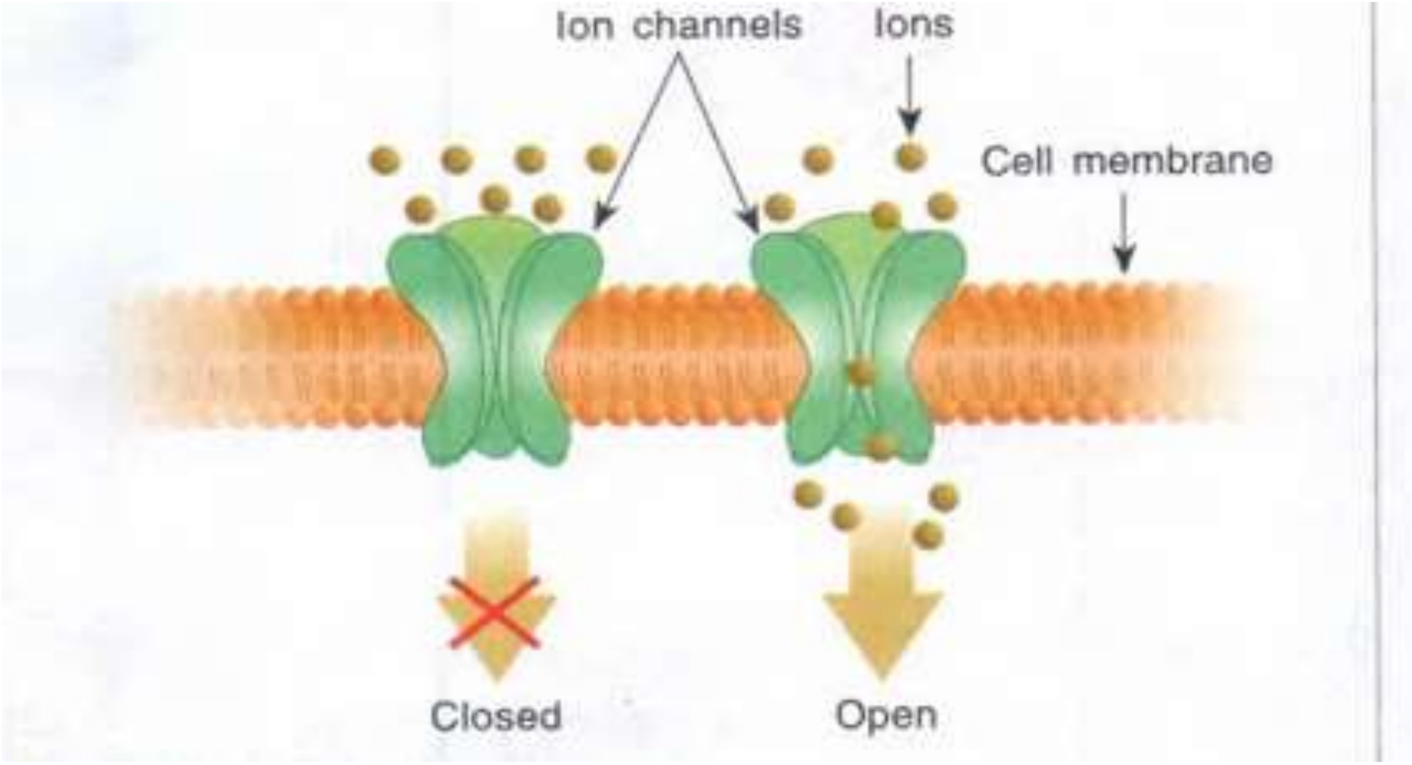
(d) molelcuar size:The permeability of cell membrane to a substance falls rapidly with increase in molecular weight in the range between 10,000 to 60,000. This is why glucose diffuses faster than large proteins.

(e) Lipid solubility.

- Lipid soluble molecules (0_2 , CO_2 , N_2 and alcohols) diffuse rapidly with ease through the lipid layer of the membrane.

- Water soluble molecules (ions, glucose, urea) can cross the cell membrane slowly as they diffuse through the aqueous channels formed by transmembrane proteins.

- **Ion channels ·**
- 'Ions' also utilize ionic channels to cross the cell membrane. Some channels are continuously open, whereas others are 'gated'.
- There are ion channels specific (for Na^+, K+, Ca2+ and cl-) and non-specific (for cations or anions). Each type of channel exists in multiple forms with different properties. Most are made up of identical or very similar protein subunits.
- Applied: Ion channel mutations cause a variety of channelopathies - diseases that mostly affect muscle and brain tissue and produce: periodic paralysis, myotonia, myasthenia or convulsions.


Ion channels
Ions
Cell membrane
Closed
Open

- **Gated channels** have gates that open or close either:
- (i) by alteration in membrane potential (voltage gated) e.g. Na^+ and Ca^{2+} channels; or
- (ii) when they bind a ligand i.e. either an ion or a specific molecule (ligand gated) The ligand is either external (e.g. neurotransmitter or a hormone) or internal (e.g. intracellular Ca^{2+}, cAMP, or G protein prod uced in the cells).
- Some channels are also opened by mechanical stretch (mechanosensitive channel), which play an important role in cell movement.

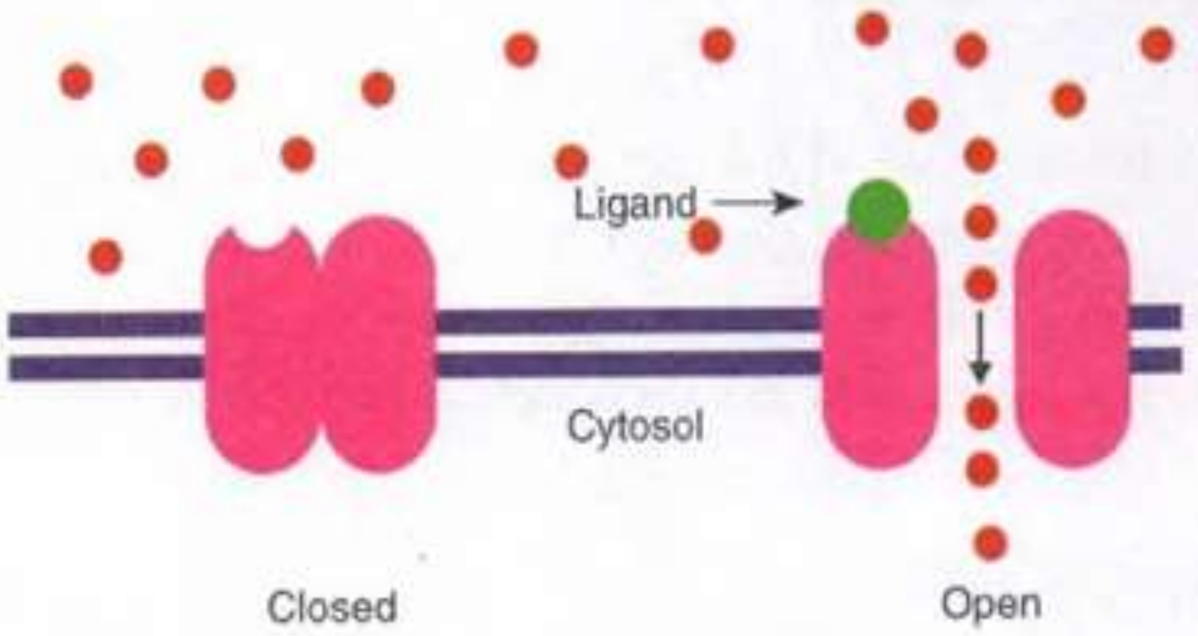


Fig. 2.2 Ligand gated channels

- **2. Facilitated Diffusion**

Characteristic features

(i) It is a carrier-mediated process that enables molecules that are too large to flow through membrane channels by simple diffusion. For example,

(a) glucose transport by the glucose transporter (GLUT) across intestinal epithelium, and

(b) the transport of glucose into RBCs, muscles and adipose tissue in the presence of insulin.

(ii) It is more rapid than simple diffusion.

(iii) The carrier protein undergoes repetitive spontaneous configurational changes during which the binding site for the substance is alternately exposed to the ICF and ECF.

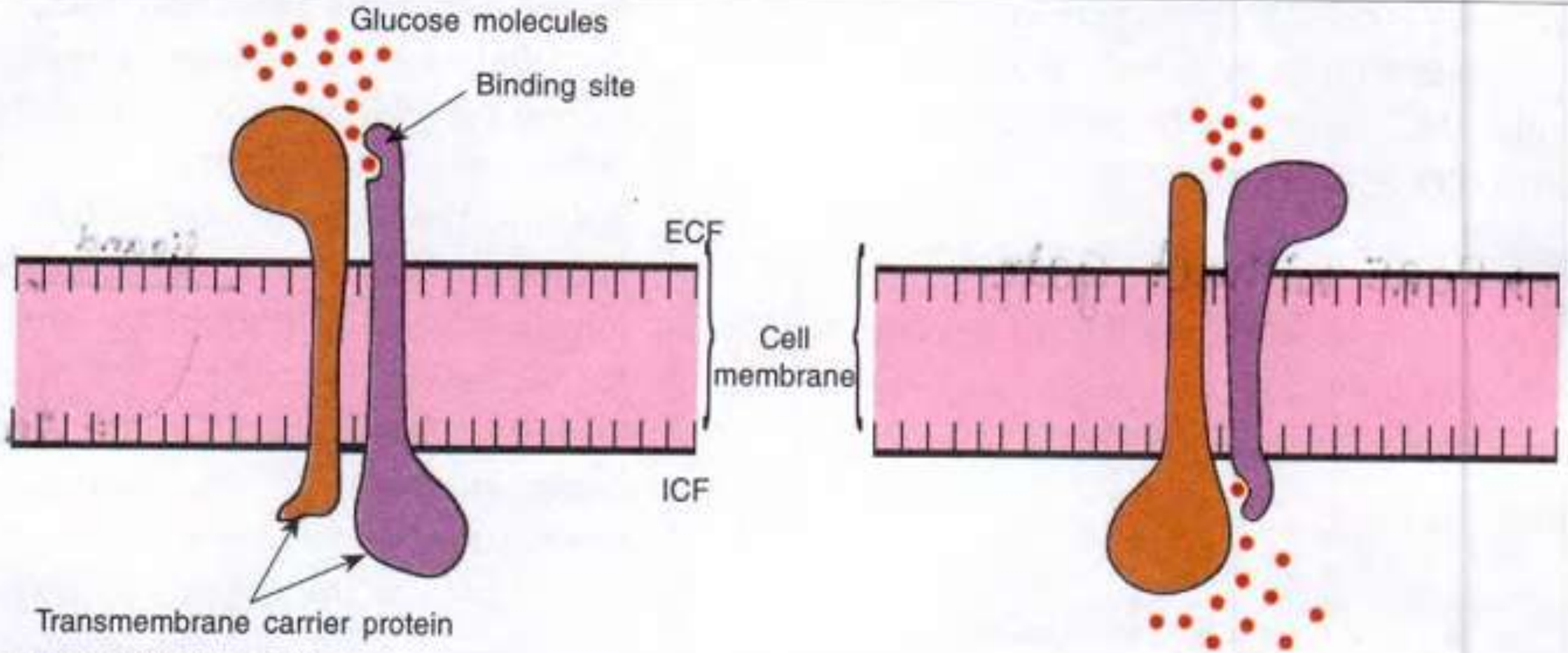


Fig. 2.3 The facilitated diffusion of glucose

(iv) Its rate of diffusion increases with increase in concentration gradient to reach a plateau when all the binding sites on the carrier proteins are filled . This is called 'saturation’.

(v) There are many types of carrier proteins in membranes, each type having binding sites that are specific for a particular substance.

B. OSMOSIS

Definition: Osmosis is the passive flow of the solvent e.g. water across a selectively permeable membrane (i.e. membrane permeable to solvent but not to the solute), into a region where there is a higher concentration of a solute to which the membrane is impermeable.

The Osmotic Pressure

The tendency for m9vemenf of solvent molecules to pass across a membrane from a low concentration of solute to a region of greater solute concentration can be prevented by applying pressure to the more concentrated solution. The amount of pressure exactly required to prevent solvent migration (i.e. osmosis) is called the osmotic pressure of the solution

- Osmotic pressure of a solution is related to the number of particles (molecules or ions) dissolved in the solution rather than their size, type, molecular weight or chemical composition.
- The coUoidal osmotic pressure due to the plasma colloids is called ONCOTIC PRESSURE

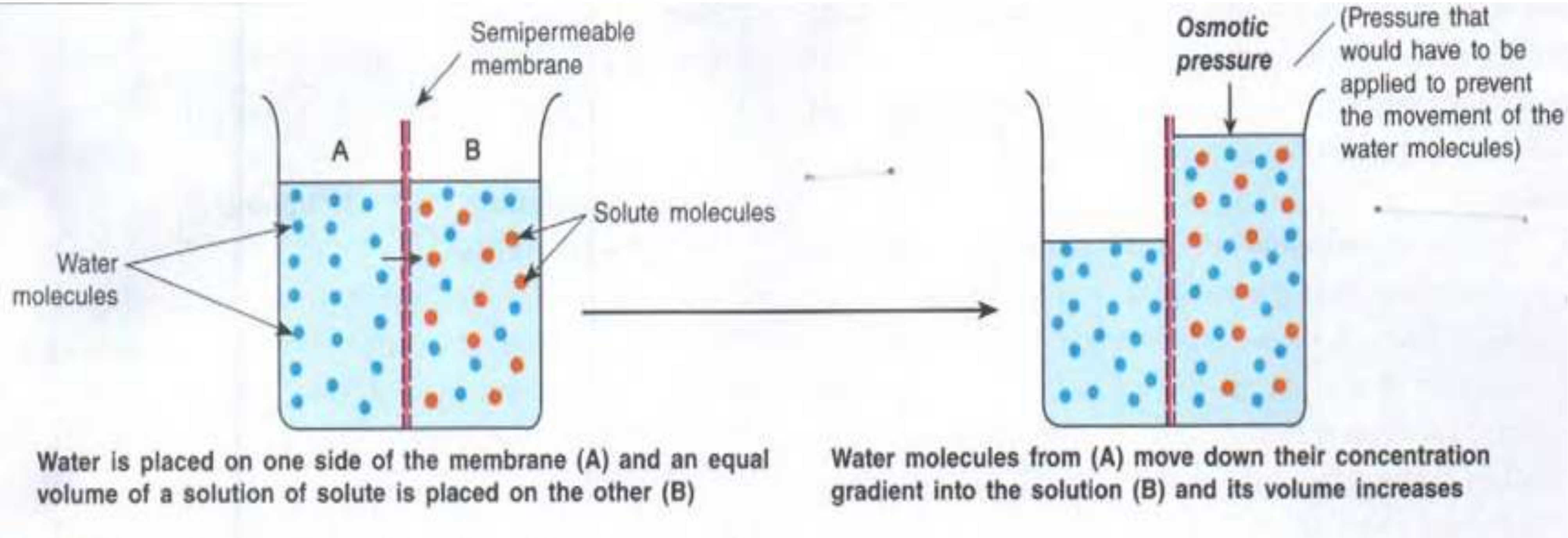


Fig. 2.5 Diagrammatic representation of osmosis

- Since the body fluids are not ideal solutions, the number of particles free to exert an osmotic effect is reduced due to interaction among the ions. Thus, it is actually the effective electrolyte's concentration in the body fluids rather than the number of equivalents of an electrolyte in solution that determines its osmotic effect.
- **Osmolal Concentration of Plasma: Tonicity**
- The term concentration refers to the total concentration of solute particles in a solution, irrespective of their chemical composition. The concentration of osmotically active particles is expressed in osmoles (osm) or 'milliosmoles' (1/1000 of 1 osm)
- **Osmolarity**

the number of osmoles per litre of solution e.g. plasma

- **Osmolality**

the number of osmoles per kilogram of the solvent.

- osmolarity is affected by the volume of the various solutes in the solution and the temperature, while the osmolality is not. osmotically active substances in the body are dissolved in water, and as the density of water is 1, so osmolal concentration is expressed as osm/L of water.
- The osmolality of normal human plasma is 290 mosm/L.
- The osmolality of a solution relative to plasma is called tonicity.
- **Isotonic solutions**

Solutions that have the same osmolality as plasma are said to be isotonic (e.g. 0.9% sodium chloride soluteon or 5% glucose solution)

- **Hypertonic solutions**

Solutions that have the greater osmolality than plasma

- **Hypotonic solutions**

Solutions that have the lesser osmolality than plasma

- Relative contribution of the various plasma components to the total osmolal concentration of plasma

1. Approximately 270 of the2 90 mosm/ L of normal plasma are_contributed by Na^+ and its accompanying anions, mainly Cl^- because there is no net movement of these osmotically active particles into the cells and these particles are not metabolised.

2. Although the concentration of the plasma proteins is large (average 6.4--8.3 gm / dL), they normally contribute less than 2 mosm/ L because of their very high molecular weights.

3. The major non-electrolytes of plasma, glucose and urea, which are in equilibrium with the cells (i.e. easily crosses most cell membranes) contribute about 5 mosm/ L. But this can be quite large in hyperglycemia or uremia.

- Clinical significance
- The total plasma osmolality is important in assessing dehydration, overhydration, and other fluid and electrolyte abnormalities. For example:

1. Hyperosmolality can cause coma (Hyperosmolar coma) by causing water to flow out of the cells i.e. cellular dehydration.
2. The flow of water into or out of the capillaries depends on whether the colloidal osmotic pressure or oncotic pressure (osmotic pressure produced by plasma proteins) is greater or lesser than the hydrostatic pressure of the blood (produced by systemic arterial blood pressure). When water flows into or out of capillaries, it carries dissolved particles with it. This force is called solvent drag. Its effects are very small in the body.

- **ACTIVE TRANSPORT PROCESSES**
- Here, substances are transported against their chemical and electrical gradient. This form of transport requires energy and is called active transport. It includes:

(A) Primary active transport processes,

(B) Secondary active transport processes,

(C) Carrier type processes, and

(D) Vesicular transport processes

Because active transport processes require energy, they are often referred to as **pumps.**

- **A. PRIMARY ACTIVE TRANSPORT PROCESSES**
- They directly use the energy obtained from the **hydrolysis of adenosine triphosphate (ATP**). ,The primary active transport system consists of:

1. Sodium-potassium (Na^+ - K^+) pump,
2. Calcium ($Ca^{2+)}$ pump, and
3. Potassium hydrogen (K^+ - H^+) pump.

1. SODIUM-POTASSIUM (NA^+ - K^+) PUMP OR NA^+ - K^+ ATPASE

It is the most common pump found in all parts of the body.

It uses the membrane-bound ATPase as a carrier molecule i.e. an enzyme that catalyses the hydrolysis of ATP.

ATPase is composed of 6 subunits, three alpha and three beta. Sodium and potassium transport occurs through alpha subunit.

- Alpha subunit has:

(i) ATPase enzymatic activity i.e. the ability to convert ATP to adenosine diphosphate (ADP), thereby releasing energy; and

(ii) binding sites on its intracellular and extracellular faces. The former contains binding sites for three Na+ ions and an ATP molecule whereas the latter contains binding sites for two K+ ions.

Mechanism of operation

The operation of the Na+- K+ pump consists of two steps

Step 1: Binding of 3Na+ ions and ATP to a carrier protein inside the cell transfers high energy phosphate group from ATP to alpha subunit of ATPase (phosphorylation). This causes change in configuration of protein resulting in 3Na+ ions to move out of the cell.

Step 2: When 2K+ ions bind to the carrier protein on the outside of the cell, the alpha subunit-phosphate bond is hydrolysed (dephosphorylation). This causes second change in configuration of protein resulting in 2K+ ions to move into the cell.

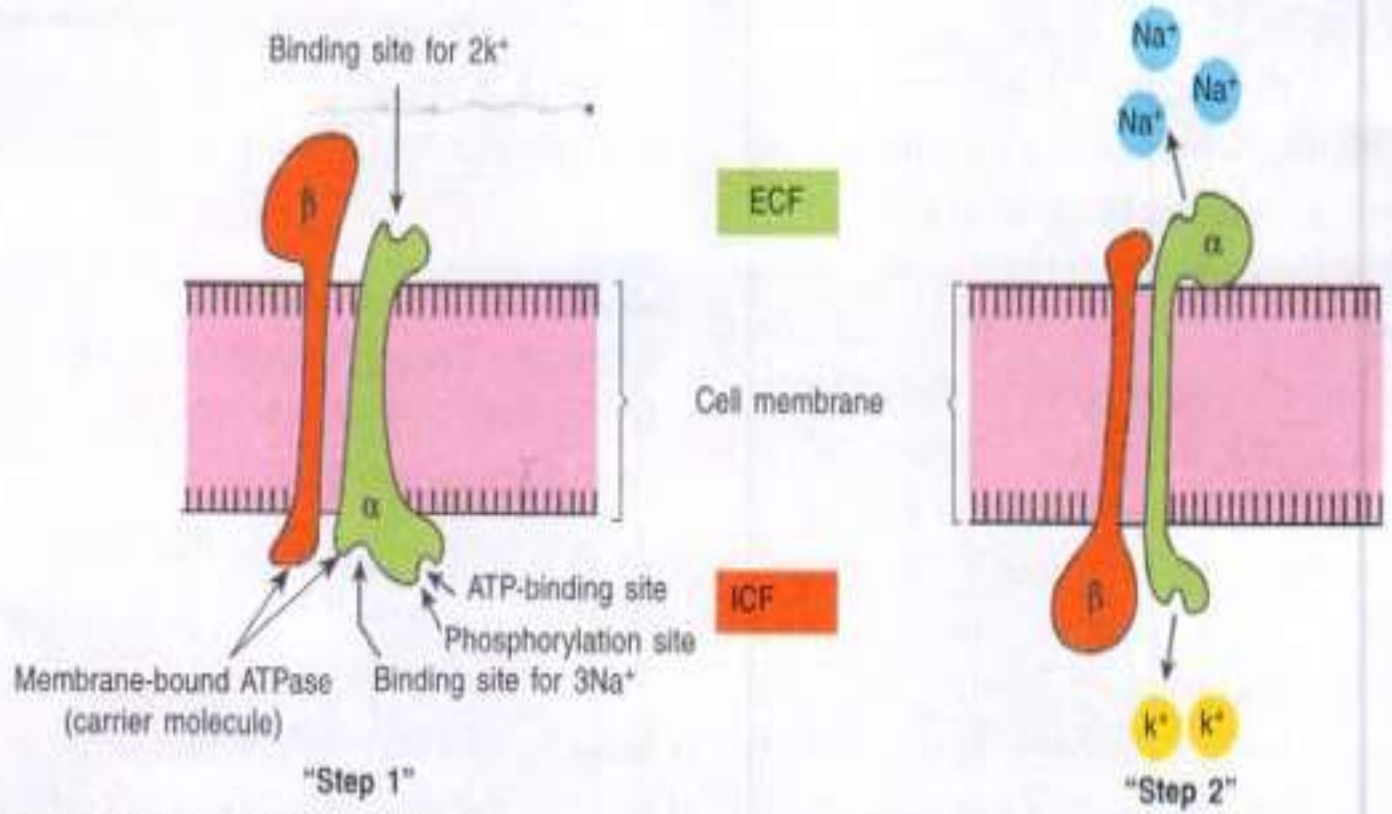


Fig. 2.6 Mechanism of operation of Na^+ – K^+ pump

- **Functions**

1. Na+ - K+ pump is responsible for maintaining the high K+ and low Na+ concentrations in the cell. it is an electrogenic pump with a coupling ratio of 3/2 and produces net movement of positive charge out of the cell. This electrical potential is a basic requirement in nerve and muscle fibers for transmitting electrical signals.

2. Active transport of Na+ ions and K+ ions is one of the major energy-using processes in the body. It accounts for a large part of the basal metabolism.

3. It helps in regulation of normal cell volume and pressure .

- **Inhibition of the pump**

1. The pump requires binding by Na+, K+ and ATP for its operation. Therefore, if the concentration of any of these substances is too low, the pump does not function.

2. When temperature is reduced.

3. During oxygen lack.

4. Metabolic poisons e.g. 2,4 dinitrophenol (DNP) that prevents the formation of ATP.

- **Na+-K+ pump activity is increased by**:

thyroid hormones, insulin, aldosterone and G-actin, whereas dopamine inhibits its activity.

- **Clinical Significance**
- Digitalis, a drug used for the treatment of heart failure, increases myocardial contractility by binding to the extracellular face of the alpha-subunit and interfering with the dephosphorylation step of the transport process. This inhibits the pump thereby increasing intracellular Ca2+ concentration and ultimately leads to increased myocardial contractility.
- **2. Calcium (Ca2+) pump or Ca2+ ATPase**

(i) It is one of the ATPase other than Na+ - K+ ATPase. It is present in the sarcoplasmic reticulum of muscle cells, which maintains the intracellular ionic Ca2+ concentration below 0.1 mmol/L.

(ii) It is also located in the cell membrane and in many cell organelle membranes. In the cell membrane, the direction of Ca2+ transport is from cytoplasm to ECF. In cell organelle membranes it is from cytoplasm into the organelle lumen.

3. Potassium-hydrogen (K+ - H+) pump or K+ - H+ ATPase (or H+ - K+ ATPase)

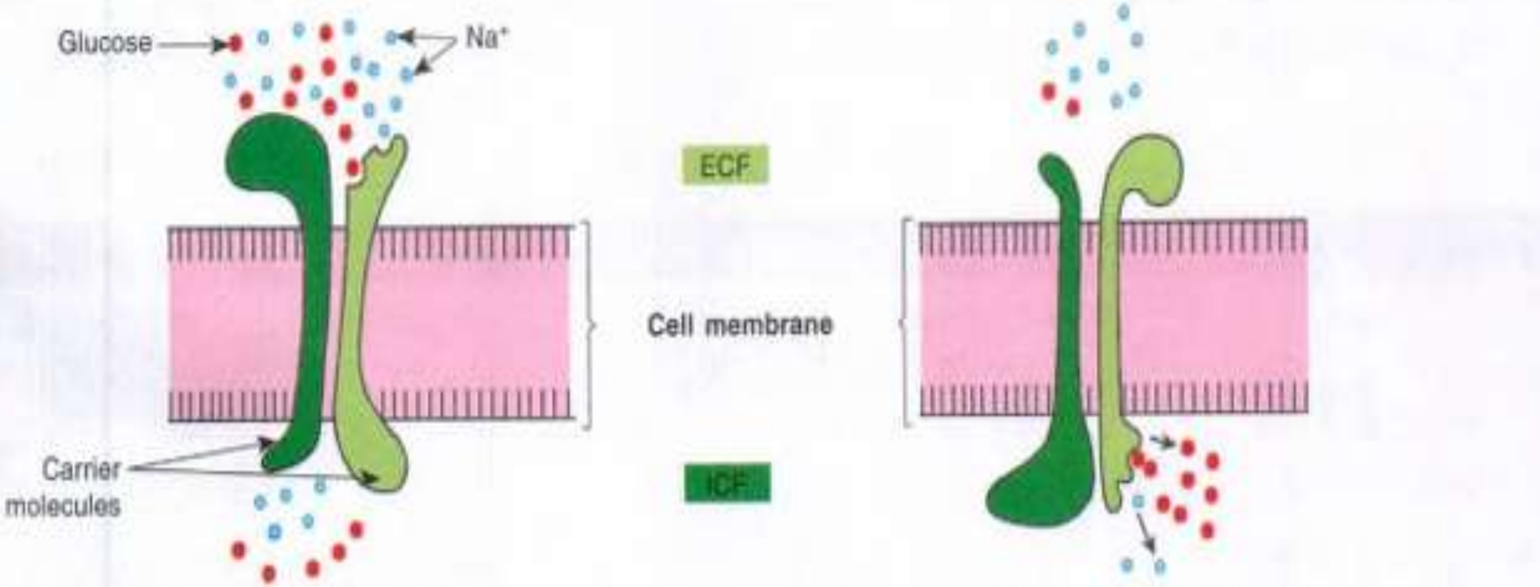
Hydrogen ion is actively transported across the cell membrane by the carrier protein called hydrogen pump. It also obtains energy from ATP by the activity of ATPase. The hydrogen pumps that are present in two important organs have some functional significance.

1. Stomach: Hydrogen pumps in parietal cells of the gastric glands are involved in the formation of hydrochloric acid.

2. Kidney: Hydrogen pumps in epithelial cells of distal convoluted tubules and collecting ducts are involved in the secretion of hydrogen ions from blood into urine.

- **SECONDARY ACTIVE TRANSPORT**
- Secondary active transport is the transport of a substance with sodium ion, by means of a common carrier protein. When sodium is transported by a carrier protein, another substance is also transported by the same protein simultaneously, either in the same direction (of sodium movement) or in the opposite direction. Thus, the transport of sodium is coupled with transport of another substance. For example:
- (1) Glucose and amino acids are reabsorbed from the proximal renal tubules or absorbed from the intestinal lumen only if Na^+ binds to the protein and is transported down its electrochemical gradient at the same time.
- (2) Calcium is exchanged from the cytoplasm of cardiac and other muscle cells for extracellular Na^+, called Na^+ - Ca^{2+} exchanger. This causes muscle relaxation.

- Mechanism of secondary active transport When Na+ binds to the carrier molecule, the carrier molecule increases its affinity for the substances to be transported. When both Na+ and the substance are bound to the carrier molecule, the carrier undergoes a configurational change during which both molecules are transported across the membrane.
- In some cases, both Na+ and the substance are transported in the same direction, whereas in others they are transported in opposite directions.



(A) The affinity of the protein carrier for glucose is increased in the presence of Na^+. The glucose and Na^+ pass through the membrane together.

(B) Once inside the cell, the Na^+ dissociates from the carrier, reducing the carrier's affinity for glucose and causing the glucose to dissociate from the carrier.

Fig. 2.7 Secondary active transport of glucose (*i.e.* active transport that uses an indirect energy source)

- **C. CARRIER TYPE PROCESSES**

Carriers are transport proteins that binds ions and other molecules and then change their configuration, moving the bound molecules from one side of the cell membrane to the other.

- **Types**

l. Uniporters are carriers that transport a single particle in one direction, such as the facilitated diffusion of glucose.

2. Symporters (co-transporters) transport two particles together in the same direction, such as the secondary active transport of glucose.

3. Antiporters (counter transporters) transport molecules in opposite directions i.e. they exchange one substance for another. For example:

(i) Na+ - K+ pump which moves 3Na+ out of the cell in exchange for 2K+ that moves into the cell.

(ii) Na+ - Ca2+ exchangers in the muscle cells.

(iii) Na+ - H+ exchangers in the renal tubules.

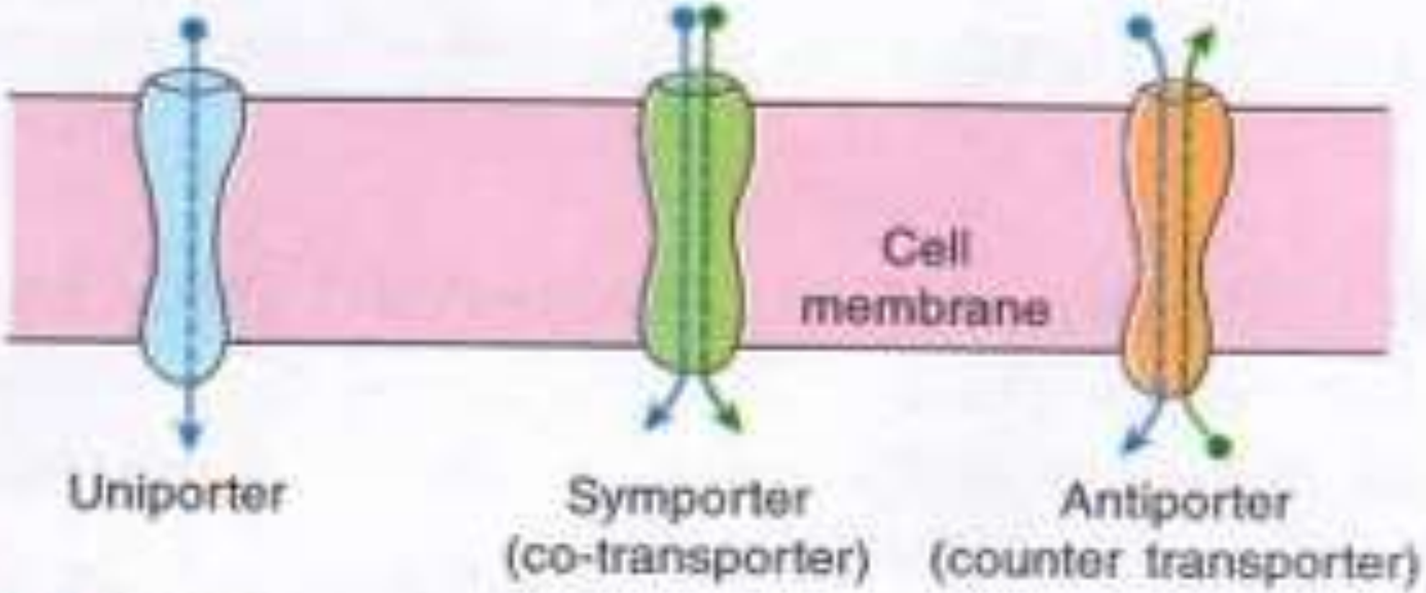


Fig. 2.8 Carrier type processes

- **D. VESICULAR TRANSPORT PROCESSES or TRANSCYTOSIS**

Many substances are transported across the cell membrane by endocytosis and exocytosis.

1. Endocytosis - 2 types:

(i) Phagocytosis (cell eating). It is the process by which extracellular substances (bacteria, dead tissue, foreign particles etc.) are engulfed by the cells. The substance makes contact with the cell membrane, which then invaginates. The endocytic vesicle pinches off from the cell membrane and fuses with another intracellular vesicle e.g. lysosome, from which the ingested substance is released into ICF.

If the substance ingested is in solution form, the process is called **pinocytosis (cell-drinking).**

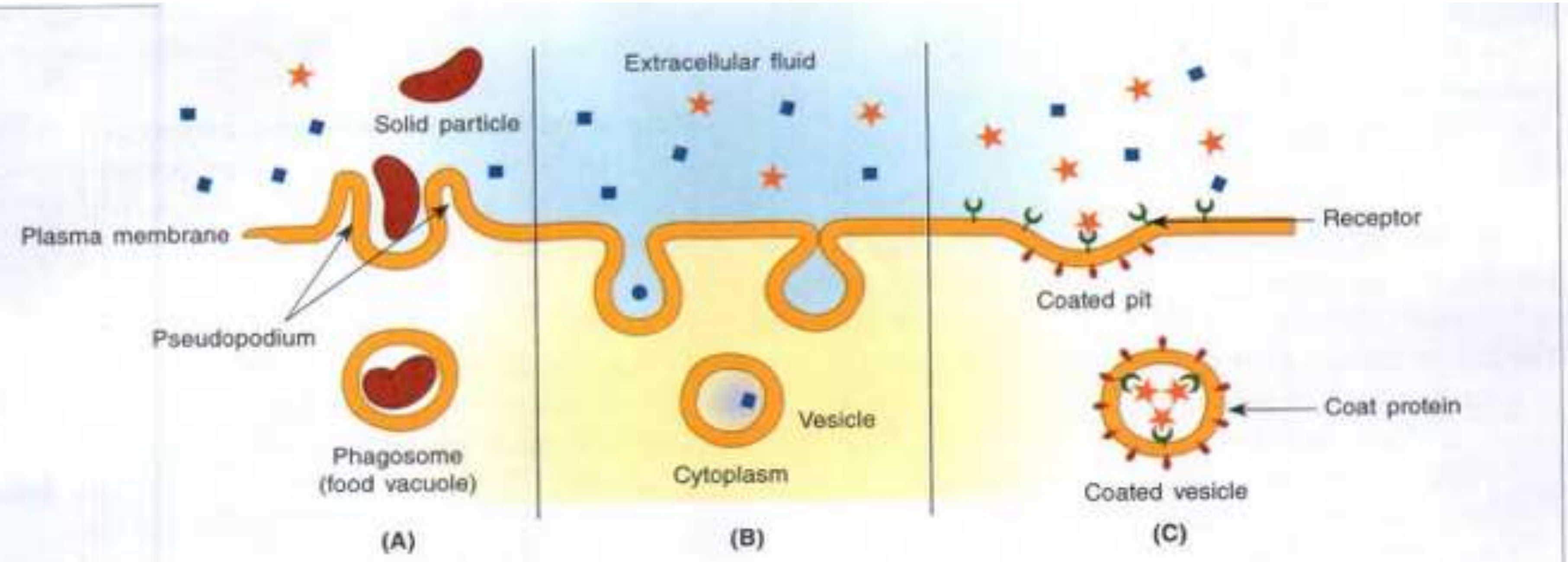


Fig. 2.9 Sequence of events in endocytosis (A), Pinocytosis (B) and Receptor mediated endocytosis (C)

(ii) Receptor mediated endocytosis - the material to be transported first binds to a receptor, and then the receptor-substance complex is ingested by endocytosis. For example, transport of iron and cholesterol into the cells.

2. Exocytosis - Here substances secreted by the cell are trapped within vesicles or granules which fuse with the cell membrane and release their contents to the ECF. This leaves the contents of the vesicles or granules outside the cell and the cell membrane intact. It requires Ca2+ and energy. Hormones, digestive enzymes and synaptic transmitters are examples of substances transported out of the cell by this process.

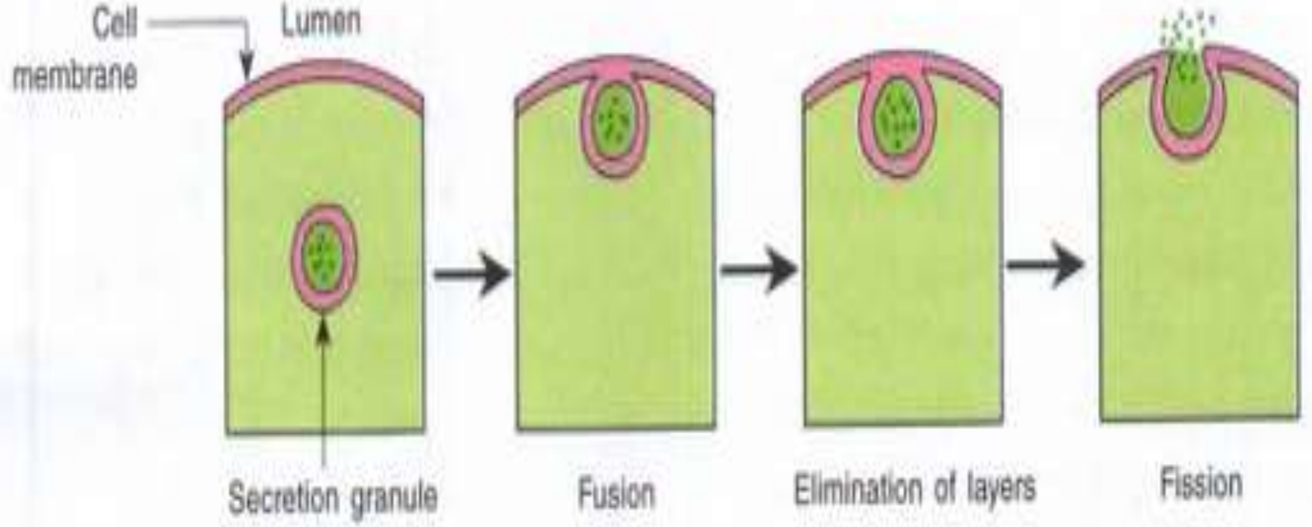


Fig. 2.10 Sequence of events in exocytosis

Assessment

Differentiate between:

(i) active and passive transport processes

(ii) osmotic and oncotic pressure

(iii) endocytosis and exocytosis

(iv) isotonic and isosmotic solutions

(v) simple and facilitated diffusion

(vi) osmolarity and osmolality

(viii) primary and secondary active transport processes.

Depict diagrammatically

(i) mechanism of operation of Na• K• pump. (ii) Secondary active transport (iii) Phenomenon of Osmosis (iv) Sequence of events in encocytosis and exocytosis

- List the major processes that brings about the transport of substances across the cell membranes.
- **MCQs**

(1) Rate of diffusion of a substance from a region of its higher concentration to a region of lower concentration is directly proportional to:

(a) Molecular size of the substance

(b) Thickness of the membrane

(c) Temperature

(d) Water solubility of the substance

(2) Gated ionic channels open or close by:

(a) Alteration in membrane potential

(b) Only when they bind to an external ligand

(c) Only when they bind to an internal ligand

(d) Depending on the lipid solubility of an ion

(3) A major force affecting the distribution of water and solutes in different body compartments is:

(a) Diffusion (b) Active transport processes (c) Osmosis (d) Sodium-potassium pump

(4) Active transport processes:

(a) Are often referred as pumps
(b) Are most used processes to move substances through the cell membrane
(c) Always use the energy obtained from transport of other substances
(d) Help transport of substances across cell membrane along the electro-chemical gradient

(5) Sodium-potassium pump is characterised by all of the following except:

(a) Requires binding by only Na+ and K+ for its activation
(b) Uses membrane bound ATPase as a carrier molecule
(c) ls responsible for maintaining high K+ and low Na+ concentration in the cell
(d) Accounts for a large part of the basal metabolism

(6) A large part of the basal metabolism is due to:

(a) Operation of sodium-potassium pump

(b) Flow of large molecules through membrane channels by facilitated diffusion

(c) Phenomenon of osmosis

(d) Sodium dependent secondary active transport

(7) Sodium potassium pump can be inhibited by all, except:

(a) lf concentration of Na ... , K+ and ATP is too low

(b) When temperature is reduced

(c) If plasma Ca^{2+} concentration decreases

(d) Oxygen lack

THANKS