Transport across Cell membrane

Every living cell must acquire from its surrounding the raw materials for biosynthesis and for energy production and must release to its environment the byproducts of metabolism. A few non-polar compounds can dissolve in the lipid bilayer and cross the membrane unassisted but for polar or charged compounds or ions, a membrane protein is essential for transmembrane movement. In some cases a membrane protein simply facilitates the diffusion of a solute down its concentration gradient, but transport often occurs against gradient of concentration, electrical charge, or both, in which case solutes must be "pumped" in a process that require energy. The energy may come directly from ATP hydrolysis or may be supplied in the form of movement of another solute down its ~~concentration~~ electrochemical gradient with enough energy to carry another solute up its gradient. Ions may also move across membranes via ion channels formed by proteins, or they may be carried across by ionophores, small molecules that mask the charge of the ions and allow them to diffuse through the lipid bilayer. With few exceptions, the traffic of small molecules across the plasma membrane is mediated by proteins such as channels, carriers or pumps. Within the Eukaryotic cell, different compartments have different concentrations of metabolic intermediates and products and of ions, and these, too must move across intracellular membranes in tightly regulated, protein-mediated process.

The membrane ~~prof~~ protein can be broadly classified into :-

(I) Passive ~~diffusion~~ transport - including passive
(II) diffusion and facilitated diffusion.

(II) Active transport:

[I] Passive transport of small molecule:- In passive diffusion, the substance moves from a higher concentration to a lower concentration, generally without the help of any transport system, until the concentration of the substance in both side of the membranes the same. For a charged molecule, the situation becomes ~~too~~ ~~because~~ ~~for~~ ~~ex~~ more complicated, since the movement depends on electrochemical potential.

1. Passive transport of ions through ion channels- Ion fluxes across cellular membranes mediate a variety of essential biological processes, ~~including~~ ~~the~~ ~~following~~ ~~cell~~ ~~volume~~ ~~regulation~~ like muscle contraction, exocrine cell secretion, exciation of neuron for signal transmission, etc. These ion fluxes, involving passive transport, are mainly fascilitated by a diverse family of integral membrane proteins called ion channels (each ion channel is a single channel protein) although the ion fluxes in other cases, may also be facilitated by active transport and symport or antiport. & These ions channels differ from simple aqueous pores in (i) ion selectivity (flow of only selective ion is performed)
(ii) activation gating (channels opening is regulated)
(iii) inactivation gating (channels closing is regulated)
Ion channels are hydrophobic pores formed by "channel proteins"

which differ from 'Carrier protein' ~~and~~ or 'pumps' involved in active transport of substances across plasma membrane.

~~Ion channels are hydrophilic pores formed by 'channel protein'~~.

It is estimated that more than one million (upto one billion = 10^9) ions can pass through one channel per second, a rate which is 1000 times greater than the fastest rate of transport mediated by any carrier protein (For a Na^+ channel, it is estimated that more than 8000 Na^+ ions pass each millisecond, when the channel is open) Another difference is that ion channels can not be coupled to an energy source to carry out active transport. Therefore, ion channels mediate only passive transport (downhill) to allow diffusion of ions (eg. Na^+, Ca^+, K^+, & Cl^-) down their electrochemical gradients across a plasma membrane, although this movement of ion is regulated in a very sophisticated manner. These ion channels (specially Na^+ & K^+ ion channels) are specially used in the nerve cells for receiving, conducting and transmitting signals in the form of an 'action potential'. ~~The~~ following two distinct families of ion channels are known

(I) Voltage-activated channels - activated by change in voltage due to transport of K^+, Na^+ and Ca^{++}.

(II) Ligand gated channels - activated by neurotransmitters like acetylcholine, serotonin, glutamate and gamma-amino butyric acid (GABA)

Family of channels	Subfamilies of channels	Excitatory or Inhibitory
(1) Voltage-gated Cation channels	Na^+ channels, K^+ channels, Ca^{++} channels	Excitatory
(2) Ligand-gated ion channels (i) Cation channel	Acetylcholine-gated Na^+ channel, Serotonin-gated Na^+ channels, Glutamate-gated Na^+ channels	Excitatory
(ii) Anion Channels	GABA gated Cl^- channels, Glycine gated Cl^- channel	Inhibitory

(b) Ion-gated channels
(c) Nucleotide-gated channels

[II] Passive transport :- facilitated diffusion

Transport rate of many ions and small molecules across the plasma membrane need to much higher than anticipated from passive diffusion, to sustain vital life processes for example :- in human red blood cells (RBCs) these rates for chloride ions and glucose were 10^6 and 10^7 times larger than those across simple bilayer membrane and have been attributed to specific Carrier proteins, which facilitate diffusion and having two features in common - (1) they

facilitate movement of solutes in thermodynami-cally favoured direction (ΔG) and
(ii) they display affinity and specificity for the solute to be transported. Consequently, facilliated diffusion rates reach a saturation point (Vmax) with increase in the concentration of solute.

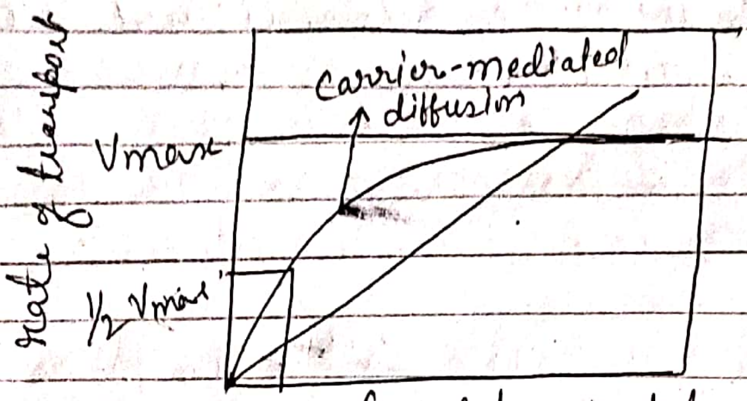

Fig - Comparision of the kinetics of simple diffusion and carrier mediated diffusion.

Carrier proteins involved in fascilltated diffusion may be classified as follows -

(i) Uniporters - when a single solute is transported from one side of the membrane to the other.

(ii) Symporters - when transfer of one solute depends on the simultaneous or sequential transfer of a second solute in the same ~~basa~~ direction

(iii) Antiporters - where transfer of one solute depends on the simultaneous or sequential transfer of second solute, but in opposite direction.

For instance, Glucose transport in facilitated diffusion (high to low) is mediated by uniporters (glucose transporter) but the glucose transport from low to high conc. (as happens in intestine & kidney) involves transport of with the transport of Na^+ ions. The anion transporter, on the other hand, belongs to the category of antiporters, where Cl^- and HCO_3^- moves in opposite direction.

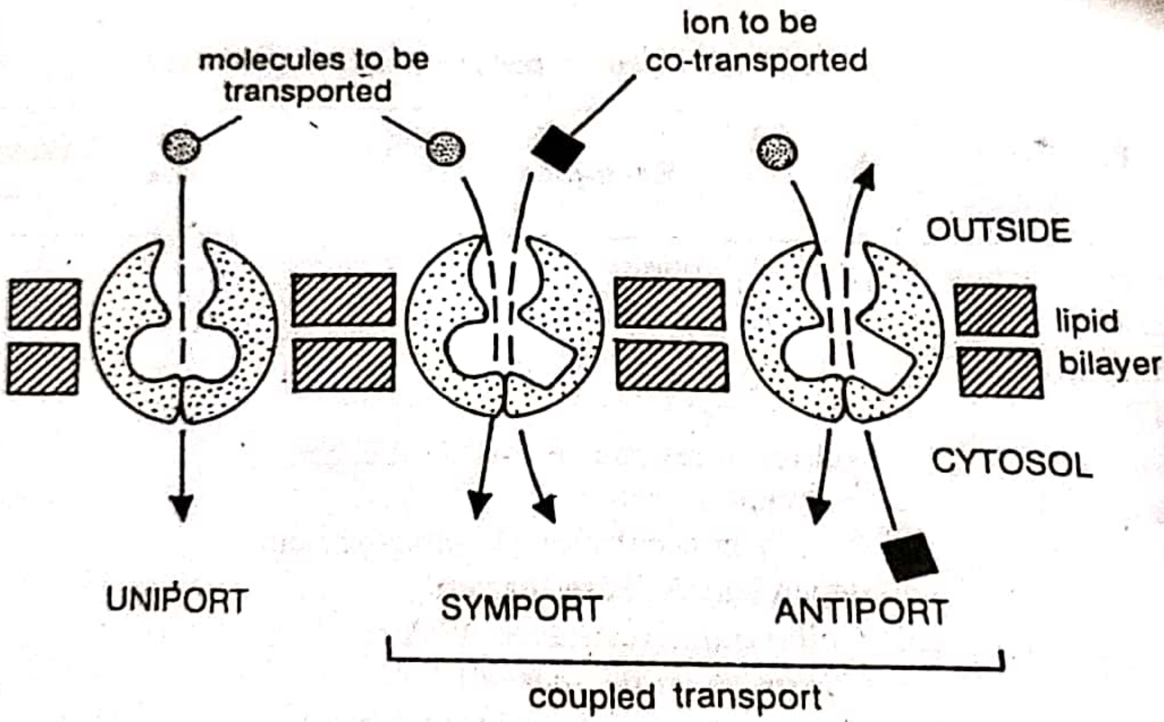

Fig. 14. Three types of carrier mediated transport (uniport symport and antiport (redrawn from Alberts *et al.*, *Molecular Biology of the Cell*, 1994).

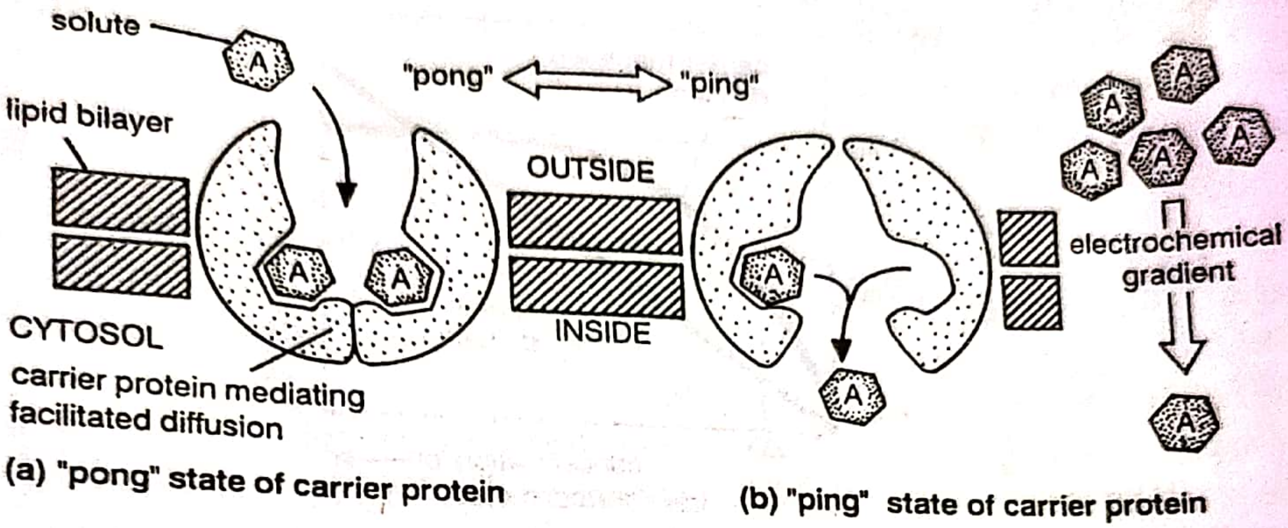

Fig. 15. Reversible conformational change from 'pong' to 'ping' state in carrier protein to mediate facilitated diffusion of a solute along the electrochemical gradient (redrawn from Alberts *et al., Molecular Biology of the Cell,* 1994).

The above transport involves a reversible Conformational change in (pong to ping state) Carrier protein, so that the solute binding site of Carrier protein is alternately exposed first on one side of the membrane and now known to be multipass transmembrane proteins, it is not likely that a carrier protein tumbles (or rotates) in the membrane shuttle back and forth across the lipid bilayer, as was earlier visualized. The ping-pong model of the mechanism involved in the use of Carrier protein in facilitated diffusion is shown in fig (above).

Active transport :- When a molecule moves from lower concentration to higher Concentration as is often ~~[illegible]~~ required in the cells, energy input is required and the transport is described as 'Active transport'. Mostly, the energy is derived from ATP. Active transport is always mediated by carrier proteins or 'Pumps'.

Note (Passive transport may or may not involve Carrier proteins, Ion channels are never involved in active transport; they are involved in passive transport only).

(1) ATP driven transport system

(a) Na^+, K^+ - ATPase system (Sodium pump). All animal cells actively throw out Na^+ ions and take in K^+ ions, the ~~th~~ two process being fascilitated by an integral protein called Na^+, K^+-ATPase pump or Sodium pump, which operates as an antiporter. This pump is also exploited to ~~trans-port~~ drive transport of sugar and amino-acids and operates then as a Na^+ - sugar or Na⁺ amino acid symporter. In most cells, Na^+ concentration is 10mM and K^+ concentration is 100mM, the reverse being the situation in extracellular space (Na^+, 100-140 mM) and K^+, 5-15mM). It is necessary, because K^+ is needed for many functions, for which Na^+ is inhibitory. This includes the following functions:

(i) Na^+, K^+ and Cl^- and other ion gradient help neuron to communicate;

(ii) They also regulate cell volume and cell shape

(iii) They help in transport of aminoacids, sugars, nucleotides and other substances.

(b) Ca^{2+}-ATPase system - Ca^{++} is an important ion, taking part in signal transduction pathways in virtually all cells leading to control of many functions including muscle contraction. Free Ca^{++} has low concentration in cytosol relative to that outside the cytosol or in E.R. Ca^{++} concentration is also low near the muscle fibers and all Ca^{++} is accumulated in a complex network of vesicles called Sarcoplasmic reticula or SRs in the cytoplasm of muscle cells. Flow of Ca^{++} ions down its steep gradient, i.e from SR to cytosol or from outside the cell to its interior is one means of transmitting signals rapidly across the membrane. The maintenance of steep gradient of Ca^{++} across the membrane is, therefore essential for cell function. Low Ca^{++} ion concentration in cytosol is maintained by Ca^{++} pumps actively transporting Ca^{++} ions out of the cytosol to SR or outside the cell. One of these pumps is an ATPase. Another Ca^{++} pump is an antiporter, driven by Na^+

Nerve impulses induce SR to release Ca^{++} leading to rise in cytoplasmic level of Ca^{++}, thus stimulating muscle contraction. Relaxation of muscle requires that cytosolic Ca^{++} levels are reduced to the resting level; this is acheived by Ca^{++} ATPase, which is most abundant in SR membrane and pumps two Ca^{++} ions, per ATP molecule hydrolysed, from cytosol into SR.

(C) H^+, K^+– ATPase- In the stomach a highly acidic environment (pH = 0·8 – 1·0) is essential for digestion of food, the pH in the parietal cells of the gastric mucosa ~~~~ being 7·4, thus providing a pH of gradient of 6·6, which is maintained by H^+ K^+–ATPase enzyme. This enzyme through hydrolysis of ATP, pumps H^+ ions out of the mucosal cells into the stomach in exchange for equal number of K^+ ions, thus making transport electrically neutral as against sodium pump or Calcium pump, which are electrogenic. K^+ are pumped back out of the cells together with Cl^- ions, thus together making HCl inside the stomach.

(d) ABC transporter superfamily (for transport of peptides and drugs)

The ABC transporters represent a class of ATPases (carrier proteins) ~~that was characterized for the first time from bacteria~~, Each of ABC transporters has an 'ABC binding Cassette' hence the name ABC transporter. These are considered to be of great Clinical importance, one of them being responsible for disease cystic fibrosis. These transporters help in transport of great variety of substances including aminoacids, sugars, inorganic ions, polysaccharides, peptides & even proteins. ~~Some examples of ABC~~

(1) Light driven active transport system:- Two light driven transport system which have been studied in detail

(2) Ion-gradient driven active transport system-
~~Amino acid and sugar transport: (Symport and antiport) The gradients of ions (cations or anions) established by ATPase or by li's~~