Transport across cell membrane

All cells are generally separated from their surrounding environment by plasma membrane. In addition, the eukaryotic cells are compartmentalized by intracellular membranes that form the boundaries and internal structures of various organelles.Thesebiological membranes are semi-permeable in nature that is their permeability properties ensure that the specific molecules and ions readily enter the cell and the waste products leave the cell. These movements of solutes into the cell are mediated through the action of specific transport proteinsthat arepresent on the cell membrane. Such proteins are therefore required for movements of ions, such as Na^+, K^+, $Ca2^+$, and Cl^-, as well as metabolites such as pyruvate, amino acids, sugars, and nucleotides, and even water. Transport proteins are also responsible for biological electrochemical phenomena such as neurotransmission.

Cell membranearchitecture in transport across cell membrane:

The cell membrane plays an important role in transport of molecules. Because it acts as a semi-permeable barrier, allowing specific molecules to cross while fencing the majority of organically produced chemicals inside the cell. Electron microscopic examinations of cell membranes reveal the development of the lipid bilayer model (fluid-mosaic model). The model consists ofphospholipid, which has a polar (hydrophilic) head and two non-polar (hydrophobic) tails. These phospholipids are aligned tail to tail so the non-polar areas form a hydrophobic region between the hydrophilic heads on the inner and outer surfaces of the membrane.

Permeability of molecules across phospholipid bilayer:

Most of the molecule will diffuse across a protein-free lipid bilayer down its concentration gradient, if provided enough time. The diffusion rate is the function of the size of the molecule and its relative solubility in oil. In general, the smaller the molecule and the more soluble in oil (the more hydrophobic or non-polar), the more rapidly it will diffuse across a cell membrane. Small non-polar molecules, such as O_2 and CO_2, readily

dissolve in cell membrane and therefore diffuse rapidly across them whereas small uncharged polarmolecules, such as water or urea, also diffuse across a bilayer, but much more slowly but ethanol diffuses readily. Conclusively it can be said that lipid bilayers are highly impermeable to charged molecules (ions) by considering its size also because the charge and high degree of hydration of such molecules prevents them from entering the hydrocarbon phase of the bilayer. Thus, these bilayers are 10^9 times more permeable to water than to even such small ions as Na^+ or K^+(**M. Lodish et al., 2003**).

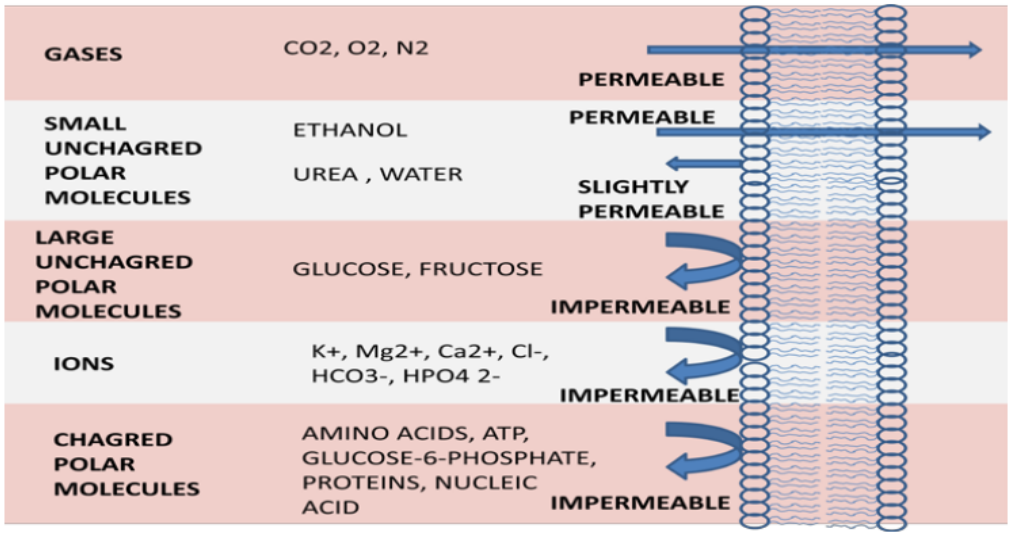

Figure 1:Relative permeability of a pure phospholipid bilayer to various molecules. A bilayer is permeable to small hydrophobic molecules and small uncharged polar molecules, slightly permeable to water and urea, and essentially impermeable to ions and to large polar molecules.

Thermodynamics of transport :

The diffusion of a substance A, across the two sides of a membrane thermodynamically resembles a chemical equilibration.

$A(out) \rightarrow A(in)$

In the following sections, the free energy of a soluteA, varies with its concentration:

$$\overline{G}_A - \overline{G}_A^{o\prime} = RT \ln[A]$$

$$\bar{G}_A = \bar{G}_A^{o,} = RTin\,(A)$$

where

$G_A$is the chemical potential(partial molar free energy) of A (the bar indicates quantity per mole)

$G°`_A$ is the chemical potential of its standard state.

Thus, a difference arises in the concentrations of the substance on two sides of a membrane and generates a chemical potential difference:

$$\Delta\bar{G}_A = \bar{G}_A(in) - \bar{G}_A(out) = RTin\left(\frac{[A]_{in}}{[A]_{out}}\right)$$

If the concentration of A outside the membrane is greater than that inside, ΔG_A for the transfer of A from outside to inside will be negative and the spontaneous net flow of A will be inward. Conversely, if [A] is greater inside than outside, ΔG_A is positive and an inward net flow of A can occur only if an exergonic process, such as ATP hydrolysis, is coupled to it to make the overall free energy change.

The transmembrane movement of ions also depends in charge differences across the membrane, thereby generating an electrical potential difference which is given by:

ΔA=A(in) – A(out),

whereΔAis termed the membrane potential.Consequently, if A is ionic, must be amended to include the electricalwork required to transfer a mole of A across the membrane from outside to inside:

$$\Delta\bar{G}_A = RTin\left(\frac{[A]_{in}}{[A]_{out}}\right) + Z_A\,°\mathrm{F}\,\Delta A$$

$$\Delta\overline{G_A} = RT\ln\left(\frac{[A]_{in}}{[A]_{out}}\right) + Z_A\mathcal{F}\Delta\Psi$$

where

Z_A is the ionic charge of A

F, the Faraday constant, is the charge of a mole of electrons (96,485 C /mol; C is the symbol for coulomb)

G_A is now termed the electrochemical potentialof A.

The membrane potentials of living cells are commonly as high as 100 mV (note that 1 V = 1 J /C).

Types of transport process:

Two types of transport processoccuracross the membrane.

1. Non-mediated transport
2. Mediated transport

Non-mediated transport occurs through the simple diffusion process andthe driving force for the transport of a substance through a medium depends on its chemical potential gradient. Whereasmediated transportrequires specific carrier proteins. Thus, the substance diffuses in the direction that eliminates its concentration gradient; at a rate proportional to the magnitude of this gradient and also depends on its solubility in the membrane's non-polar core. Mediated transport is classified into two categories depending on the thermodynamics of the system:

1. Passive-mediated transport, or **facilitated diffusion:**In this typeof process a specific molecule flows from high concentration to low concentration.

2. Active transport: In this typeof process a specific molecule is transported from low concentration to high concentration, that is, against its concentration gradient. Such an endergonic process must be coupled to a sufficiently exergonic process to make it favorable ($\Delta G < 0$).

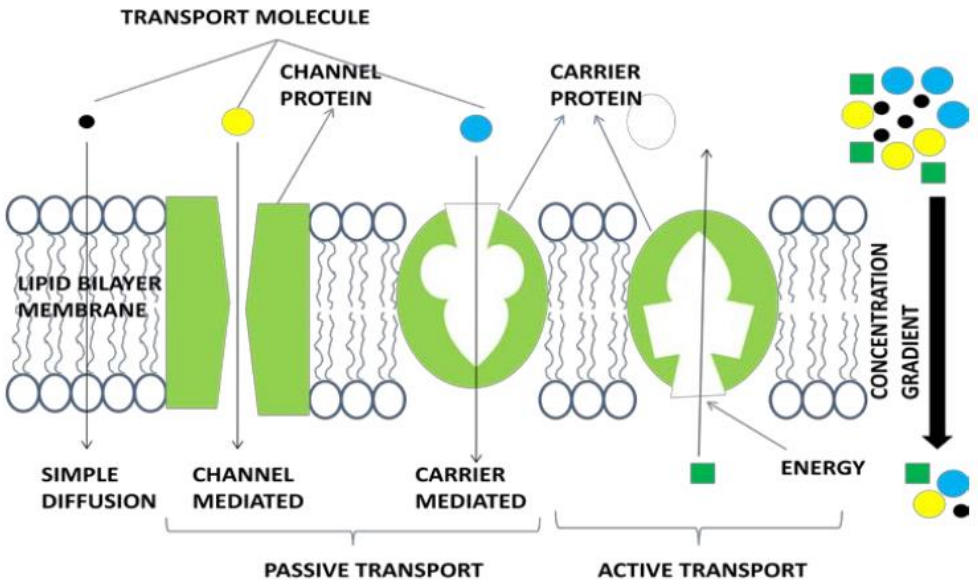

Figure 2: Mediated transport. (A) Passive transport and (B) Active transport

Passive mediated transport:

Substances that are too large or polar diffuse across the lipid bilayer on their own through membrane proteins called carriers, permeases, channels and transporters. Unlike active transport, this process does not involve chemical energy. So the passive mediated transport is totally dependent upon the permeability nature of cell membrane, which in turn, is function of organization and characteristics of membrane lipids and proteins.

Types of passive transport:

1. **Diffusion:**

The process of the net movement of solutes from a region of high concentration to a region of low concentration is known as diffusion. The differences of concentration between the two regions are termed as concentration gradient and the diffusion continues till the gradient has been vanished. Diffusion occurs down the concentration gradient.

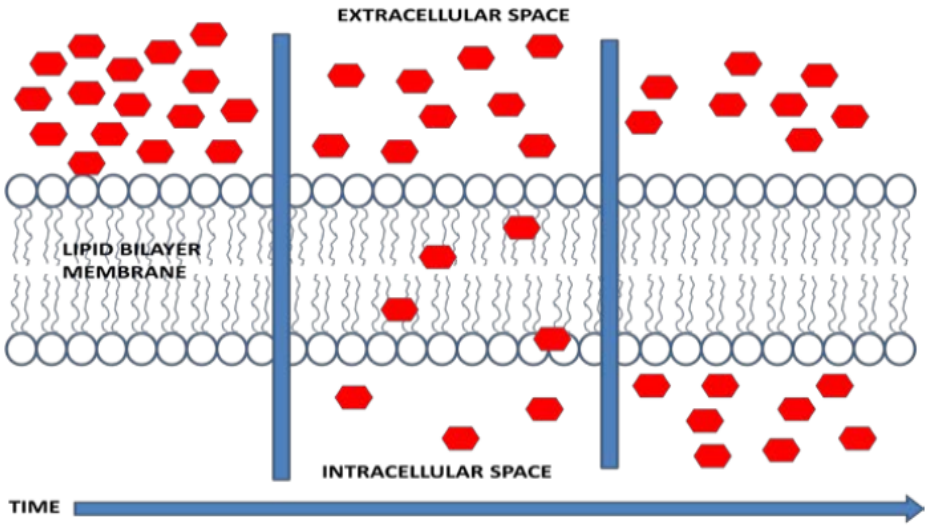

Figure 3: Diffusion.Extracellular space contains high concentration of solutes than intracellular space and hence the solutes move from extracellular space to intracellular space till there is no concentration gradient between the spaces.

2. Facilitated diffusion :

The process of the movement of molecules across the cell membrane via special transport proteins that are embedded within the cellular membrane is known as facilitated diffusion or called carrier-mediated diffusion. Many large molecules, such as glucose, are insoluble in lipids and too large to fit into the porins, therefore, it will bind with its specific carrier proteins, and the complex will then be bonded to a receptor site and moved through the cellular membrane.

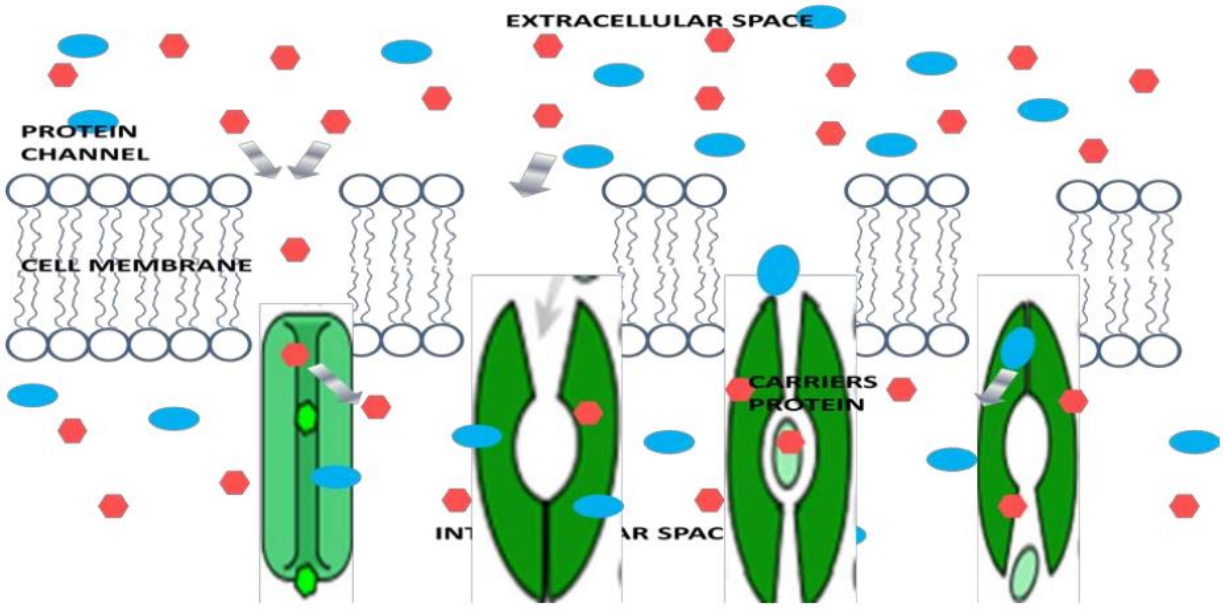

Figure 4: Facilitated transport.Movement of the solutes from extracellular space to intracellular space via carrier proteins and down its concentration gradient.

3. Filtration:

Filtration is the process of the movement of water and solute molecules across the cell membrane due to hydrostatic pressure generated by the system. Depending on the size of the membrane pores, only solutes of a certain size may pass through it. The membrane pores of the Bowman's capsule in the kidneys are very small, and only albumins (smallest of the proteins)can filter through. On the other hand, the membrane pores of liver cells are extremely large, to allow a variety of solutes to pass through and be metabolized.

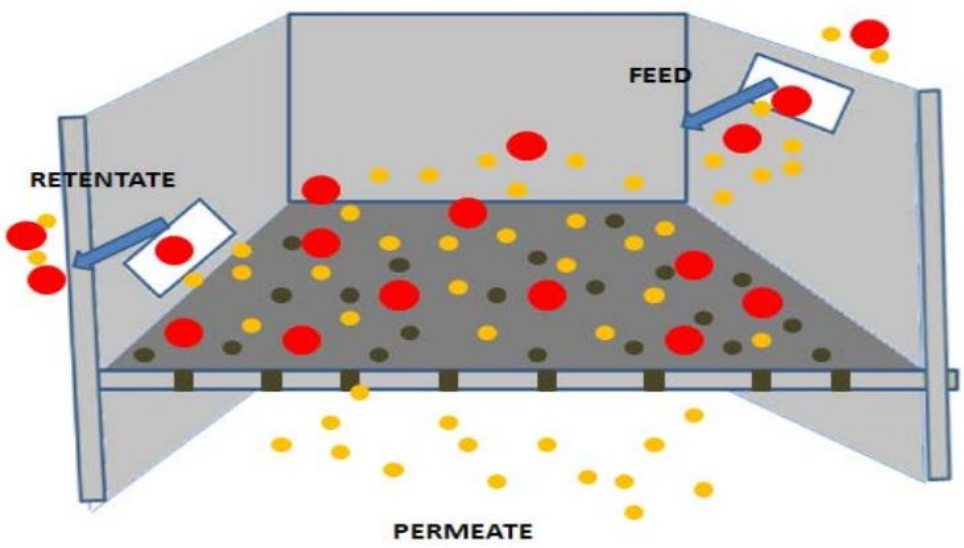

Figure 5: Filtration

4. Osmosis:

Osmosis is the type of diffusion of water molecules across a semi- permeable membrane, from a solution of high water potential to a region of low water potential. A cell with a less negative water potential will draw in water but this depends on other factors as well such as solute potential (pressure in the cell e.g. solute molecules) and pressure potential (external pressure e.g. cell wall).

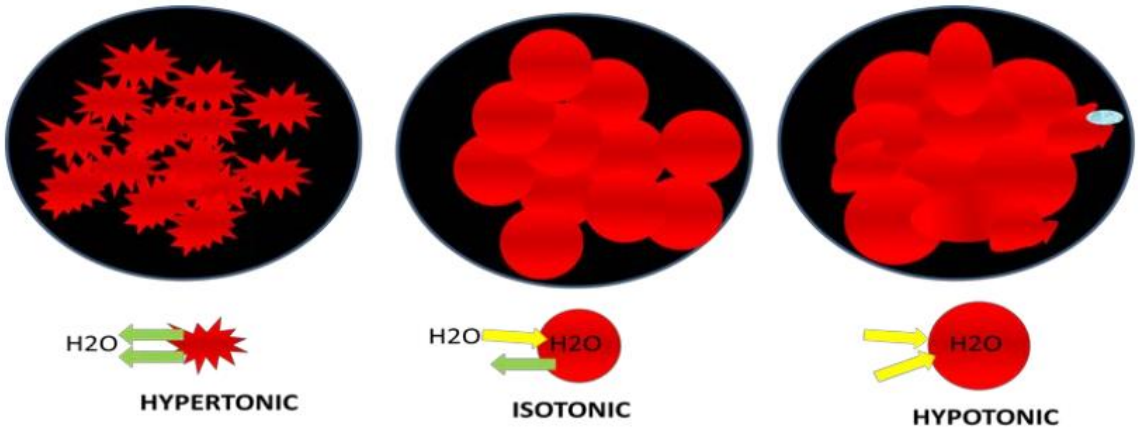

Figure 6: Osmosis.(A) In hypertonic solution, there are more solute molecules outside the cell, which causes the water to be sucked in that direction which leads to the shrinkage of cells. (B) In isotonic solution, there is equal concentration of solute on both sides, henceforth the water with move back in forth. (C) In hypotonic solution, there are less solute molecules outside the cell, since salt sucks and water will move inside the cell. The cell will gain water and grow larger, and finally burst.

Active transport:

Active transport is the movement of a substance against its concentration gradient (i.e. from low to high concentration). It is an endergonic process that, in most cases, is coupled to the hydrolysis of ATP.

Types of active transport:

1. **Primary active transport:**Primary active transport, also called direct active transport, directly uses energy to transport molecules across a membrane.
   Example:Sodium-potassium pump, which helps to maintain the cell potential.

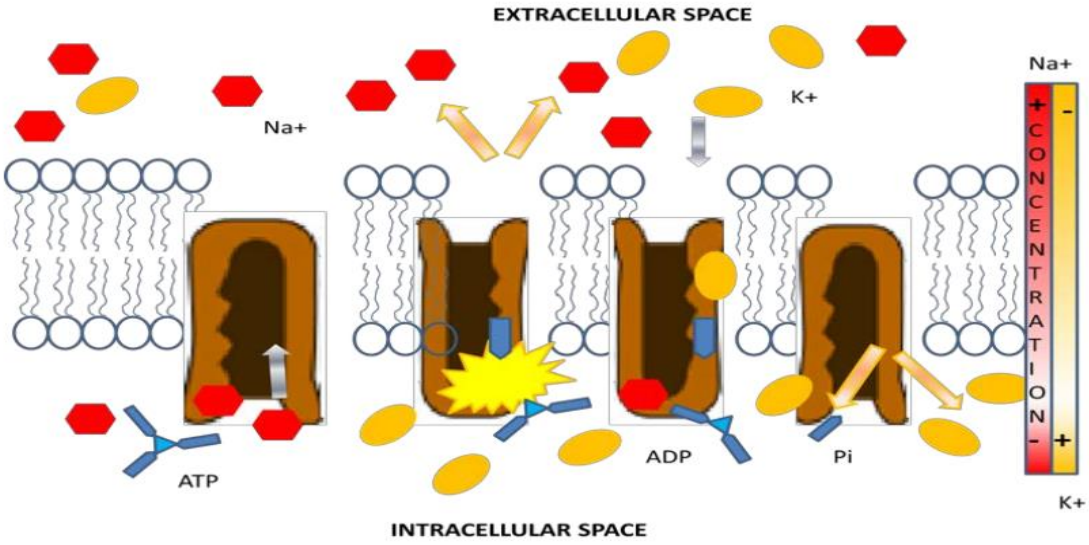

Figure 7: Primary active transport.The action of the sodium-potassium pump is an example of primary active transport.

2. **Secondary active transport:**Secondary active transport or co-transport, also uses energy to transport molecules across a membrane; however, in contrast to primary active transport, there is no direct coupling of ATP; instead, the electrochemical potential difference created by pumping ions out of the cell is instrumental.

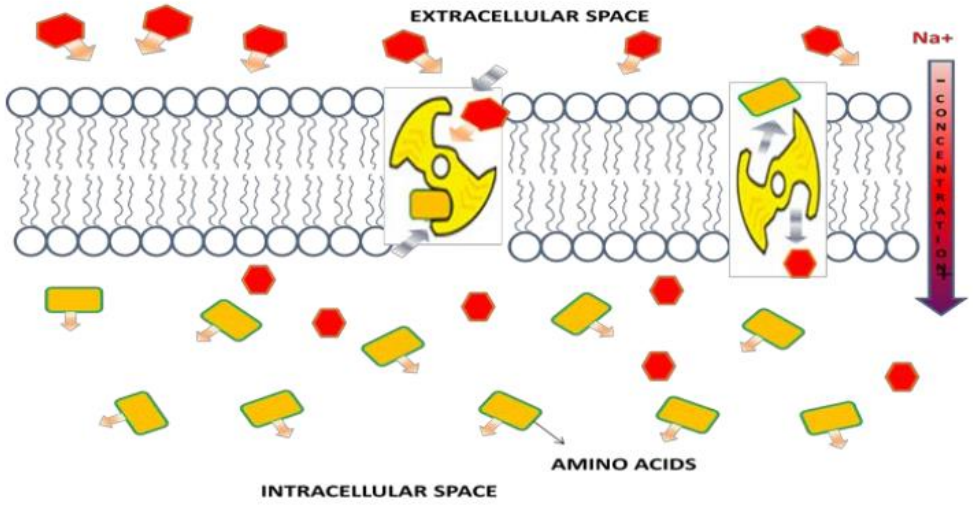

Figure 8: Secondary active transport

The two main forms of active transport are antiport and symport.

(a) Antiport:

In antiport two species of ion or solutes are pumped in opposite directions across a membrane. One of these species is allowed to flow from high to low concentration which yields the entropic energy to drive the transport of the other solute from a low concentration region to a high one.Example: the sodium-calcium exchanger or antiporter, which allows three sodium ions into the cell to transport one calcium out.

(b) Symport:

Symport uses the downhill movement of one solute species from high to low concentration to move another molecule uphill from low concentration to high concentration (against its electrochemical gradient).

Example: glucose symporterSGLT1, which co-transports one glucose (or galactose) molecule into the cell for every two sodium ions it imports into the cell.

Examples:

(A) (Na^+–K^+)–ATPase

(Na^+ - K^+)–ATPaseactive transport system is commonly found in the plasma membranes of higher eukaryotes, which was first characterized by Jens Skou. This transmembrane protein consists of two types of subunits: a 110-kD non-glycosylated α- subunit that

contains the enzyme's catalytic activity and ion-binding sites, and a 55-kD glycoprotein β-subunit of unknown function. Sequence analysis suggests that the α- subunit has eight transmembrane α-helical segments and two large cytoplasmic domains. The β- subunit has a single transmembrane helix and a large extracellular domain. The protein may function as an (αβ)2 tetramer *in vivo*.

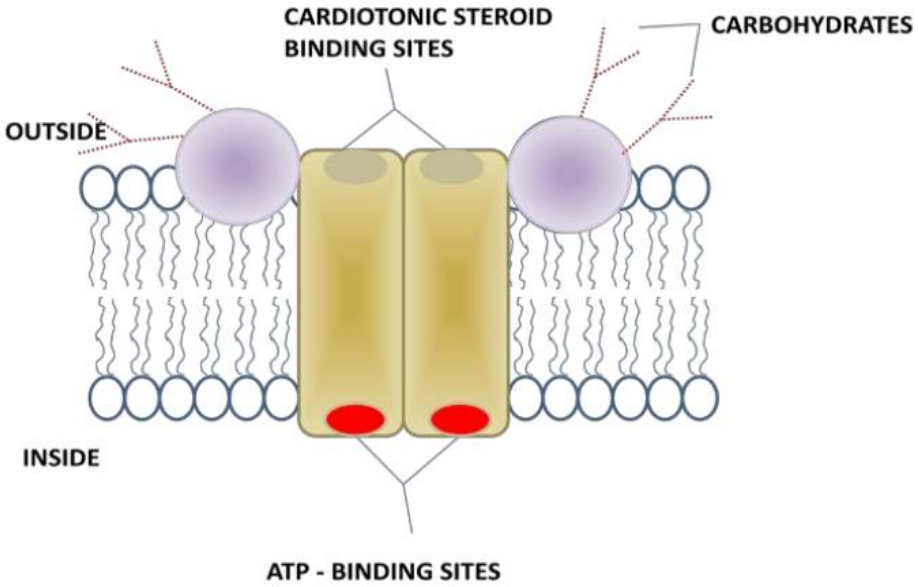

Figure 9: (Na^+ - K^+) – ATPase.This diagram shows the transporter's dimeric structure and its orientation in the plasma membrane. Cardiotonic steroids bind to the external surface of the transporter, thereby inhibiting transport.

The (Na^+ – K^+)–ATPase is also called as the (Na^+ – K^+) pumpbecause it pumps 3 Na^+ out of and 2 K^+ into the cell in presence of hydrolysis of intracellular ATP. The overall stoichiometry of the reaction is:

$$3\ Na^+(in) + 2\ K^+(out) + ATP + H_2O \rightarrow 3\ Na^+(out) + 2\ K^+(in) + ADP + Pi$$

(B) Ion Gradient–Driven Active Transport

For example, cells of the intestinal epithelium take up dietary glucose by Na^+ - dependentsymport. This process is an example of secondary active transport because Na^+ gradient in these cells is maintained by the (Na^+–K^+)–ATPase.The Na^+ –glucose transport system concentrates glucose inside the cell. Glucose is then transported into the capillaries through a passive-mediated glucose uniport (which resembles GLUT1).

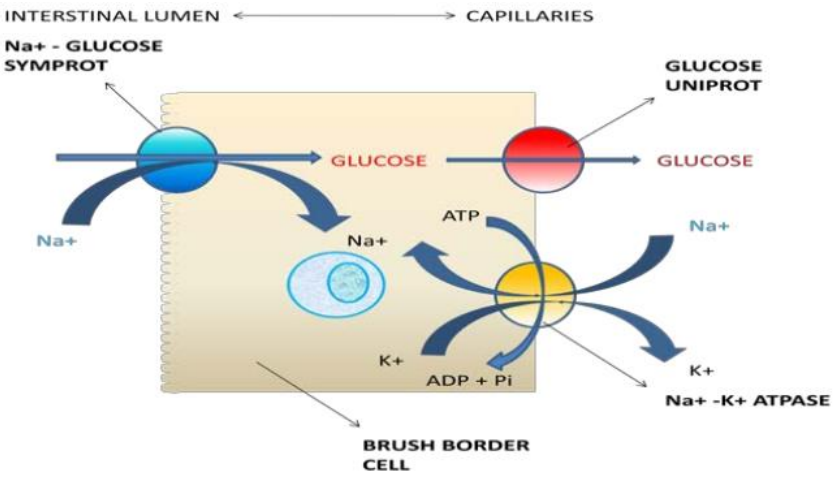

Figure 10: Glucose transport across Interstinal epithelium.The brushlike villi lining the small interstine greatly increases the surface area (a), thereby facilating the absorption of the nutrients. The brush border cells from which the villi are formed (b) concentrate glucose from the interstinal lumen in symport to Na^+ (c), a process that is driven by (Na^+ - K^+) – ATPase, which is located on the capillary side of the cell and functions to maintain a low internal [Na^+]. The glucose is exported to the bloodstream via a passive-mediated uniprot system similar to GLUT1.

Differentiating mediated and non-mediated transport:

Glucose and many other compounds can enter cells by a non-mediated pathway; that is, they slowly diffuse into cells at a rate proportional to their membrane solubility and their concentrations on either side of the membrane. The flux(rate of transport per unit area) of asubstance across the membrane increases with the magnitude of its concentration gradient. If glucose moves across a membrane by means of a transport protein, its flux is no longer linear.

This is one of four characteristics that distinguish mediated from non-mediated transport:

1. **Speed and specificity**-The solubilities of the chemically similar sugars D-glucose and D-mannitol in a synthetic lipid bilayer are similar. However, the rate at which glucose moves through the erythrocyte membrane is four orders of magnitude faster than that of D-mannitol. The erythrocyte membrane therefore contains a system that transports glucose and that can distinguish D-glucose from D-mannitol.

2. **Saturation**-The rate of glucose transport into an erythrocyte does not increase infinitely as the external glucose concentration increases. Such an observation is evidence that a specific number of sites on the membrane are involved in the transport of glucose; which becomes saturatedat high [glucose] and the plot of glucose flux versus [glucose] is hyperbolic. The non-mediated glucose flux increases linearly with [glucose].

3.**Competition**-The curve is shifted to the right in the presence of a substance that competes with glucose for binding to the transporter; for example, 6-*O*benzyl-D-galactose.Competition is not a feature of non-mediated transport, since no transport protein is involved.

4.**Inactivation**-Reagents that chemically modify proteins and hence may affect their functions may inhibit the rapid, saturatable flux of glucose into the erythrocyte.

Interesting facts:

- The binding of the neurotransmitter acetylcholine at certain synapses opens channels that admit Na+ and initiate a nerve impulse or muscle contraction.
- Sound waves bending the cilia-like projections on the hair cells of the inner ear open up ion channels leading to the creation of nerve impulses that the brain interprets as sound.
- Mechanical deformation of the cells of stretch receptors opens ion channels leading to the creation of nerve impulses.
- The crucial roles of the Na+/K+ ATPase are reflected in the fact that almost one-third of all the energy generated by the mitochondria in animal cells is used just to run this pump.

- ABC transporters must have evolved early in the history of life. The ATP-binding domains in archaea, eubacteria, and eukaryotes all share a homologous structure, the ATP-binding "cassette".