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Human red blood cells-2

Omar S. Hajjawi

Department of Biology, Arab American University, P.O.Box 240, Jenin, Israeli Occupied Territories of Palestine.

Email address:
ohajjawi@aauj.edu

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Abstract: Biochemists and cell biologists, who are interested in membranes, tend to regard the human red blood cell ambivalently. On one hand, red blood cells lack nuclei and the various intracellular organelles, yet that are highly specialized for a particular respiratory function. On the other hand, the human red blood cell presents an excellent model for membrane transport function.

Keywords: Human Erythrocyte, Electrochemical Potential, Donnan Equilibrium, Haemoglobin, Red Blood Cell Shape, Permean Ions, Osmotic Pressure, Band 3, Facilitated Transport, K^+/Cl^- Cotransport, $K^+(Na^+)/H^+$ Exchanger, Na^+/K^+-Atpase, Anion Transport.

6. Transport Systems in the Human Red Blood Cell

Why are membranes so important to cells? The most obvious answer is that membranes enclose and define the limits of living cells. We should also note that a membrane represents a natural kind of aggregation of amphipathic molecules, i.e. molecules containing both hydrophobic and hydrophilic ends. The packing of such molecules in a bilayer also represents a natural arrangement for a boundary between two different aqueous phases (Fig. 13). In addition, membranes are the natural "habitat" for many relatively nonpolar molecules formed by metabolism. Included are many proteins with hydrophobic surfaces. Thus, it is not too speculative to believe that proteins could exist which could traverse the membrane, presenting hydrophilic patch to one side or the other.

Water is present in native membranes, and proton magnetic resonance studies [162,164] indicate that much of it is associated with protein. Most of the water is loosely bound, the molecules being considerably less mobile than liquid water, and a little is tightly bound comparable with water in a solid hydrate.

After: Singer, S.J. and Nicolson, G. L. (1972)"The fluid mosaic model of the structure of cell membranes", *Science*, vol. 175, pp. 723; Wessells, N.K. and Hopson, J.L. (1988) *Biology*, p.108.New York: Random House, Inc.

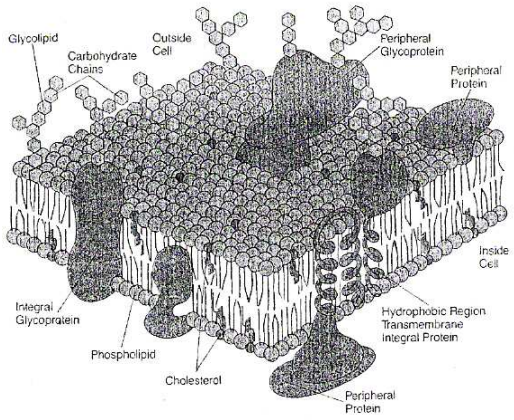

Fig. 13. *The fluid-mosaic model of membrane structure updated.*

The human red blood cell membrane which possesses both Na^+/ K^+ activated Mg^{2+} dependent-ATPase and Ca^{2+}-ATPase, supports cation concentration gradients. As a result, freely permeable anionic species also form concentration gradients (Table 5) which are further influenced by impermeable anionic cytoplasmic proteins [164]. The human red blood cell possesses a membrane potential (E_m) which is typically -10 mv [165].

After: Tyuma, I and Shimizu, K. (1970)"Effect of organic phosphates on the difference in oxygen affinity between fetal and

Adult human hemoglobin", *Fed.Proc.,* vol.29, pp.1112-1114; Lepke, S. and Passow, H. (1976)"The effect of pH at hemolysis on the reconstitution of low cation permeability

in human erythrocyte ghosts ", *Biochim. Biophys. Acta*., vol.455, pp.353 -370; Geers, C. and Gros, G. (2000)"Carbon dioxide transport and carbonic anhydrase in blood and muscle", *Physiol Review*, vol. 80 (2), pp.681-715.

Table 5. *Distribution of inorganic ions in the arterial human red blood cell.*

	H^+	OH^-	HCO_3^-	Cl^-	Na^+	K^+
Intracellular medium	$6.25x10^{-8}$	$1.6x10^{-7}$	16	77	16	134
Extracellular medium	$3.99x10^{-8}$	$2.5x10^{-7}$	25	115	140	4
$[Ion]_{in}/[Ion]_{out}$	1.56	0.64	0.64	0.67	0.11	33.5

(Concentrations are given in mM)

The red blood cell membrane is rather impermeable towards hydrophilic molecules owing to its hydrophobic nature. However, selective exchange of substances between the intracellular and extracellular compartments is achieved *via* three main permeation modes: simple diffusion, facilitated diffusion and active transport (Table 6 and Fig.14).

Adapted from: Crane, R.K. (1977)"The gradient hypothesis and other models of carrier-mediated active transport", *Rev.Physiol. Biochem.Pharmacol*., vol.78, pp.99-159; Deuticke, B. (1977)" Properties and structural basis of simple dif- fusion pathways in the erythrocyte membrane", *Rev.Physiol. Biochem. Pharmacol*., vol.78, pp. 1-98; Lieb, W.R. (1982)"*A Kinetic Approach to Transport Studies", in Red Cell Membranes a Methodological Approach*, Ellory, J.C. and Young, J.D. (eds).London: Academic Press Inc (London) Ltd; Horton, H.R., Moran, L.A., Scrimgeour, K.G., Perry, M.D. and Rawn, J.D. (2006) *Principles of Biochemistry*, 4th edn.,p.278.Upper Saddle River, NJ: Pearson Education, Inc.

Table 6. *Properties of major transport systems in the human red blood cell.*

	Property	**Simple diffusion**	**Facilitated transport**	**Active transport (primary & secondary)**
i	"Transporter"	Lipid	Protein	Protein
ii	Net flux	Ceases at electro-chemical equilibrium	Ceases at electro-chemical equilibrium	Possible to move a solute up electro-Chemical gradient
iii	Energy coupling	No	Indirectly (*via* membrane bound ATPase)	Directly (*via* membrane bound ATPase)
iv	Specificity	Low	High (capable of distinguishing between enantiomers)	High (capable of distinguishing between enantiomers)
v	Saturation	None	Exhibit saturation	Exhibit saturation
vi	Counter transport	No	Yes	Irreversible under physiological conditions

*Adapted fro*m: Wessells, N.K. and Hopson, J.L. (1988) *Biology*, p.111. New York: Random House, Inc.; Seifter, J., Ratner, A. and Sloane, D. (2005) Concepts in Medical Physiology, p.16. Baltimore, MD: Lippincott Williams & Wilkins; Nelson, D. L. and Cox, M.M. (2008) *Lehninger Principles of Biochemistry*, 5th edn., p.389. New York: W.H.Freeman and Company.

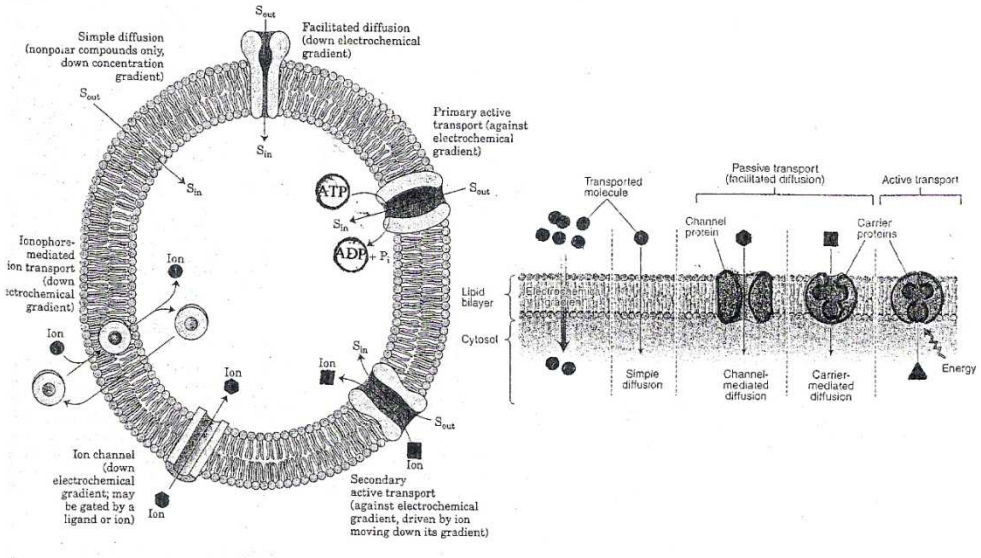

Fig. 14. *Types of transport.*

Transport kinetics is the movement of molecules across cell membranes in action from one aqueous environment to another. It is therefore restricted to movement of solute molecules and of water. Gases, such as oxygen and carbon dioxide, which are important in cellular metabolism, pass in and out of the cell in a dissolved state and the limiting factor in the rate of transfer is the extent to which the gases are soluble in the aqueous environment. Carbon dioxide is very soluble in water and passes freely through membranes but oxygen has a much more limited solubility and this becomes a limiting factor in cellular metabolism.

6.1. Simple Diffusion

Random Brownian (thermal) movement of molecules in solution cause a solute to disperse from areas of high concentration until the solution is homogeneous [166]. This process of passive diffusion can also occur across the red blood cell membrane (Fig.15), although the apolar core of the bilayer hydrocarbon chains adds a serious constraint on the type of molecule that can diffuse into the cell [133,167,168]. Charged molecules and large molecules are almost entirely excluded from this permeation mechanism and even small molecules such as water diffuse at 10^{-2}-10^{-3} times the rate of that observed across an aqueous barrier [43].

The two sides of the trough contain solutions with high and low salt concentrations, separated by a porous membrane. Free water molecules and sodium and chloride ions move randomly. The more concentrated ions on the right side strike the permeable membrane pores in more frequently than do the less concentrated ions on the left side. As a result, more sodium and chloride ions move from right to lift than the reverse until equilibrium is reached. Water behaves the same way, i.e. high concentration of water molecules move from left to right according to concentration gradient (the more diluted sodium chloride solution on the left, the higher concentration of water molecules and where water's free energy is higher too). So net movement of water and of Na^+ and Cl^- ions occur in the opposite directions until concentrations on both side are in equilibrium state. In simple diffusion, removal of the hydration shell is highly endergonic and the energy of activation ($\Delta G^{\#}$) for diffusion of the solute, whereas a transporter protein reduces the level of $\Delta G^{\#}$ by forming noncovalent interactions with the dehydrated salt and by providing a hydrophilic transmembrane passage.

Adapted from: Donnan, F.G.(1924)"The theory of membrane equilibria", Chem Rev.,vol. 1, pp.73-90; Wessells, N.K. and Hopson, J.L. (1988) *Biology*, p.110. New York: Random House, Inc.; Nelson, D. L. and Cox, M.M. (2008) *Lehninger Principles of Biochemistry*, 5th edn., p.390. New York: W.H.Freeman and Company.

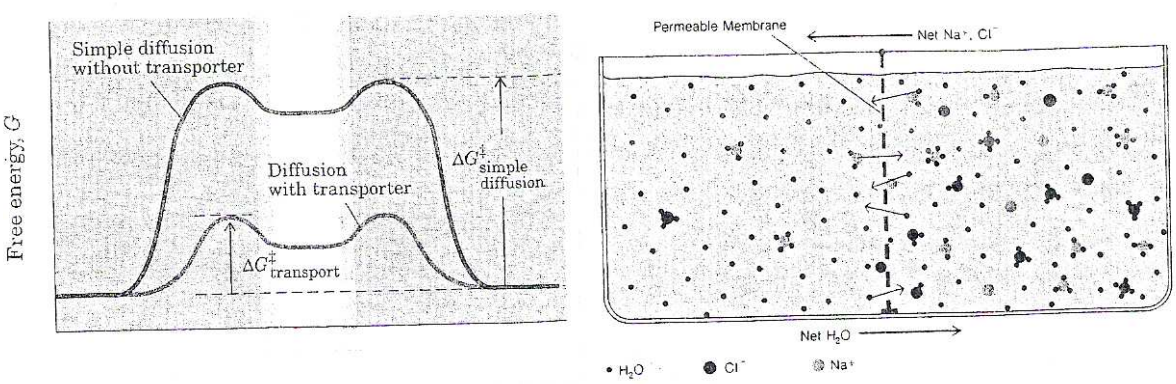

Fig.15. *A simple diffusion system and energy changes.*

The force responsible for simple diffusion is strictly speaking not a concentration gradient (c), but a gradient of chemical potential (μ). These two quantities are related (Eq.13) [169].

$$c = e^{\mu / RT} \tag{13}$$

where R is gas constant and T the absolute temperature.

Empirically, this diffusion is described by Fick's first law of diffusion [171,172],

$$J = \left(\frac{dn}{dt}\right) = -DA\left(\frac{dc}{dx}\right) = -DA\frac{d e^{\mu / RT}}{dx} \tag{14}$$

where J is the diffusion flux, dn/dt is the number of molecules per unit time passing through the membrane of surface area A and thickness x, under I finite concentration gradient c. D is the diffusion coefficient or diffusivity which is a small number in usual units ($cm^2.\ s^{-1}$) and in aqueous solution it does not change rapidly with molecular weight, M_{wt} . The negative sign signifies that solute moves in direction of decreasing concentration. However, as these differential rates depend partly on the nature of the membrane, D must also contain membrane specific factors [172]. D can also be expressed as ωRT where ω is the mobility; R is the gas constant, and T the absolute temperature.

By analogy with Ohm's Law, R = V / I (Resistance = Voltage divided by Current), the diffusion coefficient D can be considered as a conductance which is equivalent to the

reciprocal of resistance, R_m , or frictional coefficient between the diffusate and membrane [173]. Therefore, the computed value of the erythrocyte membrane resistance, which is ~$10^5 - 10^6$ ohm.cm^2 [36,174] can be employed for further insight into the nature of ion conductivity.

The classical interpretation of diffusion in terms of molecules changing place within one another in solutions as a result of random thermal motion is that of Einstein [171,175]. He derived two important equations which are still used in the interpretation of diffusion measurements. The first equation (Eq. 15), Stokes-Einstein equation, shows that the diffusion coefficient for a specified molecular species varies in different solvents and is inversely proportional to the frictional,

$$D = \left(\frac{RT}{L}\right)\left(\frac{1}{f}\right) = \frac{KT}{6\pi r \eta} \qquad (15)$$

coefficient f between solute and solvent, RT the kinetic energy expression, L the Avogadro number (6.022 x 10^{23} mol^{-1}), K Boltzmann's constant (1.381 x 10^{-23} JK^{-1}), T absolute temperature (^oK), r molecular radius and η viscosity of solution. Assuming spherical solute molecules of radius r in a medium of viscosity η, in which the solute obeys Stokes' Law, $f = 6\pi\eta r$ [176].The diffusion coefficient and molecular size can be related theoretically, and in practice the assumptions are imperfectly valid.

We can see from Eq. 15 that, as a transport mechanism, diffusion in free solution is not very selective with respect to molecular size; the values of D are roughly proportional to $M_{wt}^{-½}$ for small molecules and $M_{wt}^{-⅓}$ for larger ones [177]. Perhaps more important from the point of view of membrane transport is the comparison between diffusion in water and oil; taking vegetable oils as roughly analogous media to biological membranes. D for the same substance in oil would be 10^{-2} fold that in water, or less [178].

Einstein's important equation (Eq.16) in biology is used to calculate Δ, the distance moved by a molecule in a very short,

$$\Delta^2 = 2D\tau \qquad (16)$$

time τ during which dc/dx is assumed to be effectively unaltered [171,175]. In this form, the equation applies to a situation in which the concentration gradient is unidirectional. For diffusion in three dimensions Eq.17 replaces Eq.16.

$$\Delta^2 = 6D\tau \qquad (17)$$

Movement of ionized solutes are influenced also by potential (electrical) gradients, but the rate of flow of the solute may still be described in simple terms by the Nernst Planck equation [179],

$$J = -\omega C \left(\frac{RT}{C}.\frac{dC}{dX} + zF\frac{d\psi}{dX}\right) \qquad (18)$$

where z is number of electrical charges on permeating molecules, F is the Faraday (96,500 coulomb/mol) , $d\psi/dx$ is electrical potential gradient across membrane and the expression in brackets is the combined force due to concentration and electrical gradients, that is, the electrochemical gradient. The characteristics of solute movement through membranes by simple passive permeation can be described completely by these equations.

Studies of the rates of passive movements of a variety of solutes across cell surface membranes have provided significant information on the chemical and physical nature of these barriers [180]. Quantitative analysis of permeability phenomena is complicated by the simultaneous movement of solute and solvent molecules, but methods have been devised which circumvent this and facilitate quantitative comparisons of permeability characteristics of various natural and artificial membranes [35]. For instance, methods have been developed for following volume change in erythrocytes which result from the creation of a transmembrane concentration gradient with respect to a penetrating non-electrolyte solute. The graph of volume change against time can be extrapolated to zero time to obtain an initial rate of transfer [181]. Further extrapolations from experiments with a variety of solutes, e.g. glycerol, sucrose, urea, formamide, and a variety of concentration gradients provided kinetic parameters which have been expressed in terms of hypothetical pores radii (3.8-4.2Å) through which permeants might pass [168,182]. The calculations involve a number of assumptions concerning the applicability of particular physical laws to movement of solutes through membranes, but the values obtained for pore radii have provided a useful basis for comparing the permeability characteristics of red blood cell membranes to water and other small uncharged molecules [163].

6.2. Facilitated Transport

Many substances glucose [183,184], amino acids [185,186], and anions [46,187,188,189] can penetrate the erythrocyte membrane more rapidly than would be predicted from their chemical and physical properties on the basis of their diffusion coefficients (Eq. 14). Therefore, there is evidence of an extra mechanism, the kinetics of which is readily distinguishable from the passive permeation; it shows a much lower activation energy (Fig. 16) and somewhat less marked both temperature and pH dependence, and no metabolic energy is required to drive the process although it could be argued that energy is expended in maintaining an intact membrane. The net transport of molecules is therefore always in a direction of decreasing electrochemical potential. This gradient provides the driving force for facilitated diffusion irrespective of whether this is a gradient of the solute transported or another molecular species to which movement of the first is coupled [38,190].

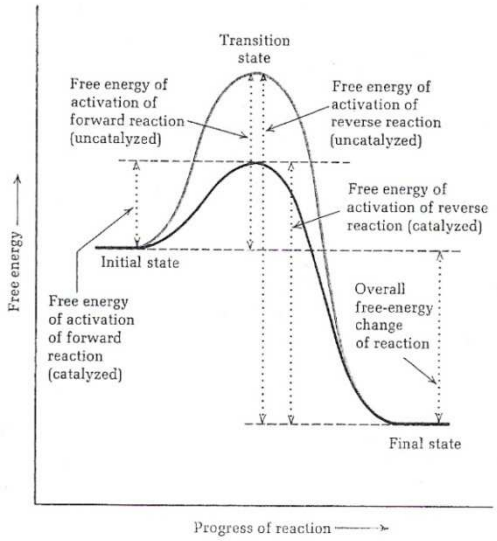

Fig. 16. *Energy profile for a chemical reaction, uncatalyzed and catalyzed.*

The mechanism is identified as a mediated permeation in which some specific membrane bound proteins play a role. Passive and mediated permeations are more generally distinguishable on the basis of differences in the kinetics and specificities of the two processes. A system which mediates solute movement is invariably of limited capacity and should eventually become saturated. The simple diffusion coefficient and the Nernst-Planck equations (Eq. 15, Eq. 18) of passive permeation are not appropriate for describing the kinetics of mediated transport. The most useful attempts to study the transporters of such systems in action have assumed a characteristic affinity (K_m) of the solute molecule with some protein component of the membrane. So, the translocation of solutes *via* such processes is analogous to enzyme-substrate intermediate complexation, in which such a formation of ternary complex in the membrane decreases the activation energy of solute transport [133,191].

A chemical reaction such as $[A_{extracellurar}] \rightarrow [P_{intracellular}]$ takes place because of electrochemical potential gradient. Note the difference between the magnitude of activation energy ($\Delta G^{o\ddagger}$) and the standard free energy change of the reaction (ΔG^{o}). When a given population of [A] molecules possess enough energy to attain activated condition, i.e. transition state, in which the probability is very high that a chemical bond will be made or broken to form product [P]. This transition state is at the top of the energy barrier separating the reactants, $A_{extracellurar}$], and the resultants, $[P_{intracellular}]$. The rate of the reaction (or transport) is proportional to the concentration of this transition-state species. The rate of chemical reaction can be accelerated by addition of a catalyst. Catalysts combine transiently with the reactants to produce a transition state having a lower energy of activation than the transition state of the uncatalyzed reaction. When the reaction resultants are formed, the free catalyst is regenerated.

Adapted from: Nelson, D. L. and Cox, M.M. (2008) *Lehninger Principles of Biochemistry*, 5th edn. p.25. New York: W.H.Freeman and Company.

A number of enzyme poisons are known to markedly and specifically inhibit facilitated transport when added in concentrations low enough to exclude any non specific inhibition on membrane permeability [192]. Also, the transport sites possess stereo chemical specificity to discriminate between D- and L-stereoisomers of certain solutes [181,193,194]. Such characteristics have been confirmed for reconstituted preparations in phospholipids vesicles [195,196]. Certain kinetic features have been attributed to facilitated transport, for instance 'uphill' movement of solutes [36,136] and self-inhibition [88,117] Since there is similarity between the kinetics of facilitated transport systems and enzyme reactions, the flux $J_{1\rightarrow2}$ of a permeant in one direction is described by adopting a Michaelis-Menten [197] type expression,

$$J_{1\rightarrow2} = \frac{J_{max}\ C_1}{K_m + C_1} \qquad (19)$$

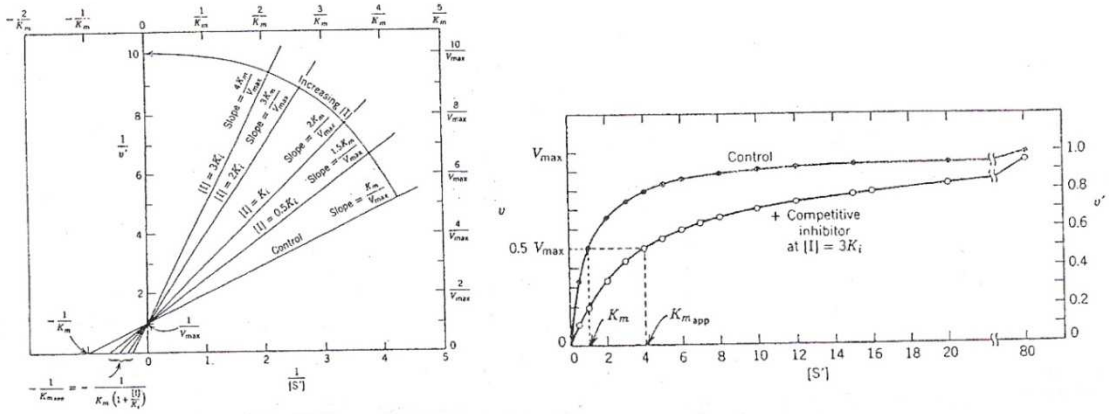

Fig. 17. *Graphical determination of V_{max} and K_m .*

where $J_{1\rightarrow2}$ is the flux from compartment 1 to compartment 2, J_{max} is the maximum rate of flux, i.e. the plateau value at saturation of the mediated system, K_m is the affinity constant and it can be expressed as the permeant

concentration at which $J = J_{max \div 2}$, and C_1 is the concentration of solute in compartment 1 (Fig. 17). The flux expression given in Eq. 19 refers the movement of solute in one direction only, but solutes may move with equal facility in the reverse direction. The net solute

A plot of transport velocity, v, against substrate concentration, [S], in the presence and in the absence of a fixed concentration of a competitive inhibitor. Also, a Lineweaver-Burk double reciprocal, 1/v versus 1/[S], plot in the presence of different fixed concentrations of a competitive inhibitor. Transporter kinetics: V_{max} is the constant rate reached when the transporter is completely saturated with the substrate. The slope of the line is K_m / V_{max} , the y intercept is $1/ V_{max}$ and the x intercept is $1/ K_m$.

After: Michaelis, L. and Menten, M.L. (1913)"Die kinetik der invertinwirkung", *Biochem.Z.*, vol. 49, pp. 333-369.

flux is the difference between influx and efflux (Eq.20).

$$\text{Net flux} = J_{1\rightarrow 2} - J_{2\rightarrow 1} \qquad (20)$$

where 1 and 2 refer to opposite sides of the membrane.

6.3. Active Transport

In much the same way that simple diffusion cannot account for the rates of carrier mediated diffusion across membranes, the rate of permeation, and particularly the steady-state distribution of some of the most important physiological substances, defy explanation in terms of spontaneous diffusion. The low intracellular sodium (Na^+) and high potassium (K^+) concentrations found in red blood cells , and the uptake of a variety of sugars, amino acids and other substrates necessarily involves mediated permeation against electrochemical potential gradients, a coupled energy supply is essential [146,198]. Such transport can only be accomplished at the expense of metabolic energy and an important feature of active-transport systems is that they are all unidirectional in their energy-requiring function.

The standard free energy change for the movement of uncharged molecule from one side a membrane at concentration C_1 to the other at concentration C_2 is given by the usual equation [199],

$$\Delta G = -2.3\ R\ T \log K'_{eq} + 2.3\ R\ T \log \frac{C_2}{C_1} \qquad (21)$$

K'_{eq} a simple diffusion process is unity. That is, at diffusion equilibrium, the concentration of the solute is the same on both sides of the membrane. Thus, ΔG for the movement of the solute from side 1 to side 2 under nonequilibrium conditions is given by

$$\Delta G = 2.3\ R\ T \log \frac{C_2}{C_1} \qquad (22)$$

Eq. 22 gives the free energy of dilution or concentration. That is, the difference in chemical potential of a solute at two different concentrations. If C_1 is greater than C_2, ΔG is negative. This says that the molecules of solute will spontaneously move from compartment 1 to compartment 2 (a conclusion we intuitively reach without any equations). The red blood cells have the ability to transport and accumulate certain compounds against large concentration gradient (Hald et al., 1948; Lepke and Passow, 1973; Lew et al., 2003). The ΔG for such transport processes is clearly positive and, consequently, energy must be supplied. That is, the uphill transport of a molecule must be coupled somehow to an exergonic reaction in order to make the overall ΔG zero or negative. The mechanisms of energy coupling as well as the mechanisms of transport itself are subjects of intensive research.

Active transport systems (Na^+/ K^+, Mg^{2+} , Ca^{2+} pumps) also create and maintain ionic gradients, allowing the cell precise control over its internal physiological environment [38,200,201]. One pump, often called the sodium pump, maintains a low Na^+/ K^+ ratio inside the red blood cells in the face of a high Na^+/ K^+ ratio in the intracellular medium [180,202,203], whereas Ca^{2+} pump maintains the intracellular concentration at a much higher level than that of the extracellular medium [204]. Most transport processes are mediated by specific membrane protein transporters; the term "permease" is often used for such membrane transport systems. Interesting examples of active transport are provided by the distributions of ions across membranes in living red blood cell systems (Table 5). There is direct evidence that the transporter does not move bodily through the membrane, but instead straddles the membrane, part of the molecule being at the outside surface and part at the inside surface of the membrane. For example, the ATP (adenine triphosphate) splitting molecule which transports K^+ into intracellular medium and Na^+ out of it against the concentration gradients [205]; the transporter molecules function by actually transporting legands across the lipid membrane as a result of solute-transporter protein conformational changes (Fig. 18).

This active transport system is primarily responsible for maintaining the intracellular [Na^+] and [K^+] at 16mM and 134mM, respectively, whereas their extracellular concentrations are 140mM and 4mM, respectively for setting-up and generating the membrane potential. It does this by transporting out of the cell three sodium cations for every two potassium cations transported into the cell. Step 1: One subunit of the protein hydrolyzes the ATP and transfers the P_i to an aspartate side chain on another subunit. Intracellular $3Na^+$ ions anchored to transporter binding site. Step2: The phosphorylation of one subunit causes a conformational change in the transporter in which the $3Na^+$ ions are effluxed the extracellular medium. Step 3: While the transporter is outwards facing and its sub unit is still phosphorylated, extracellular $2K^+$ ions access their binding site. Step 4: The hydrolysis of P_i bond (dephosphorylation) causes conformation change in the transporter, in which the transporter is inwards facing and the $2K^+$ ions are influxed.

The hydrolysis of a single ATP per transport cycle provides sufficient free energy (~ -12kcal.mole) to drive the uphill transport of these cations.

Adapted from: Campbell, M.K. and Farrell, S.O. (2006) *Biochemistry,* 5th edn.p.201. Belmont, CA: Thompson Learning, Inc.

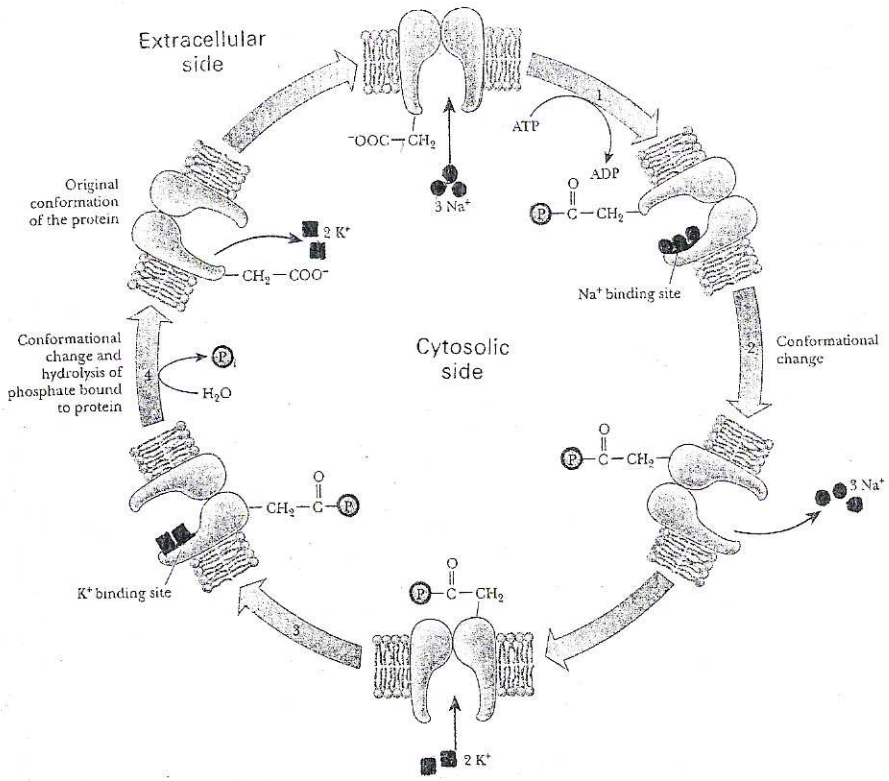

Fig.18. *Postulated mechanism of sodium-potassium ion pump.*

A number of specific transporters have now been identified, but the precise mechanisms by which they catalyze the transport have not been established as yet.

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