TRANSMEMBRANE ION AND WATER TRANSPORTS IN ERYTHROCYTE VOLUME HOMEOSTASIS: AN OVERVIEW OF THE PHYSIOLOGIC PROCESSES

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ABSTRACT

Background: The intraerythrocytic concentrations of ions (Na^+, K^+, Cl^- and HCO_3^-) play key roles in maintaining erythrocyte volume homeostasis. Anisosmotic and isosomotic changes of these ion concentrations challenge erythrocyte volume to either shrink or swell, thereby sending signals to activate regulatory volume mechanisms that are mediated by ion transporters. Ion fluxes directed inwardly or outwardly with obliged water movements do restore the erythrocyte volume to its steady state. These physiological phenomena prevent the erythrocyte from becoming overhydrated or dehydrated with the consequence of intravascular haemolysis or senescent changes associated with eryptosis. **Objectives:** To review the literature on the physiological processes associated with transmembrane ion and water transports during erythrocyte volume homeostasis. **Method:** Offline and online libraries were searched with indexing tools using keywords derived from the subject area of review. **Conclusions:** The review has highlighted the physiological concepts involved in erythrocyte volume homeostasis in relation to the engaged transmembrane ion and water transport systems, which can influence experimental designs to study ion and water channel blockers and channelopathies of erythrocytes.

Keywords: Erythrocyte channelopathy, Erythrocyte volume, Homeostasis, Regulatory volume mechanism, Transmembrane transport, Water and ion channels

INTRODUCTION

Erythrocytes are produced through erythropoiesis whereby the erythrocyte volume is determined after the nucleus and organelles are eliminated.[1,2] The erythrocyte volume estimated as the mean corpuscular volume[3] is homeostatically guarded by the equilibrium of osmolarity in the intracellular and extracellular compartments.[4] Changes in transmembrane osmolarity which create osmotic gradient across the membrane automatically causes osmotic water flow across the membrane[5] leading to changes in cell volume.[6] Continuous swelling of erythrocytes leads to haemolysis[7,8] while dehydration causes an osmotic shock associated with eryptosis[9,10] and macrophagic removal of such cells in reticuloendothelial system.[11-13] The volume changes are resisted by physiological processes that produce changes in cytosolic ionic concentration in order to maintain a steady state in erythrocyte volume.[14] This present review was aimed at identifying the important physiological processes involved in erythrocyte volume homeostasis in relation to transmembrane ion and water transports. The physiological phenomena were explored through extensive literature

search in the internet and offline sources, with relevant key words, in order to articulate an overview of current concepts dealing with circumstances associated with erythrocyte volume alterations in clinical science. The definitions of some of the physiological principles used in this review are presented in Table 1.

Table 1: The regulation of cell turgor in response to changes in the osmolarity of the external environment.

Principle	Definition
Active Transport	Transport of ion against concentration gradient requiring expenditure of energy
Donnan Principle	There is electrochemical balance across the membrane irrespective of intracellular and extracellular ion concentrations
Fick's Law	Flux of ion is directly proportional to the concentration gradient
Passive Transport	Facilitated diffusion moving ion from fluid of high to low concentration
Osmosensing	Recognizing changes in environmental salinity
Regulatory Volume Adjustment	Change in cell size to normalize/rectify transient osmotic swelling or shrinking

Membrane structural composition and transmembrane transport pathways

The cell membrane of erythrocytes is made up of a lipid bilayer which does not allow free movement of molecules and ions across it. The lipids in the membrane are mostly phospholipids. These amphiphilic (or amphipathic) phospholipids consist of a hydrophilic, or polar, phosphate-containing head group attached to two hydrophobic, or nonpolar, fatty acid chains. The phospholipids assemble into a sheet or leaflet. The polar head groups pack together to form the hydrophilic surface of the leaflet, and the nonpolar fatty acid chains form the hydrophobic surface of the leaflet. Two leaflets combine at their hydrophobic surfaces to form a lipid bilayer.[15] The lipid compositions of the leaflets constituting a single lipid bilayer can differ. Whereas phosphatidyl choline is most abundant in the outer leaflet, phosphatidyl serine is found almost exclusively in the inner leaflet.[16]

Large integral or transmembrane macromolecular proteins consisting of many peptide subunits, either singly or in groups, form water-filled pores that extend across the lipid bilayer of the membrane. They create transport pathways for molecules and ions across the lipid membrane (Figure 1). These proteins involved in transmembrane transport are either carriers or channels having physiological peculiarities. They conduct passive or active ion transport.

The passive transport is a facilitated diffusion which occurs when ions move from a fluid compartment of high ion concentration to another having a lower ion concentration without expenditure of energy. The inward (influx) and outward movements (efflux) of ions across the membrane depends on the concentration gradient of the ions which can be predicted under Fick's law of diffusion which states that the *flux* of an ion across a membrane is directly proportional to the
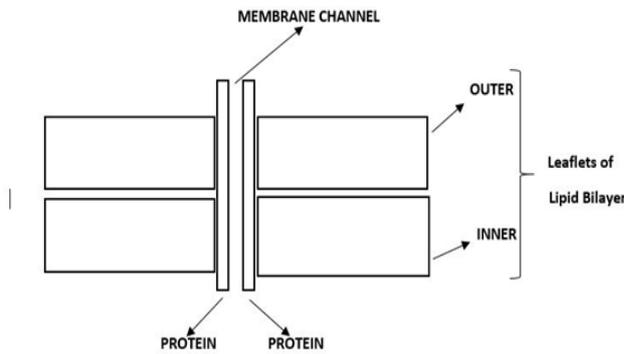
Figure 1: Protein channel across erythrocyte membrane

concentration gradient.[17] The facilitated diffusion may occur through ion transport systems that are either gated or ungated as means of regulation of the transport. The gating may be achieved by internal or external ligands, mechanosenitive proteins or voltage changes in membrane potential (Figure 2).
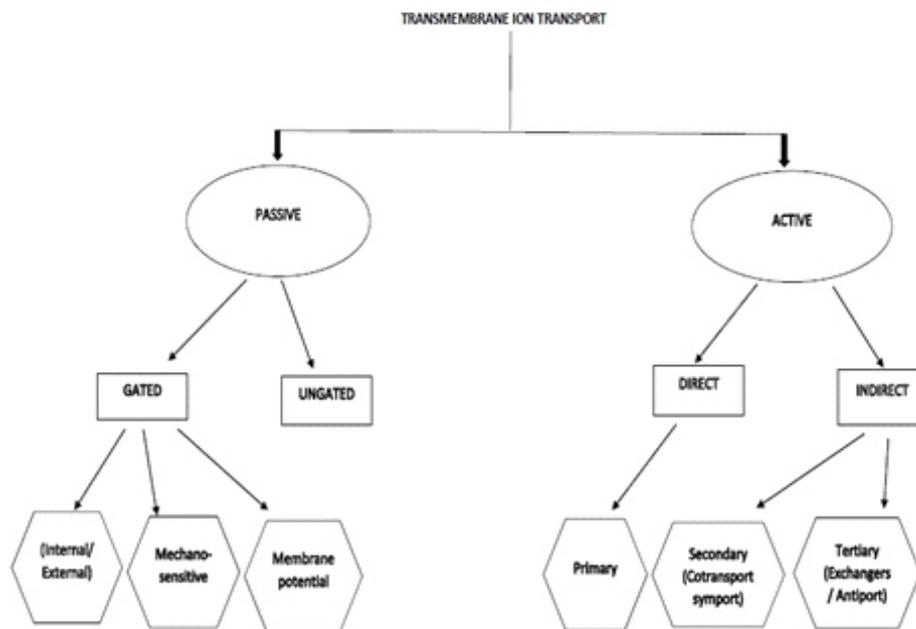

Figure 2: Types of transmembrane ion transport

Active transport of ions across a membrane requires expending energy to drive the ion. There are primary, secondary and tertiary active transports as well as direct and indirect active transports. A direct (primary) active transport occurs against the concentration gradient of ions where a driven ion is moved from a fluid compartment of lower concentration to another of higher concentration using energy from the dephosphorylation of adenosine triposphate (ATP). Indirect active transport of ions takes place by transmembrane proteins using energy stored in the gradient of a directly-pumped ion. The concentration gradient of an ion is established by

direct active transport and the energy released is used to transport another ion. Two types of indirect active transports are co-transports (secondary active transport) and exchangers (tertiary active transport). In co-transport (symport), the driving ion and another pumped ion or molecule passes through the transmembrane protein in the same direction. In exchanger (antiport) system, the driving ion diffuses through the pump in one direction providing the energy for the active transport of another ion or molecule in the opposite direction (Figure 2).

Principle of cellular osmoregulatory balance

Changes in concentration of solutes either in intracellular or extracellular fluid due to anisosmotic or isosmotic factors would cause an osmotic flow of water to the side of the membrane with a greater osmotic pressure.[18] Swelling of the erythrocyte occurs if the diffusion of water is inward while shrinkage results from an outward diffusion of water.[6] Ionic fluxes associated with these water movements are guided by Donnan principle to ensure that there is an electrochemical balance despite the irregularities in ion concentrations across the membrane[18] and cell volume is maintained at a steady state.

Osmosensing by erythrocytes

Rapid changes of cell volume are usually caused by movement of water across the cell membrane, which is driven by hydrostatic and osmotic pressure gradients across the cell membrane. Erythrocyte swelling and shrinkage exert profound effects on intracellular signalling mechanisms, which in turn modify a multitude of cellular functions including the volume regulatory mechanisms. Erythrocytes exposed to hypotonic or hypertonic extracellular fluid, initially swell or shrink, after which they tend to adjust to the original cell volume by regulatory cell volume decrease (RVD) or regulatory cell volume increase (RVI), respectively.[6]

Erythrocytes are able to detect volume changes by signals picked by sensors that transmit to and activate various ion regulatory transporters.[19] The signals could be as a result of dilution or macro-molecular crowding of the intracellular mileu,[14, 20] changes in ionic strength or concentrations of specific ions, and mechanical or chemical changes in the lipid bilayer.[21]

Alteration of steady state volume causes the activation of Band 3 protein, an anion exchanger (AE_1) which activates volume regulatory ion channels.[22, 23] Stretching of the membrane also activates a mechanosensitive non-selective cation channel, Piezo 1[24] that is involved in erythrocyte volume homeostasis.[25] Piezo 1 is a stretch activated cation channel that opens and ultimately counteracts the increase in water influx to avoid erythrocyte lysis during swelling by allowing the influx of calcium[26] which would influence Ca^{2+}-activated-K^+ channels (Gardos channels) to open for efflux of K^+.[27-32]

The electrochemical concentration and osmotic gradient across the membrane activates swelling-sensitive osmolyte channels[33] and volume sensitive outwardly rectifying anion channels (VSOACs)[34, 35, 36] that determine its permeability to and efflux of K^+ and Cl^-.[37] Kinases act as sensors for transmitting signals of cell volume change.[38] Kinases are inactivated by protein dilution during cell swelling to facilitate influx of K^+ and Cl^- and activated by protein crowding during cell shrinkage[14] to inhibit K^+Cl^- efflux. The presence of kinases ensures that effective RVI occurs while the presence of kinase inhibitors reduces RVI.[39-41] Kinases also mediate phosphorylation of proteins which is important for ion transport.[37,42, 43]

Protein phosphatase has been reported to activate and also regulate KCl cotransport.[44] Inhibition of protein phosphatase abolished swelling activated K^+ transport in human erythrocytes.[44] The concentration of oxygen in red cells has been reported to affect KCl cotransport.[37, 45] At low oxygen levels, cells had a deactivated KCl co- transporter that was observed by cell swelling due to accumulation of K^+ via the Na^+/K^+, Cl^- cotransporter and osmotically obliged water.[37] An increase in temperature of the erythrocyte can activate KCl cotransport.[46, 47] Changes in intracellular pH can also alter ion fluxes and affect KCl cotransport.[37, 48]

Intraerythrocytic ion composition controlled by transmembrane ion transport

Na^+, K^+, Cl^- and HCO_3^- are intra-erythrocytic ions that are osmotically relevant and their concentrations maintain volume homeostasis. Interspecies and intraspecies differences occur in cation transport and in intracellular concentrations of Na^+ and K^+.[49, 50] Erythrocytes possess a Cl^--dependent, Na^+-independent K^+

transport system cotransporting K^+ and Cl^- in a 1:1 stoichiometry that is independent of membrane potential.[51] K^+-Cl^- cotransporters (KCCs),[19] Na^+-K^+-Cl^- cotransporter[52] and Ca^{2+} activated K^+ channel[53] are present in erythrocytes for transporting K^+. The coupled movements of Na^+ and K^+ across erythrocyte membranes are accomplished by a membrane-bound enzyme which demonstrates ATPase activity when incubated with Na^+ and K^+ transporting $3Na^+$ and $2K^+$ for each ATP split.[54-56] Maintenance of a low intracellular calcium concentration is necessary for preserving the integrity of erythrocytes. This is achieved by low membrane permeability to calcium in the inward direction and by an active efflux mechanism by the membrane bound enzyme Ca^{2+} -Mg^{2+}-ATPase.[57] Erythrocytes actively extrude Ca^{2+} using a calcium pump having Ca^{2+} activated Mg^{2+} dependent ATPase activity. The calcium pump is activated by a calcium binding protein called calmodulin.[58]

Transmembrane water transport through water channels
Aquaporin proteins are made up of six transmembrane α-helices arranged in a right-handed bundle with the amino and the carboxyl terminal located on the cytoplasmic surface of the membrane.[68-73] The architecture of the aquaporin channel allows water molecules to pass only in single file while electrostatic tuning of the channel interior controls aquaporin selectivity against any charged species[74-81] implying that only water molecules pass through the aquaporin water pore and transport of any ion as well as protons and hydroxyl ions is abolished.[82-86]

Estimation and variation of erythrocyte volume
The erythrocyte volume is assessed by the estimation of mean corpuscular volume (MCV) which is calculated with packed cell volume and erythrocyte count.[87] The MCV can also be estimated by the use of volume-sensitive automated blood cell counters like the electronic Coulter counter.[88]

During erythrocyte maturation, the size of the cell decreases and ratio of cytoplasm to nucleus increases with the size of the nucleus diminishing until it completely disappears at maturation.[89]

Variation in erythrocyte volume could be observed when the cell is reduced (dehydrated) or increased (over hydrated) in size probably due to anisosmotic or isosmotic changes.[6] The variations could also be caused by membrane ion channel disorders[90, 91] leading to an abnormally increased efflux or influx of cations and water.

Regulatory volume adjustments in erythrocytes
Regulatory volume decrease (RVD): A regulatory volume decrease (RVD) of cells is brought about by a net loss of cell solute together with osmotically obliged water. The RVD is achieved by increasing membrane permeability to solutes with an outwardly directed electrochemical gradient such as K^+. The RVD occurs with the progressive net loss of cellular K^+, Cl^- and amino acids until the reduced cell volume has been attained and net fluxes cease.[92]

In many cells, swelling leads to the activation of non-selective cation channels.[93] These channels do not directly serve cell volume regulation but allow the passage of Ca^{2+}, which then enters the cells and activates Ca^{2+}-sensitive K^+ channels.[93]

Stimulation of Na^+-Ca^{2+} exchanger due to parallel extrusion of Ca^{2+} by the Ca^{2+}-ATPase was reported in swollen erythrocytes.[28]

Regulatory volume increase (RVI):
Cell shrinkage inhibits K^+ and Cl^- channels, preventing cellular electrolyte loss.[93] The major ion transport systems accomplishing electrolyte accumulation in shrunken cells are the Na^+-K^+-$2Cl^-$ cotransporter[95] and the Na^+/H^+ exchanger. The latter alkalinizes the cell leading to parallel activation of the Cl^--HCO_3^- exchanger. The H^+ and HCO_3^- exchanged for NaCl by the Na^+-H^+ exchanger and the Cl^--HCO_3^- exchanger are replenished within the cell from CO_2. Na^+-K^+-ATPase is also activated in RVI to replace accumulated Na^+ with K^+.[94]

Some cells have been reported not to undergo RVI when exposed to hypertonic extracellular fluid. But the same cells will show RVD if exposed to hypotonic extracellular fluid; and if re-exposed to isotonic fluid, they will first shrink and then display RVI (secondary RVI or RVI on RVD). The inability of these cells to undergo primary RVI could be due to increased intracellular Cl^- activity.[94]

Implications in pathophysiology
Under normal circumstances, erythrocyte volume is always homeostatic but certain disorders (inherited or acquired) can alter the volume by either increasing (overhydrating) or decreasing (dehydrating) it resulting in haemolysis or eryptosis, respectively. This may be due to disorder during erythropoiesis,[96] increased concentration of intracellular calcium,[97] absence of membrane proteins[98] and mutations of membrane proteins[99,100] or alterations in the activities of channels[92,23] that are necessary for RVD and RVI. Overhydrated hereditary stomacytoses are caused by inherited autosomal genes that trigger an abnormal increase in Na^+ influx making the erythrocyte to be overhydrated. Dehydrated hereditary stomacytoses cause an excessive efflux of K^+. Sickle cell disease, thalassemia, and hereditary spherocytosis are genetic disorders that cause erythrocytes to be dehydrated.[8,98] Some heavy metals like lead have been reported to alter erythrocyte volume.[101] Aquaporins have been reported to be involved in the pathophysiology of inflammatory diseases[102-105] by influencing movement of water alone or with either cerebrospinal fluid or glycerol across membranes[105,106] in the gastrointestinal tract[107], salivary glands[108], skin[109], renal system[106,110,111] and brain[112] and altering erythrocyte volumes.

Conclusions
Erythrocyte volume is maintained at steady state not only by effective fluxes of ions via ion channels and carriers, but also by the presence of adequate aquaporins that facilitate obliged water movement across the membrane. A good knowledge of the types and functions of transport pathways available for ions and water across membranes can influence how researchers will design experiments.

Conflict of Interest
The author declares that there is no conflict of interest.

Authors' Contribution
The author was the only one involved in the literature search, collation and integration of the information, and writing of the literature review.

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