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Review Article:

The role of Membrane potential and calcium homeostasis in sickle erythrocyte sickling

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ABSTRACT:

Sickle cell anaemia (SCA) is a genetic haemoglobin disorder characterised by the production of haemoglobin S (HbS) which polymerises on deoxygenation and causes sickling, dehydration, haemolysis and vaso-occlusion of erythrocytes. Polymerisation of HbS is the key event in sickling, but alterations in membrane potential and calcium homeostasis are important in regulating erythrocyte hydration and sickling evolution. Changes of ion transport occur in sickle erythrocytes with increased calcium permeability and activation of calcium sensitive potassium channels, especially the Gardos channel. Intracellular calcium increases lead to activation of potassium efflux, loss of chloride and water, hyperpolarisation of the membrane, and dehydration of the erythrocyte. This results in an increased intracellular concentration of HbS which favours polymer formation and speeds the transition from the normal biconcave erythrocyte to the sickled form. Mechanosensitive pathways like Piezo1 might be involved in calcium influx and activation of Gardos-mediated potassium loss during membrane deformation. These ionic abnormalities reduce the deformability of the erythrocytes, increase the fragility of the membrane and contribute to haemolysis and microvascular obstruction. Membrane potential, calcium homeostasis, ion-channel activity and cellular hydration interplay is thus important for insight into the pathophysiology of sickle cell anaemia. Therapeutic interventions aimed at ion transport pathways, particularly calcium-activated potassium channels and associated mechanisms, may reduce erythrocyte dehydration and the propensity for sickle cell polymerisation and sickling. This review addresses the relationship between membrane potential and calcium homeostasis in sickle erythrocyte sickling and discusses their potential importance in developing targeted treatments.

Keyword: Sickle cell anaemia, sickle erythrocytes, membrane potential, calcium homeostasis, keywords.

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INTRODUCTION

Sickle cell anaemia (SCA) is an inherited haemoglobinopathy caused by mutation in the B-globin gene resulting in production of abnormal haemoglobin S (HbS). When the oxygen tension decreases, HbS polymerises and the red blood cells (RBCs) become elongated, rigid and sickle shaped [1]. Although HbS polymerisation is the fundamental molecular event responsible for sickling, the extent of sickling of a given erythrocyte is heavily influenced by its state of hydration, membrane properties, intracellular concentrations of ions, and calcium homeostasis. Specifically, changes in membrane potential and intracellular calcium concentration are important components of the cellular processes that promote erythrocyte dehydration and increase HbS polymerization [2].

The erythrocyte membrane maintains the gradients of sodium, potassium, chloride and calcium between the intra- and extravascular compartments. The gradients create the membrane potential and control cell volume and hydration. Changes in these regulatory processes may enhance calcium influx and activate calcium-sensitive potassium channels such as the Gardos channel in sickle erythrocytes. This loss of potassium and water leads to densely packed, dehydrated cells with an increased intracellular HbS concentration. This creates a significant link between ion homeostasis and HbS polymerisation during deoxygenation [3,4].

Membrane Potential of the Red Cell

The membrane potential is the electrical potential difference across the erythrocyte membrane resulting from the asymmetric distribution and movement of ions across the membrane. While mature RBCs are devoid of nuclei and do not generate stereotypical action potentials as in neurones, their membrane potential is

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physiologically relevant since it is coupled to ion flux, membrane transport and regulation of cell volume [5].

Major ion transport systems contributing to the maintenance of ionic gradients in erythrocytes are Na+/K+-ATPase, calcium pumps, potassium channels, chloride pathways and potassium-chloride cotransport systems. The Gardos channel is of particular interest since it is activated by intracellular calcium and is a pathway for potassium efflux. Opening of the Gardos channel causes significant hyperpolarisation of the membrane as potassium leaves the cell. Studies with human erythrocytes have shown that activation of the Gardos-channel may result in a change of the membrane potential from about -12 mV to values much more negative [6,7], indicating a strong correlation between potassium permeability and membrane potential.

Patients with sickle cell anaemia have also been shown to have altered membrane potential and electrolyte balance. Nnodim et al reported significantly lower membrane potential and altered electrolyte concentrations in sickle cell anaemic individuals compared with controls. These results are in line with the idea that changes in erythrocyte membrane function in SCA are related to alterations in ionic homeostasis [8].

Calcium Homeostasis of Sickle Erythrocytes

Mature erythrocytes maintain their calcium concentration at a very low level. This low intracellular Ca2+ concentration is maintained by membrane transport mechanisms, such as the plasma membrane calcium ATPase (PMCA). Calcium entry is limited under normal conditions and excess intracellular Ca2+ actively extruded [9].

In sickle erythrocytes however, calcium permeability may be increased by deoxygenation and membrane deformation. Polymerisation of sickle haemoglobin causes alterations in the membrane structure which can activate permeability pathways for cation entry and Ca2+ entry into the cell. Experimental studies have shown that the deformation of the membrane can activate calcium permeable pathways for a short period of time which leads to an increase in the calcium concentration in the cell and subsequent activation of calcium-dependent potassium currents [10].

An increase in intracellular Ca^{2+} is particularly significant because calcium is a signal for Gardos channel activation. Opening of this channel permits K+ to leave the erythrocyte. Chloride and water then follow the ionic gradient, causing dehydration of the cell. KCNN4 encodes the Gardos channel, one of the major calcium-sensitive potassium pathways in human erythrocytes [11].

The Gardos Channel and the Membrane Potential

The relationship between calcium homeostasis and membrane potential is especially clear in the case of the Gardos channel. The channel is opened by increased intracellular Ca2+ leading to K+ efflux. The efflux of positively charged potassium causes hyperpolarisation of the erythrocyte membrane by making the cell interior more negative.
This mechanism is important in sickle cell disease because dehydration increases the concentration of HbS in the erythrocyte. Therefore, as oxygen levels decrease, dehydration favours polymerisation of HbS in sickle cells. Gardos-channel-mediated dehydration has been described as especially important in sickle erythrocytes, because even limited channel activation can lead to profound cellular dehydration [12].

Membrane potential and calcium entry interaction

Recent studies have provided evidence that the relationship between membrane potential and calcium homeostasis may be more complex than a one-way pathway. The Gardos channel, when activated, can cause membrane hyperpolarisation, and this change in membrane potential can affect other calcium permeable pathways [13].

Experimental studies on Gardos channel dysfunction suggest an interaction between the Gardos channel, voltage-dependent calcium channels and the mechanosensitive Piezo1 channel. Fluctuations in membrane potential were caused by stochastic activation of Gardos channel in this model. These changes may promote calcium entry through voltage sensitive pathways thus establishing a feedback relationship between K+ conductance, membrane potential and intracellular Ca2+. [14]
This mechanism is especially important because it shows that the membrane potential is not just a side-effect of ion-channel activity. Changes in membrane potential can, in turn, affect subsequent movements of ions. Thus, membrane potential and calcium homeostasis may

dynamically interact in determining the physiological state of the sickle erythrocyte [15].

Calcium, HbS Polymerisation and Dehydration

The most important relationship between calcium homeostasis and sickling occurs on deoxygenation. Polymerisation of HbS induces structural changes in the erythrocyte that may enhance membrane permeability and permit abnormal ionic movement. Calcium enters the cell and activates the Gardos channel. This causes K + loss and water loss.
This dehydration leads to an increase in the intracellular concentration of HbS. Dehydrated red cells can polymerise HbS more readily as oxygen tension falls because polymerisation is highly dependent upon HbS concentration. This is a positive feedback loop in which deoxygenation promotes sickling, sickling promotes abnormal calcium entry, calcium activates potassium efflux, potassium efflux causes dehydration, and dehydration increases the likelihood of further HbS polymerization [16].

The significance of this pathway is that it connects the molecular abnormality of HbS with the physiological abnormalities of the erythrocyte membrane [17].

Piezo1: a regulator of calcium homeostasis

Piezo1 is a mechanosensitive ion channel expressed in erythrocytes and involved in the mechanostimulation of the cell membrane. As red blood cells are constantly deformed in their passage through the circulation, Piezo1 offers a pathway by which mechanical stress can modulate intracellular calcium.

Studies in sickle erythrocytes have shown that Piezo1 activation can increase intracellular calcium, activate the Gardos channel, induce membrane hyperpolarisation, decrease erythrocyte deformability and promote sickling of sickle RBCs under deoxygenated conditions. Increased adhesion of sickle RBCs to laminin has also been associated with Piezo1 activation [18]. These findings suggest that the control of calcium in sickle red cells is affected by mechanical as well as chemical or oxygen-dependent changes. This provides another mechanism by which membrane function may be involved in sickling and vaso-occlusive processes [19].

Calcium Homeostasis and Red Blood Cell Deformability

Normal RBC are required to have a high level of deformability to flow through narrow capillaries. This property may be impaired by changes in membrane ion transport that are calcium-dependent. The Gardos channel is activated by the increase in intracellular Ca^{2+}, resulting in the loss of K^+ and water, which makes the erythrocyte smaller and denser [20]. Dehydrated sickle red cells are less deformable than normal red cells. Further, successive cycles of sickling and unsickling can cause membrane and cytoskeleton damage. Thus, dehydration, HbS polymerisation and membrane damage act together to produce rigid erythrocytes [21].

The effects are much larger than the cell. Sickle red blood cells are stiff and not easily deformed and have a hard time getting through the microcirculation and can help cause blockage of vessels. Thus calcium homeostasis and membrane potential disturbances may indirectly contribute to vaso-occlusion by altering erythrocyte hydration and rheological properties [22].

Calcium and Haemolysis: Membrane Damage

Long-lasting disturbances of calcium homeostasis may also contribute to the injury of membranes and to the premature destruction of erythrocytes. The increased intracellular calcium activates a number of calcium dependent cellular processes and can lead to membrane alterations such as phosphatidylserine exposure. Calcium-dependent activation of membrane enzymes and changes in the cytoskeleton can also affect membrane integrity.

In sickle cell disease these processes are taking place in an erythrocyte already under oxidative stress and repeated mechanical injury from cycles of sickling and unsickling. Thus abnormal calcium handling may contribute to the shortened life span of sickle RBCs and chronic haemolysis[23].

Therefore, the association between calcium and erythrocyte membrane function is multidimensional, since calcium modulates potassium channels, potassium channels change membrane potential and cell volume, and excessive calcium accumulation might be involved in membrane remodelling and cellular destruction [24].

K^+-Cl^- Cotransporter Role

The Gardos channel is a major pathway for calcium influx leading to erythrocyte dehydration, but the potassium-chloride cotransporter (KCC) also contributes to volume regulation. KCC co-transports K^+ and Cl^- over the membrane. It is upregulated in sickle erythrocytes and may be involved in the loss of intracellular KCl and water.

Studies of sickle-cell cation homeostasis have identified three major pathways involved in solute loss and erythrocyte dehydration: the deoxygenation-induced cation conductance, the calcium-activated Gardos channel, and the K^+-Cl^- cotransporter [25].

Thus, the dehydration of sickle RBCs cannot be explained by calcium-dependent potassium channels alone. Instead, it is the outcome of the interplay of multiple membrane transporters, whose activities depend on oxygen tension, cell volume, intracellular ions, and properties of the membrane [26].

Therapeutic Implications

The inter-relationship between calcium homeostasis, membrane potential and sickling have important therapeutic implications. One approach that has been investigated to maintain red cell hydration is blocking the Gardos channel, since excessive calcium-activated potassium loss results in dehydration.

Pharmacologic studies have shown that Gardos channel blockade can reduce potassium loss and red blood cell dehydration. Thus, Gardos-channel inhibitors such as senicapoc have been studied in clinical trials in sickle cell disease. The general objective of these strategies is to alter the cellular environment in which HbS polymerisation takes place, by preserving erythrocyte hydration and decreasing the formation of dense sickle cells [28].

Another potential avenue for further investigation is the identification of Piezo1 as an additional regulator of calcium entry. Therapeutic manipulation should be sufficiently selective to decrease pathological ion fluxes without disturbing normal cellular function, as calcium signalling and ion transport are critical for normal erythrocyte physiology [29].

CONCLUSION

Membrane potential and calcium homeostasis are key elements of the cellular mechanisms of sickle erythrocyte sickling. HbS polymerisation remains the fundamental molecular event in sickle cell disease but erythrocyte hydration and membrane ion transport have an overriding influence on the severity and progression of sickling.

The increased calcium entry into sickle erythrocytes can activate the Gardos channel, leading to K+ efflux, hyperpolarisation of the membrane, chloride and water loss, and cell dehydration. This increase in intracellular HbS concentration promotes further polymerisation of HbS upon deoxygenation. The interaction between Gardos channel activity, membrane potential, Piezo1 and other calcium permeable pathways meanwhile point to calcium homeostasis and membrane potential as a dynamic regulatory system rather than independent processes.

Thus, the relationship between Ca 2+ entry, membrane potential, potassium efflux, erythrocyte dehydration, and HbS polymerisation provides an important framework for understanding sickle-cell pathophysiology. It also provides a scientific basis to explore the possibility of targeting membrane ion channels and calcium-regulatory mechanisms to ameliorate erythrocyte dehydration, sickling, haemolysis and vaso-occlusive complications.

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