Erythrocyte as a Therapeutic Target

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Abstract
Erythrocytes are powerful components of blood flow designed to scavenger or deliver nitric oxide (NO) and oxygen to all cells in the body and transport carbon dioxide from them to the lungs. Blood components started to be quantified and erythrocyte blood shapes used as diagnostic and prognostic tools in clinical practice. Erythrocytes have hemorheological, hemostatic and pro or anti-inflammatory properties enlarging their physiological implications in health and disease. As blood component the erythrocytes establish interaction with others white blood cells, platelets, plasma lipoproteins and vascular endothelial cells. The aim of this mini review is highlight the signaling pathway of nitric oxide in which some steps explain the efficacy of some therapeutic drugs already used and could point new targets for further application in inflammatory vascular diseases.

Keywords: Erythrocyte; Nitric oxide; Acetylcholinesterase; Forskolin; CD47; Fibrinogen

Abbrevations: AChE: Acetylcholinesterase; NO: Nitric Oxide; RBCs: Red Blood Cells; GIP: Glucose-Insulin-Potassium; PKC: protein kinase C;

Mini Review

More than two centuries ago was discovered in blood the presence of erythrocytes and its vital function as the unique oxygen carrier binding to hemoglobin which molecular and structural characterizations were later described [1-5]. Erythrocytes with different shapes are observed in association with some hemoglobinopathies for example sickle cell disease, or in those resulting from inserted compounds into specific membrane domains [6,7].

Erythrocyte metabolism provides metabolites able to regulate the oxygen affinity for hemoglobin such as 2,3-bisphosphoglycerate and others to participate as coenzymes in antioxidant pathways [8]. Several therapeutically drugs cause hemolysis in humans with glucose-6-phosphate dehydrogenase null gene [9]. A reducing environment inside of erythrocytes ensures the active form of hemoglobin with its ferric ion and the normal interaction between biomolecules of the membrane bilayer and the proteins of cytoskeleton [10]. However, when erythrocytes show higher pro-oxidant activity contribute to abnormal bioreological functions associated with inflammatory vascular diseases [11,12]. They can be a trigger or a consequence of micro or macro circulation dysfunction. Acquired ability of erythrocytes to combine with partners of hemostatics components generate red thrombus and help the rolling and adhesion of white blood cells to vascular endothelial wall [13,14].

Erythrocytes are enucleated blood components, but are more than sacks of hemoglobin during the semi life of 120 days comporting different signaling pathways in which is included the final stage of apoptosis (eryptosis) that has been evidenced [15,16]. The appearance in plasma of exovesicles enriched with the acetylcholinesterase (AChE) originated from erythrocyte membrane, the phosphatydilserine exposition in the outer membrane of erythrocyte in addition to kinetic changes of the AChE evaluated in older erythrocytes are biomarkers of red blood cells senescence (RBCs) [17,18]. Previously AChE in erythrocytes was evidenced as a biomarker of its membrane integrity [19].

Depending on the degree of endothelium integrity the circulating acetylcholine (ACh) induce vasodilatation or vasoconstriction according the amount of nitric oxide (NO) synthesised and released [20,21]. The NO released from endothelial cells and platelets is scavenged by erythrocyte and blood cell free haemoglobin [22].

Erythrocyte membrane AChE is involved in the nitric oxide (NO) signal pathway as evidenced, for the first time, using blood
samples from blood donors in several in vitro studies in the
begin of this century [23,24]. No metabolism provides several
NO derivative molecules such as nitrite, nitrate, peroxynitrite
and S-nitro glutathione (GSNO) behavior the last one as NO
reservoir such as S-nitrosohemoglobin [23,24]. The signal
transduction pathway mediated by the enzymatic complex
form AChE-ACh is coupled to Gαi protein, adenylyl cyclase (AC),
band3 protein, protein kinase C (PKC) and phosphodiesterase-3
(PDE-3) [24]. The ACh concentration used is below its substrate
congestion correspondent to the velocity maximum obtained in the bell
shape kinetic curve [25,26]. Higher NO efflux occurs under the
influence of AChE-Ach complex, in simultaneous with the
band3 protein phosphorylation [23,24]. Compounds that inhibit
the protein tyrosine kinase or protein tyrosine phosphatase
induce inhibition or activation on AChE enzyme activity [24].
Used two types of AChE inhibitors, velnacrine maleate and
timolol generate inactive or less active enzyme AChE-inhibitor
complexes that impaired NO efflux from erythrocytes in relation
to the active form ACh- AChE [23,27].

In patients with open angle glaucoma, over expression of
eNOS and nNOS, decreased levels of cGMP (intermediate in NO
signaling) and of nitrite (NO metabolite) in aqueous humour and
increased erythrocyte AChE activity were described [28-30].
When blood samples from glaucoma patients is incubated in-vitro in
presence of timolol, no changes in the NO efflux neither in
the GSNO content of erythrocytes were evidenced besides
both molecules are in higher concentrations than the normal
values obtained in health humans [31]. This study showed that
no reinforcement will occur in the amount of nitrogen reactive stress characteristic of glaucoma patients, by timolol application
[31].

Insulin resistance can be eliminated in some patients with
sepsis by continuous intravenous infusion of insulin in the
form of glucose-insulin-potassium (GIP) regimen that improves
survival [32,33]. When blood samples from patients with septic
shock where incubated in-vitro with insulin increased the
amount of GSNO and the concentration of NO inside erythrocytes
was maintained between the normal values [34]. A positive
association was observed between NO efflux from erythrocytes
and perfused vessel density at sub-lingual microcirculation [34].
So the GIP regimen protected from nitrogen reactive stress [34].

When fibrinogenemia is mimicked in-vitro NO efflux
from erythrocyte increases, in dependence of band3 protein
phosphorylation, returning to normal levels when in presence of
either ACh or timolol showing dependency of the AChE
enzyme conformational states and of the lower levels of cyclic
adenosine Monophosphate (cAMP) concentrations [27,35-37].
When the inhibitor of the erythrocyte Casein Kinase 2, (a cytosol
protein that phosphorylated band 3 protein), is present in the
erythrocytes suspensions at high fibrinogen concentration the
NO efflux level is maintained between normal values confirmed
its dependence of band 3 de phosphorylating for be rescued by
RBCs [38].

Is very interesting that the forskolin, activator of AC enzyme
normalize the levels of NO efflux from erythrocytes in in-vitro
model of hyper fibrinogenemia, is nowadays used to alleviate
patients with glaucoma [39].

As mentioned above glaucoma patient’s present increase
nitrogen reactive species in aqueous humor and NO efflux from
their erythrocytes are higher than healthy humans [28,31].
So, one explanation for the forskolin therapeutic success in
glaucoma patient’s could result from NO efflux from their
erythrocyte be dependent of lower cAMP levels. This make sense
because glaucoma is an inflammatory disease where patients
have increased levels of fibrinogen which is known its binding
to erythrocyte membrane CD47 that by association with Gαi protein
and AC inhibition decreased cAMP concentrations. [37,40,41].
Besides, this is a clue need to be explored.

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