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REVIEW

Molecular Interactions between Erythrocytes and the Endocrine System

Charalampos PAPADOPOULOS, Ioannis TENTES, Konstantinos ANAGNOSTOPOULOS

Laboratory of Biochemistry, School of Medicine, Democritus University of Thrace, Alexandroupolis, Greece

ABSTRACT

Hormones are secreted by the endocrine glands and reach their targets after circulating in the blood. Many studies have documented that erythrocytes can bind hormones, and possible interactions have been reported. Erythrocytes are responsive to signaling initiated after binding of epinephrine, norepinephrine, estrogen, progesterone, thyroid hormones, parathyroid hormone, and angiotensin. Signaling results in regulation of cellular metabolism and membrane fluidity. In addition, erythrocytes are circulating pools for dopamine, thyroid hormones, cortisol, and aldosterone. Erythrocyte function and structure are regulated by endocrine signals, while erythrocytes are important constituents for the transport of hormones in the body.

Keywords: erythrocyte, hormones, endocrine system, nitric oxide, metabolism.

INTRODUCTION

Erythrocytes have recently emerged as important contributors to the regulation of immunity (1, 2). Furthermore, we have recently described the current literature that indicates that red blood cells constituted a dynamic pool of cholesterol and signaling lipids (2). In addition, erythrocytes comprise an important pool of the bioactive gas, nitric oxide (NO) (3). However, evidence points also toward the direction of an erythrocyte-hormone interaction and/or transport (Figure 1). Thus, in this review we have tried to summarize the current knowledge regarding the molecular interactions between erythrocytes and hormones in mammals, with a particular interest in humans. However, as the interaction of erythrocytes with insulin and non-neuronal acetylcholine has already been summarized in other excellent reviews (4, 5), it will not be discussed here. In addition, the interaction of erythrocytes with lipid hormones has recently been described as a part of metabolic interactions, and will therefore not be described (2).

Address for correspondence:
Konstantinos Anagnostopoulos, PhD
Laboratory of Biochemistry, School of Medicine, Democritus University of Thrace, 68100 Alexandroupolis, Greece
Tel./Fax: +30 25510 30502
Email: kanagnos@med.duth.gr, kanagno@gmail.com

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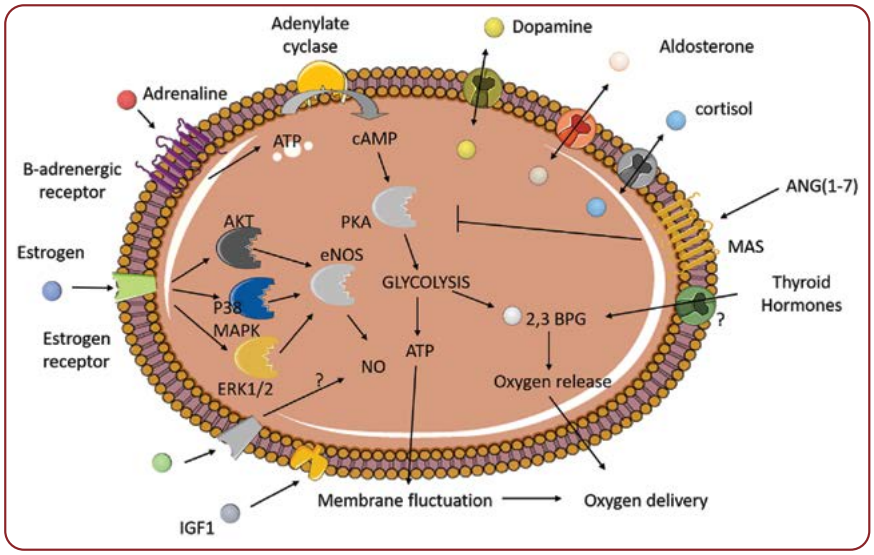

FIGURE 1. Molecular interactions between red blood cells and hormones. AKT: Rasrelated C3 botulinum toxin alpha serine/threonine-kinase ANG(1-7): angiotensin 1-7; ATP: adenosine triphosphate; 2,3 BPG: 2,3 biphosphoglycerate; cAMP: cyclin adenosine monophosphate; eNOS: endothelial nitric oxide synthase; ERK: extracellular signal-regulated kinase; IGF1: insulin-like growth factor 1; MAPK: mitogen activated protein kinase; NO: nitric oxide; PKA: protein kinase A

Epinephrine and norepinephrine

Tsukamoto and Sonenberg (6) provided the first evidence that the erythrocyte membrane possessed a functional beta-adrenergic receptor. In their experiments, both epinephrine and norepinephrine resulted in an increased activity of the cAMP-activated protein kinase of red blood cells. This mechanism was inhibited when using an antagonist for the beta-adrenergic receptor. Later, this idea has been also supported by the results of Horga *et al* (7), who showed that incubation of erythrocyte membranes with isoproterenol, an agonist for the beta-adrenergic receptor, led to the activation of adenylic cyclase. This adrenaline → beta-adrenergic receptor → adenylic cyclase → cAMP pathway was implicated in the increase of oxygen supply, which was induced by high-fat diet-induced hypoxia (8). In that study, activation of beta-adrenergic receptors induced an increase in cAMP, glycolysis, and ATP production. This pathway was correlated with an increased oxygen supply, thus aiding with the hypoxic environment. The precise mechanism for this function is not known. Nevertheless, researchers had previously shown that ATP production, induced by adrenergic signaling in erythrocytes, results in increased membrane fluctuation, a mechanism facilitating erythrocyte passage and oxygen delivery (9). However, this pathway may present resistance. Increased epinephrine levels in the blood of horses after maximal exercise resulted in a decrease of the beta-adrenergic receptors of red blood cells (10).

However, it is speculated that the mode of induction of hypoxia and subsequent adrenergic signaling in erythrocytes could lead to different intracellular pathways. Odje and Ramsey (11) showed that epinephrine resulted in augmentation of 2,3 diphosphoglycerate. Interestingly, 2,3 diphosphoglycerate, an intermediate molecule of glycolysis, also increases oxygen release since it is an allosteric modulator of hemoglobin (12). However, this pathway was found to be initiated by the production of sphingosine-1 phosphate.

Dopamine

Red blood cells have been proposed as transporters of catecholamines and especially dopamine. Azoui *et al* (13) identified a choline exchanger as a potent transporter of dopamine in the erythrocyte membrane. In addition, experimental work, both in rats and *in vitro*, proved that dopamine inserted the erythrocyte mem-

brane. Interestingly, the erythrocyte storage capacity for dopamine seems to be saturable (14).

Estrogen

Functional estrogen receptors (Era and ERb) were found in erythrocytes (15). In fact, the same study found that estrogen receptors were mainly located in the cytosol, and estrogen triggered their localization to the plasma membrane. Activation of these receptors leads to activation of AKT, ERK1/2, and p38. Additionally, eNOS activation by estrogen was reported in both genders, but women presented higher basal levels due to their exposure to higher levels of estrogen.

Progesterone

Progesterone has been found to regulate the fluidity of red blood cells (16). Interestingly, the addition of an inhibitor of NO synthase augmented this effect. These results may imply that erythrocytes also possess progesterone receptors in their membranes.

Insulin-like growth factor-1

Moris *et al* (17) report that insulin-like growth factor 1 (IGF-1) binds to a receptor of erythrocytes. In addition, there was found an increased affinity for binding to erythrocytes derived from prepubertal children in comparison with erythrocytes from adults. This was not ascribed to the number of receptors in the erythrocyte membranes in the two groups. These results may imply that specific intra-erythrocyte signaling induced by IGF-1 is taking place during puberty.

Thyroid hormones

Snyder and Reddy (18) showed that thyroid hormones upregulated the levels of 2,3 biphosphoglyceric in erythrocytes, thus implying a possible connection with the regulation of oxygen release from hemoglobin. In addition, red blood cells were deemed possible circulation pools of the thyroid hormones T3 and T4, since erythrocytes were found to trap and release both hormones at similar rates (19).

Parathyroid hormone

The parathyroid hormone binds to and induces calcium entry *via* calcium ATPase and subsequent cytoskeletal organization disruption (20).

Angiotensin

Saraiva *et al* (21) showed that angiotensin II was converted to angiotensin (1-7) and angiotensin (IV) by human erythrocytes. Next, these molecules lead to decreased Gs protein activation, mainly through the MAS receptor and partially through the angiotensin receptor 2, and subsequently, to decreased protein kinase A (PKA) activity.

Cortisol

Erythrocytes can serve as transporters of cortisol in the blood through binding and releasing with high dissociation rates (22). In addition, this transport is possibly temperature-dependent (23).

Aldosterone

Similarly, erythrocytes bind and transport aldosterone in the blood temperature dependently (24). ❑

CONCLUSION

Erythrocytes constitute both targets and transporters of various hormones in the circulation. Studies show that hormonal signals can regulate oxygen supply. In addition, erythrocytes are important, yet underappreciated transporters of hormones. We propose that red blood cells are circulating pools of hormones, cytokines, bioactive lipids, cholesterol, and damage-associated molecular patterns. Finally, oxygen release is a dynamic biochemical event regulated by external signals, and whole-body and intra-erythrocyte metabolism. Thus, erythrocytes could lead to the discovery of therapeutic targets for a disease where hypoxia and/or hormone circulation takes place. ❑

Conflicts of interest: none declared.

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