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REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

How hormones acting on their receptors influence mature erythrocytes

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SUMMARY
Anemia is the most common disorder globally and one of the conditions that general practitioners most frequently encounter. Human erythrocytes, also known as red blood cells, or RBC, are exposed to constant stress while they circulate in the blood (e.g. shear stress, osmotic stress, oxidative stress). The scope of this review was to analyze the literature data on what the hormonal receptors do on mature erythrocytes and how they relate to the risk of anemia.
We investigated the literature data in the most recent five-year period (*PubMed*, *Google Schoolar*) and analyzed the effects of hormonal receptors on four specific characteristics of mature erythrocytes: osmotic resistance, deformability/rheology, erythrocyte hemoglobin affinity to oxygen and eryptosis.
We found that the hormones have a strong impact in regulating erythrocyte survival and functionality. These receptors increase the physiological plasticity of mature erythrocytes and serve as the effective tool for deeper effects of integral regulatory mechanisms that promote their survival and whole-body homeostasis. Additionally, these hormonal receptors are closely associated with the risk of anemia: when the supportive function of hormones and their receptors is not effective, eryptosis increases and, consequently, the number of mature erythrocytes in the circulation decreases.
Keywords: physiological phenomena; blood cells; chemicals and drugs – hormones; osmotic fragility; diseases, hematologic – anemia

INTRODUCTION

Erythrocytes are the most numerous blood and body cells

Human erythrocytes, also known as red blood cells, RBC, are organelle-free cells packaged with hemoglobin that are specialized for oxygen transport. With an estimated total number of 25 trillion cells per person, erythrocyte is the most numerous cell type not only in blood but in the entire organism [1, 2].

Anemia is a condition in which the number of erythrocytes or their oxygen-carrying capacity is insufficient to meet physiological needs [1, 3]. It is one of the most widespread disorders worldwide and among the conditions most commonly encountered by general practitioners. According to World Health Organization global database, anemia affected approximately 1.76 billion individuals worldwide in 2019 [3].

Additional overlooked erythrocyte functions

Our understanding of erythrocytes as a simple "bag" that contains hemoglobin and performs its essential task as an oxygen shuttle has dramatically evolved. Over the past several decades, the efforts of cell and molecular biologists, physiologists, biochemists, and hematologists have contributed to our better understanding of the complexity of the erythrocyte structure and revealed that erythrocytes can also perform the following: serve as sink for exogenous RNA [4]; play a significant role in the immunometabolic interactions that control immunity [5]; contain an important pool of the bioactive gas – nitric oxide [6]; play a role in water- [7] and reverse cholesterol-transport [8]; and can be used as a drug carrier (pharmaceutical uses) [9].

Additionally, it is postulated that in regions of low pO_2, the mobile erythrocytes also serve as oxygen sensors and modulators of vascular tone, since they have the ability to match microvascular oxygen supply with tissue oxygen demand, by releasing ATP [10]. It is amazing how many essential complex physiological functions are provided by erythrocytes. An impressive number!

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Erythrocytes are constantly subjected to multiple stresses while circulating in the bloodstream

While travelling through rapid, dynamic, and quickly changeable circulatory system, erythrocytes face many challenging conditions and locations [1, 11]. Firstly, with each passage through the renal medulla, erythrocytes are exposed to the osmotic stress/shock, since they undergo significant changes in their hyperosmotic environment, reaching levels as high as 1200 mOsmol/L [12]. Secondly, mature erythrocytes endure the shear stress (mechanical deformation of the membrane) while passing through tight capillaries and sinusoids [13]. Thirdly, when in the lungs, they also face oxidative stress due to the elevated oxygen pressure [11]. Furthermore, during inflammation, whether it is systemic or chronic, erythrocytes are constantly exposed to circulating inflammatory mediators [14].

Consequently, all of these multiple stresses can result in molecular and structural damage of erythrocytes, ultimately leading to their degradation and quick removal from circulation. A rapid and severe reduction in erythrocyte levels results in the development of hemolytic anemia [1].

Even though erythrocytes are constantly subjected to multiple stresses, they lack the ability to replenish proteins that have lost their function, since they have lost all of their organelles by the time they mature [1, 15].

Altogether, due to all of these difficulties, erythrocytes are highly vulnerable and sensitive cells that require various defense mechanisms to support their viability and avert their premature clearance [15, 16].

The intimate relationship between erythrocytes and the endocrine system

Numerous clinical and experimental observations have confirmed that there is a close connection between the rate of hematopoiesis and endocrine hormones, as evidenced by changes in bone marrow and peripheral blood components [17, 18, 19]. For instance, hypothyroidism is related to anemia and an underactive marrow, while hyperthyroidism is linked to an excessively cellular marrow, lymphocytosis, and lymphoid hyperplasia [20].

This intimate relationship exists especially between immature erythrocytes and the endocrine system. It is well known that human erythropoietin (Epo), a glycoprotein hormone composed of 165 amino acids, is a crucial factor for the survival, viability and proliferation of erythrocyte progenitor cells [1, 17]. In bone marrow, Epo binds to the homodimeric Epo receptor, and through JAK-2/STAT-5 signaling pathways induces the expression of anti-apoptotic proteins (e.g. Bcl-xL) and promotes the survival of erythrocytic progenitors, particularly the colony-forming unit-erythroid (CFU-E) [21]. Apart from this, Epo activates genes promoting proliferation, differentiation, and maturation of immature forms of erythrocytes. Approximately four days after an increase in Epo levels, there is a rise in the number of reticulocytes and mature erythrocytes that enter the bloodstream [1, 2, 18].

In addition to Epo, the male hormone testosterone strongly stimulates erythropoiesis [1, 18]. The mechanisms by which testosterone promotes erythropoiesis are not well understood. It is hypothesized that testosterone induces erythrocytosis by stimulating the production of Epo [15]. Testosterone also acts directly on the bone marrow, increasing the number of Epo-responsive cells [1, 22, 23].

Surprisingly, comprehensive research on erythrocyte biochemical pathways, metabolism, and structure-activity relationship with a substantial number of publications has revealed that a relatively large number of endocrine hormone receptors are expressed not only on humane immature but also on mature erythrocytes [24, 25, 26]. This discovery rises the questions whether these hormonal receptors represent only the remnants of receptors from young (immature) forms of erythrocytes, or do they have their own physiological function and pathophysiological significance. Are they functional in mature erythrocytes? The literature lacks data explaining how erythrocytes have a relatively long lifespan, of 120 days, despite their low complexity and their inability to transcriptionally upregulate antioxidant (and all other stress-related) defense mechanisms. The goal of this literature review is to summarize the protective and supportive impacts of hormones on four mature erythrocyte vital characteristics: volume homeostasis (osmotic resistance and fragility), deformability/rheology, affinity of erythrocyte hemoglobin to oxygen, and eryptosis.

We investigated the literature data (*PubMed, Google Schoolar*) from the latest five years with the following keywords employed: hormonal receptors, mature erythrocytes. The number of articles found was not systematically quantified, as the focus was not on providing an exhaustive coverage of all relevant studies but rather on identifying representative and key sources that support the narrative analysis.

ERYTHROCYTE VOLUME HOMEOSTASIS

Preserving of cellular volume homeostasis is essential for the survival of erythrocytes [1]. Disturbance of this homeostasis, a feature of several inherited anemias, leads to abnormal erythrocytes. Several pathways mediate water and solute homeostasis in normal erythrocytes, where cellular volume is primarily controlled via the sodium–potassium ATPase pump (Na^+/K^+ATPase), that maintains the intracellular low sodium, high potassium composition by actively transporting sodium out of and potassium into the erythrocytes [1].

Hormones that affect the function of Na^+/K^+-ATPase and RBC osmotic fragility

Thyroid-stimulating hormone (TSH) is a glycoprotein synthesized by the thyrotrophs of the anterior pituitary gland and its main role is to stimulate the thyroid gland to secrete thyroxine (T_4) and triiodothyronine (T_3). TSH

acts through TSH receptors (TSHr), which are G-protein coupled receptors [1].

Balzan et al. [27] identified the TSHr on human erythrocyte membranes in 2007. Subsequently, in 2009, they demonstrated that TSH binds to TSHr, affecting Na^+/K^+-ATPase [28]. Additionally, Mendonça-Reis [29] in 2024 found that TSH enhanced erythrocyte resistance to hemolysis by inhibiting the AMPK-dependent pathway and activating the PI3K/Akt signaling pathway.

Further, research indicates that individuals with subclinical hypothyroidism exhibit decreased Na^+/K^+-ATPase function in erythrocytes, suggesting its potential role as an early indicator of hypothyroidism [17]. Moreover, elevated TSH levels in sickle cell anemia patients correlate with disease severity and duration, implying a potential influence of TSH on disease progression [20]. The identification of a functional TSHr in erythrocytes and the elucidation of associated pathways suggest that TSH can influence erythrocyte behavior and fate.

From a physiological point of view, it seems reasonable to assume that TSH enhances the osmotic resistance of erythrocytes to hemolysis in a state of elevated metabolism, since all the end-products of metabolism are osmotically active, and because of that they inevitably induce osmotic stress to erythrocytes.

Angiotensin II (Ang II) can enhance erythrocyte osmotic resistance and decrease hemolysis, particularly beneficial for individuals with sickle cell anemia [12]. Although the precise mechanisms by which Ang II influences erythrocytes are not entirely clear, it is understood that the ATR_2 receptor can impact multiple signaling pathways related to cell survival and osmotic control.

Cortisol binds to the erythrocyte membrane, impairing epinephrine binding and resulting in an increase in the microviscosity of the membranes and a rise in Na^+/K^+-ATPase activity [30, 31].

Endothelin-1 (ET-1), a peptide hormone composed of 21 amino acids, is a potent vasoconstrictor in humans. Within erythrocytes, ET-1 enhances the activity of protein disulfide isomerase, an enzyme involved in regulating ion channels that promote potassium and water loss from cells, resulting in erythrocyte dehydration and heightened susceptibility to hemolysis [32]. In sickle cell anemia, elevated ET-1 activity can induce dehydration of sickle erythrocytes, increasing their stiffness and propensity to aggregate. Investigations into ET-A receptor antagonists as potential therapies aim to mitigate these adverse effects, potentially enhancing the well-being of individuals with sickle cell anemia.

See Table 1 for hormones influencing erythrocyte osmotic resistance/fragility.

Table 1. Hormones influencing red blood cells' osmotic resistance/fragility

Increases osmotic resistance	Decreases osmotic resistance
TSH	Endothelin-1
Angiotensin II	
Cortisol	

RBC FLEXIBILITY AND RHEOLOGY

The hemorheologic responses involved in the body's reactions to stress, energy regulation, and growth are not fully understood [18, 33]. Erythrocyte flexibility refers to the cells' capacity to adjust their shape in response to dynamically changing flow conditions. The indicators that expressed the erythrocyte membrane flexibility are RBC deformation index (RDI: 0.47–0.55) and erythrocyte rigidity index (Male: 7.16, Female: 7.14) [33]. The hormones can either enhance or reduce red cell deformability, thereby aiding in adjusting microcirculatory blood flow accordingly [30]. The stiffening of erythrocytes may either be reversible or part of the sequence of events culminating in programmed red cell death (eryptosis).

Hormones that improve the RBC flexibility/rheology

Catecholamines, during stress, regulate erythrocyte rheology via α- and β-adrenergic receptors [25, 33]. This is consistent with the other classical effects of catecholamines mediated by β-adrenergic receptors (vasodilation, increased cardiac output, etc.) that all lead to an increased blood flow. The effect of these hormones on erythrocyte deformability is mostly under the control of intracellular Ca^{2+}-regulating pathways [25]. In contrast to this beneficial effect of catecholamines on erythrocyte deformability in physiological conditions, a decreased erythrocyte deformability was observed in untreated pheochromocytoma [34].

Erythropoietin improves red cell deformability [16, 17, 30]. Chronic kidney disease-associated hemorheological disturbances (reduced erythrocyte deformability) were corrected with treatment using recombinant human Epo (rhEPO) [35]. In cancer patients, rhEPO increases red cell deformability and decreases red cell aggregation [30].

TSH. The results indicate that the TSHr decreases hemoglobin S polymerization and enhances the deformability and adhesion of sickle erythrocytes [29].

Leptin, a hormone released by adipocytes, has been shown to improve erythrocyte deformability via a NO- and cGMP-dependent mechanism [30]. Aditionally, the specific binding of leptin to erythrocytes delivers pancreatic hormones and stimulates ATP release [36]. Leptin is involved in regulatory loops that link energy stores and circulation [16].

Hormones that impair the RBC flexibility/rheology

On the other hand, several hormones have been identified to decrease erythrocyte membrane flexibility.

Thyroid hormones. Erythrocytes also exhibit receptors for the thyroid hormone [20]. Whether thyroid hormones are regulators of blood rheology remains unclear, but a decrease in erythrocyte deformability has been reported to exist in hyperthyroidism [20, 37, 38] and to be reversible after the successful treatment of the disease [20, 37].

Prostaglandins. PGE_2 decreases the deformability of erythrocytes and increases their aggregability [15, 39].

Female sex hormones. The effects of sex hormones on erythrocyte rheology may contribute to the very complex mechanisms of ovulation and, consequently, play a role in the regulation of fertility [16, 26].

Insulin-like growth factor 1 (IGF-1). Clinical report from an exercise-test in 39 male elite athletes indicates that elevated levels of IGF-1 are associated with lower erythrocyte deformability at high shear rates [33].

Apelin is a cytokine that is predominantly secreted by adipocytes [1]. In rats with reduced erythrocyte deformability due to the experimental induction of diabetes and ischemia-reperfusion injury of the heart, apelin-13 has been shown to restore this loss of erythrocyte deformability [40].

Melatonin can elevate the erythrocyte deformability in experimental sepsis due to its nitric oxide scavenging activity and antioxidant effect [41]. However, pinealectomy alone did not lead to any statistically significant alterations in erythrocyte deformability, but when melatonin was added, a significant decrease was observed [42]. Therefore, this issue remains controversial and requires further study.

See Table 2 for hormones influencing erythrocyte flexibility.

OXYGENATION OF HEMOGLOBIN

The function of erythrocyte 2,3 diphosphoglycerate (2,3-DPG), an intermediate molecule of glycolysis, is to bind to deoxyhemoglobin and facilitate oxygen transport. Hormones may modulate hemoglobin's capacity to bind and release oxygen, by affecting the level of erythrocyte 2,3-DPG.

Thyroid hormones. Tokay et al. [43] showed that thyroid hormones upregulated the levels of 2,3-DPG in erythrocytes, thus implying a possible connection with the regulation of oxygen release from hemoglobin. The hormone's effects on 2,3-DPG synthesis may provide a biochemical explanation for the shift in the oxyhemoglobin dissociation curve seen in thyroid disorders.

Dehydroepiandrosterone (DHEAS) has been linked to changes in the deoxygenation rate of hemoglobin, which could influence hemoglobin's affinity for oxygen [17, 44, 45].

See Table 3 for hormones influencing oxygenation of hemoglobin.

ERYTHROCYTE ERYPTOSIS

Eryptosis refers to the premature, stress-triggered suicidal death of erythrocytes, which is distinct from accidental hemolysis or cellular senescence [2, 15].

Eryptotic effect is triggered by endocannabinoids. Anandamide, a type of endocannabinoid, has been reported to induce eryptosis, by increasing the activity of erythrocyte cytosolic Ca^{2+}, resulting in the cell shrinkage and, subsequently, the induction of eryptosis [46].

Anti-eryptotic hormones

Inhibition of eryptosis is crucial in certain therapeutic situations, such as in patients with sickle cell anemia, who experience elevated eryptosis levels that can exacerbate anemia [18]. Numerous hormones can inhibit eryptosis, some of which are mentioned bellow.

Erythropoietin not only stimulates erythrocyte development in the bone marrow (erythropoiesis), but also exhibits direct anti-eryptotic properties, as it reduces Ca^{2+}-mediated eryptosis by inhibiting non-selective cation channels [15].

Catecholamines also have an anti-eryptotic effect, by impairing the Ca^{2+} cation channels' ability to enhance the entry of Ca^{2+} ions [47].

Leptin and thyroid hormones have been associated with maintaining erythrocyte deformability, indicating a potential anti-eryptotic effect [16, 20].

Melatonin. While the effects of melatonin on erythrocyte deformability remain controversial, some studies suggest that melatonin may have an anti-eryptotic effect

Table 2. Hormones influencing red blood cells' flexibility

Improve RBC flexibility	Reverse the loss of RBC flexibility	Impair RBC flexibility	Unclear results on RBC flexibility
Cateholamines	Apelin	Catecholamines: supraphysiological levels – in untreated pheochromocytoma	Female sex hormones
Erytropoietin		Erytropoietin: subphysiological levels, in chronic kidney disease	Melatonin
TSH		Thyroid hormones	
Leptin		IGF-1	
		PGE2	

RBC – red blood cells; TSH – thyroid-stimulating hormone; IGF-1 – insulin-like growth factor 1; PGE2 – prostaglandin E2

Table 3. Hormones influencing oxygenation of hemoglobin

Decreases	Increases
Thyroid hormones	-
Dehydroepiandrosterone (DHEAS)	-

Table 4. Hormones influencing red cell eryptosis

Eryptotic effect	Anti-eryptotic effect
Endocannabinoids	Erythropoetin
	Catecholamines
	Leptin
	Thyroid hormones
	Melatonin

[41]. The beneficial effect of melatonin has been already proven to prevent oxidative stress-induced damage associated to lipid peroxidation [41].

See Table 4 for hormones influencing red cell eryptosis.

LIMITATIONS

This literature review examines the role of hormones in regulating erythrocyte survival and functionality.

The action of hormones on mature (and immature) erythrocytes involves a complex interplay between various signaling pathways and receptors, influencing erythrocyte function, survival, and responses to different physiological stressors. However, this review does not address two key points. Firstly, it does not explain the mechanism by which certain hormonal receptors are spared from removal during terminal erythrocyte maturation – specifically, how some receptors avoid the "tagging" process that leads to their autolysis (via an autophagy/exosome-mediated pathway tied to membrane remodeling). Secondly, it does not explain the complex interplay among the various signaling pathways and receptors involved. Due to these limitations, the review cannot be considered a fully "causal literature review."

This literature review can neither be considered a "systematic literature review," since it does not have strict inclusion and exclusion criteria. Compared to a systematic literature review on the same topic, this review is more subjective, as we have constructed a narrative based on selected relevant studies in accordance with our own criteria. Our focus is on interpreting results and conceptualizing ideas rather than on providing a comprehensive, objective analysis of all relevant studies.

By integrating findings from different research endeavors, we aimed to present a coherent narrative that highlights the broader picture. Thus, this literature review paper should be classified as a "narrative (contemplative) literature review." To the best of our knowledge, there is no similar integrative interpretation of this intriguing "intelligent design" that enhances the physiological plasticity of mature erythrocytes.

CONCLUSION – CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Hormonal receptors on mature erythrocytes prevent the premature, stress-induced death of erythrocytes (eryptosis) and protect the erythrocytes. Some hormonal receptors, such as those for TSH, angiotensin II, cortisol, and endothelin-1, are essential for maintaining erythrocyte volume homeostasis and osmotic resistance. Others, including receptors for catecholamines, erythropoietin, insulin, leptin, somatostatin, and thyroid hormones, regulate erythrocyte membrane deformability (flexibility) and rheology. In addition, receptors for thyroid hormones (T_3, T_4) and DHEAS mediate adjustments in the affinity of erythrocyte hemoglobin to oxygen, depending on the intensity of tissue metabolism.

When the supportive function of hormones and their receptors is not effective, eryptosis increases and, consequently, the number of mature erythrocytes in the circulation decreases. Addressing the issue of anemia is a significant challenge in modern medicine, as it is a highly complex condition involving numerous underlying pathophysiological mechanisms. Future research is needed to determine whether introducing new technologies and the development of specific hormonal receptor antagonists/agonists could prolong the life and potentially enhance the well-being of individuals with different types of anemia.

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Како хормони посредством својих рецептора утичу на зреле еритроците

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САЖЕТАК

Анемија је најчешћи поремећај здравља свуда у свету и једно од стања са којима се лекари опште праксе најчешће сусрећу. Еритроцити су изложени сталном стресу док циркулишу у крви (нпр. трпе стрес услед сила смицања, осмотски стрес, оксидативни стрес).

Циљ овог прегледног чланка је био да анализира литературне податке о томе шта хормонски рецептори раде на зрелим еритроцитима и како су они повезани са ризиком од настанка анемије.

Истраживали смо литературне податке објављене током претходних пет година (*PubMed*, *Google Scholar*) и анализирали ефекте које хормонски рецептори имају на четири специфичне карактеристике зрелих еритроцита: на осмотску отпорност, деформабилност/реологију, афинитет хемоглобина према кисеонику и ериптозу еритроцита.

Утврдили смо да хормони имају снажан утицај на регулисање преживљавања и функционалност еритроцита. Ови рецептори повећавају физиолошку пластичност зрелих еритроцита и служе као ефикасно средство за дубље деловање интегралних регулаторних механизама, који промовишу опстанак еритроцита и хомеостазу целог тела. Додатно, ови хормонски рецептори су уско повезани са ризиком од настанка анемије: када супортивна функција хормона и њихових рецептора није ефикасна, ериптоза се повећава и, као последица тога, смањује се број зрелих еритроцита у циркулацији.

Кључне речи: физиолошке појаве; крвне ћелије; хемикалије и лекови – хормони; осмотска фрагилност/отпорност; болести, хематолошке – анемија