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How hormones acting on their receptors influence mature erythrocytes

Како хормони посредством својих рецептора утичу на зреле еритроците

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How hormones acting on their receptors influence mature erythrocytes

Како хормони посредством својих рецептора утичу на зреле еритроците

SUMMARY

Anemia is the most common disorder globally and one of the conditions that general practitioners most frequently encounter. The human erythrocytes 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 do the hormonal receptors do on mature red blood cells (RBC) and how they relate to the risk of anemia.

We investigated the literature data in the last five years (*PubMed*, *Google Schoolar*) and analyzed the effects of hormonal receptors on four specific characteristics of mature erythrocytes: osmotic resistance; deformability/rheology, RBC 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 anaemia: 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

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 / енг. *shear stress*, 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 Schoolar*) и анализирали које ефекте остварују хормонски рецептори 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, сходно томе, смањује се број зрелих еритроцита у циркулацији.

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

INTRODUCTION

Erythrocytes are the most numerous blood and body cells

Human erythrocytes (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, the 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 RBC 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 1.76 billion individuals worldwide in 2019 [3].

An 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, physiologiest, biochemists and hematologists, have contributed to our better understanding of complexity of RBC structure and revealed that RBC: can 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 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 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 RBC. An impressive number!

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

While travelling through rapid, dynamic and quickly changeable circulatory system, erythrocytes face with many challenging conditions and locations [1, 11]. Firstly, with each passage through the renal medulla, RBC 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]. In addition to this, secondly, mature RBC 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]. On top of that, during inflammation, whether it is systemic or chronic, the RBC are constantly exposed to circulating inflammatory mediators [14].

Consequently, all of these multiple stresses can result in molecular and structural damage of RBC, ultimately leading to their degradation and quickly removed from circulation. If the RBC levels reduce extremely fast, this results in hemolytic anemia [1].

Even though the 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 maturated [1, 15].

Altogether, due to all of these difficulties, erythrocytes are highly vulnerable and sensitive cells, that require the 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 with 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 units-erythroid (CFU-Es) [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 erythropoietin, 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 erythropoietin [15]. Testosterone also acts directly on the bone marrow, increasing the number of erythropoietin-responsive cells [1, 22, 23].

Surprisingly, comprehensive research on RBC 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 they have their own physiological function and pathophysiological significance? Are they functional in mature RBC? 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 RBC vital characteristics: Volume homeostasis (osmotic resistance and fragility), deformability/rheology, affinity of RBC hemoglobin to oxygen and eryptosis.

We investigated the literature data (*PubMed, Google Schoolar*) in the last five years with 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 survival of the erythrocyte [1]. Disturbance of this homeostasis, a feature of several inherited anemias, leads to abnormal erythrocytes. Several pathways mediate water and solute homeostasis in normal RBC, 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 red blood cell [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. identified TSH receptor (TSHr) on human erythrocyte membranes in 2007 [27]. Subsequently, in 2009, they demonstrated that TSH binds to TSH receptors, affecting Na^+/K^+-ATPase [28]. Additionally, Mendonça-Reis in 2024 found that TSH enhanced RBC resistance to hemolysis by inhibiting the AMPK-dependent pathway and activating the PI3K/Akt signaling pathway [29].

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 TSH receptor in erythrocytes and the elucidation of associated pathways suggest that TSH can influence RBC 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 (PDI), 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 RBC osmotic resistance/fragility.

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]. RBC 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 RBC

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 regulate during stress RBC 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 RBC deformability is mostly under the control of intracellular Ca^{2+}-regulating pathways [25]. In contrast to this beneficial effect of catecholamines on RBC deformability in physiological conditions, a decreased RBC deformability was observed in untreated pheochromocytoma [34].

Erythropoietin improves red cell deformability [16, 17, 30]. Chronic kidney disease associated hemorheological disturbances (less deformable RBC) were corrected by a treatment with recombinant human erythropoietin (rhEPO) [35]. In cancer patients, rhEPO increases red cell deformability and decreases red cell aggregation [30].

TSH. The results indicate that the TSH receptor decreases hemoglobin S polymerization and enhances the deformability and adhesion of sickle erythrocytes [36].

Leptin, a hormone released by adipocytes, has been shown to improve RBC deformability via a NO- and cGMP-dependent mechanism [30]. Besides, specific binding of leptin to RBC delivers a pancreatic hormones and stimulates ATP release [37]. 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 RBC 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 RBC deformability has been reported to exist in hyperthyroidism [20, 38, 39] and to be reversible after the successful treatment of the disease [20, 38].

Prostaglandins. PGE_2 decreases the deformability of RBC and increases their aggregability [15, 40].

Female sex hormones. The effect of sex hormones on red cell rheology may be involved in the very complex mechanism of ovulation and thus 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 sportsmen indicates that elevated levels of IGF-1 are associated with lower RBC 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 RBC deformability [41].

Melatonin can elevate the RBC deformability in experimental sepsis due to its nitric oxide scavenging activity and antioxidant effect [42]. However, pinealectomy alone did not lead to any statistically significant alterations in RBC deformability, but when melatonin was added, a significant decrease was observed [43]. Therefore, this issue remains controversial and requires further study.

See Table 2 for hormones influencing RBC 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. [44] 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, 45, 46].

See Table 3 for hormones influencing oxygenation of hemoglobin.

RED CELL ERYPTOSIS

Eryptosis refers to the premature, stress-triggered suicidal death of RBC, 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 RBC cytosolic Ca^{2+}, resulting in the cell shrinkage and, subsequently, inducing eryptosis [47].

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 does not only stimulates erythrocyte development in the bone marrow (erythropoiesis), but it also has a direct anti-eryptotic properties [15], since it blunt Ca^{2+}-mediated eryptosis by inhibiting the 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 [48].

Leptin and thyroid hormones have been associated with maintaining RBC 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 [42]. The beneficial effect of melatonin has been already proven to prevent oxidative stress-induced damage associated to lipid peroxidation [42].

See Table 4 for hormones influencing red cell eryptosis.

Limitations

This literature review is about 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 response to different physiological stressors. This literature review, however, does not explain, firstly, the mechanism by which certain hormonal receptors escape their removal from RBC during terminal maturation - actually how selectively, for certain receptors there is no "tagging" of receptors for their autolysis (removal through autophagy/exosome-combined pathway due to membrane remodeling). Secondly, does not explain this complex interplay between various signaling pathways and receptors, and because of these limitations, it cannot be considered as “A causal literature review”.

This literature review can not be considered neither as “A systematic literature review”, since it does not have strict inclusion and exclusion criteria for studies. Compared to a "systematic literature review" on the same topic, this review paper is more subjective. We create a story based on selected relevant studies (according to our criteria). The focus is on the interpretation of results and conceptualization of ideas, rather than on a comprehensive and objective analysis of all relevant studies. We aimed to provide a coherent narrative on the topic by integrating findings from different studies to present the bigger picture. That's why this literature review paper belongs to the group "a narrative (contemplative) literature review". The best of our knowledge, there is no any similar integrative interpretation of this intriguing intelligent design that increase the physiological plasticity of mature erythrocytes.

CONCLUSION – CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Hormonal receptors on mature RBC prevent the premature, stress-induced death of RBC (eryptosys) and protect the erythrocytes. Some hormonal receptors (e.g. for TSH, angiotensin II, cortisol, endothelin-1) are essential for RBC volume homeostasis and osmotic resistance of RBC. The others (e.g. for catecholamines, erytropoietin, insulin, leptin, somatostatin, thyroid hormones, etc.) are involved in the regulation of RBC membrane deformability (flexibility) and rheology. In addition, receptors for thyroid hormones (T_3, T_4) and DHEAS mediate adjustment of affinity of RBC hemoglobin to oxygen, depending on 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 anaemia is a significant concern in the field of modern medicine. Anaemia is a highly complex condition involving numerous underlying pathophysiological mechanisms.

Future studies are needed to determine whether introducing a new technology 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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REFERENCES

1. Hall JE, Hall ME. Chapter 33: Red blood cells, Anemia and Polycythemia. In: Hall JE, Hall ME, editors. Guyton and Hall Textbook of Medical Physiology, 14th edition. Amsterdam: Elsevier; 2021;439-446.
2. Kojic Z. Poglavlje 12: Fiziologija krvi. U: Đurić D, urednik. Fiziologija za studente medicine - Odabrana poglavlja I deo, peto izdanje. Beograd, Medicinski fakultet Beograd - CIBID, Libri Medicorum 2022;237-263.
3. Baldi A, Pasricha SR. Anaemia: Worldwide Prevalence and Progress in Reduction. In: Karakochuk CD, Zimmermann MB, Moretti D, Kraemer K. (eds) Nutritional Anemia. Nutrition and Health. New York: Springer; 2022;3-17. [DOI:10.1007/978-3-031-14521-6_1]
4. Lam M, Oatman L, Eckart K, Klingensmith N, Flowers E, Sayegh L, et al. Human red blood cells express the RNA sensor TLR7. Sci Rep 2024;14:15789. [DOI:10.1038/s41598-024-66410-5] [PMID: 38982195]
5. Papadopoulos C, Tentes I, Anagnostopoulos K. Erythrocytes Contribute to the Immunometabolic Cross-Talk. Immunometabolism 2021;3(2):e210015. [DOI: 10.20900/immunometab20210015]
6. Leo F, Suvorava T, Heuser S, Li J, LoBue A, Barbarino F, et all. Red Blood Cell and Endothelial eNOS Independently Regulate Circulating Nitric Oxide Metabolites and Blood Pressure. Circulation. 2021;144(11):870-889. [DOI: 10.1161/CIRCULATIONAHA.120.049606] [PMID: 34229449]
7. Sugie J, Intaglietta M, Sung L. Water Transport and Homeostasis as a Major Function of Erythrocytes. Am J Physiol Heart Circ Physiol. 2018;314(5):H1098-H1107. [DOI: 10.1152/ajpheart.00263.2017] [PMID: 29393658]
8. Hung K, Berisha S, Ritchey B, Santore J, Smith J. Blood Cells Play a Role in Reverse Cholesterol Transport. Arterioscler Thromb Vascular Biol. 2012;32(6):1460-1465. [DOI: 10.1161/ATVBAHA.112.248971] [PMID 22499994]
9. Ding J, Ding X, Liao W, Lu Z. Red blood cell-derived materials for cancer therapy: Construction, distribution, and applications. Materials Today Bio 2024;(24): 100913. [DOI: 10.1016/j.mtbio.2023.100913] [PMID: 38188647]
10. Gonzales-Alonzo J. ATP as a mediator of erythrocyte-dependent regulation of skeletal muscle blood flow and oxygen delivery in humans. J Physiol. 2012;590(20): 5001-13. [DOI: 10.1113/jphysiol.2012.235002] [PMID: 22711955]
11. Jomova K, Raptova R, Alomar S, Alwasel SH, Nepovimova E, Kuca K, et al. Reactive Oxygen Species, Toxicity, Oxidative Stress, and Antioxidants: Chronic Diseases and Aging. Arch Toxicol. 2023;97(10):2499-2574. [DOI: 10.1007/s00204-023-03562-9] [PMID: 37597078]
12. Guimarães-Nobre C, Mendonça-Reis E, Passinho-da-Costa L, Miranda-Alves L, Clemilson Berto-Junior H. Signaling Pathway in the Osmotic Resistance Induced by Angiotensin II AT_2 Receptor Activation in Human Erythrocytes. Rep Biochem Mol Biol. 2021;10(2):314-326. [DOI: 10.52547/rbmb.10.2.314] [PMID: 34604421]
13. Davis M, Earley S, Li YS, Chien S. Vascular Mechanotransduction. Physiol Rev. 2023;103(2):1247-1421. [DOI: 10.1152/physrev.00053.2021] [PMID: 36603156]
14. Maruyama T, Hieda M, Mawatari S, Fujino T. Rheological Abnormalities in Human Erythrocytes Subjected to Oxidative Inflammation. Front Physiol. 2022;13: 837926. [DOI: 10.3389/fphys.2022.837926] [PMID: 35283782]
15. Qadri S, Bissinger R, Solh Z, Oldenborg P. Eryptosis in health and disease: A paradigm shift towards understanding the (patho)physiological implications of programmed cell death of erythrocytes. Blood Reviews, 2017;31(6):349-361. [DOI: 10.1016/j.blre.2017.06.001] [PMID: 28669393]
16. Huisjes R, Bogdanova A, Van Solinge W, Schiffelers M, Kaestner L, Van Wijk R. Squeezing for Life - Properties of Red Blood Cell Deformability. Front Physiol. 2018;9:656. [DOI:10.3389/fphys.2018.00656]
17. Paradopoulos C, Tentes I, Anagnostopoulos K. Molecular Interactions between Erythrocytes and the Endocrine System. Maedica 2021;16(3):489-492. [DOI: 10.26574/maedica.2020.16.3.489] [PMID: 34925607]
18. Brun JF, Varlet-Marie E, Richou M, Marcier J, Raynaud de Mauverger E. Blood rheology as a mirror of endocrine and metabolic homeostasis in health and disease. Clin Hemorheol Microcirc. 2018;1-2:239-265. [DOI: 10.3233/CH-189124] [PMID: 2966091]
19. Sørensen NN, Andreasen CM, Jensen PR, Hauge EM, Bollerslev J, Delaissé JM, et al. Disturbed bone marrow adiposity in patients with Cushing's syndrome and glucocorticoid- and postmenopausal- induced osteoporosis. Front Endocrinol (Lausanne). 2023;14:1232574. [DOI: 10.3389/fendo.2023.1232574] [PMID: 37881495]

20. Caglar SE, Tanoğlu A. Hemorheology in thyroid abnormalities: old team player, new insights. J Med Palliat Care 2023;4(6):705-709. [DOI:10.47582/jompac.1398655]

21. Gangat N, Szuber N, Tefferi A. JAK2 unmutated erythrocytosis: 2023 Update on diagnosis and management. Am J Hematol. 2023;98(6):965-981. [DOI: 10.1002/ajh.26920] [PMID: 36966432]

22. Guo W, Abou Ghayda R, Schmidt PJ, Fleming MD, Bhasin S. The role of iron in mediating testosterone's effects on erythropoiesis in mice. FASEB J. 2020; 34(9):11672-11684. [DOI: 10.1096/fj.202000920RR] [PMID: 32667087]

23. Ristić S, Kojić Z. Hepcidin - key regulator in Iron Metabolism in Humans. II Kongres udruženja hematologa Republike Srpske sa međunarodnim učešćem. Banja Luka, 2024; Knjiga sažetaka, 35.

24. Ward G, Harrison L. Structure of the Human Erythrocytes Insulin Receptor. Diabetes 1986;35(1):101-105. [DOI:10.2337/diab.35.1.101] [PMID: 3510133]

25. Horga JF, Gisbert J, De Agustín JC, Hernández M, Zapater P. A beta-2 adrenergic receptors activates adenylate cyclase in human erythrocyte membranes at physiological calcium plasma concentrations. Blood Cells Mol Dis 2000;26(3):223-8. [DOI: 10.1006/bcmd.2000.0299] [PMID: 10950942]

26. Vona R, Gambardella L, Ortona E, Santulli M, Malorni W, Carè A, Pietraforte D, Straface E. Functional Estrogen Receptors of Red Blood Cells. Do They Influence Intracellular Signaling? Cell Physiol Biochem. 2019;53(1):186-199. [DOI: 10.33594/000000129] [PMID: 31278696]

27. Balzan S, Nicolini G, Forini F, Boni G, Del Carratore R, Nicolini A, et al. Presence of a functional TSH receptor on human erythrocytes. Biomed Pharmacother. 2007;61(8):463-7. [DOI: 10.1016/j.biopha.2007.04.009] [PMID: 17570630]

28. Balzan S, Del Carratore R, Nicolini G, Forini F, Lubrano V, Simili M, et al. TSH induces co-localization of TSH receptor and Na/K-ATPase in human erythrocytes. Cell Biochem Funct. 2009;27(5):259-63. [DOI: 10.1002/cbf.1567] [PMID: 19466745]

29. Mendonça-Reis E, Guimarães-Nobre CC, Teixeira-Alves LR, Miranda-Alves L, Berto-Junior C. TSH Receptor Reduces Hemoglobin S Polymerization and Increases Deformability and Adhesion of Sickle Erythrocytes. Anemia. 2024; 2024:7924015. [DOI: 10.1155/2024/7924015] [PMID: 38596654]

30. Sloop G, Pop G, Weidman J, St Cyr JA. Hormonal Control of Blood Viscosity. Cureus. 2024;16(2):e55237. [DOI: 10.7759/cureus.55237] [PMID: 38558582]

31. Andric S, Kojic Z, Bjelic M, Mihajlovic A, Baburski A, Sokanovic S, Janjic M, Stojkov N, Stojilkovic S, Kostic T. The opposite roles of glucocorticoid and α_1-adrenergic receptors in stress triggered apoptosis of rat Leydig cells. Am J Physiol Endocrinol Metab. 2013; 304(1):E51-9. [DOI: 10.1152/ajpendo.00443.2012] [PMID: 23149620]

32. Prado GN, Romero JR, Rivera A. Endothelin-1 receptor antagonists regulate cell surface-associated protein disulfide isomerase in sickle cell disease. FASEB J. 2013;27(11):4619-29. [DOI: 10.1096/fj.13-228577] [PMID: 23913858]

33. Nader E, Skinner S, Romana M, Fort R, Lemonne N, Guillot N, et al. Blood Rheology: Key Parameters, Impact on Blood Flow, Role in Sickle Cell Disease and Effects of Exercise. Front Physiol. 2019,10,1329. [DOI: 10.3389/fphys.2019.01329] [PMID: 31749708]

34. Shi F, Sun LX, Long S, Zhang Y. Pheochromocytoma as a cause of repeated acute myocardial infarctions, heart failure, and transient erythrocytosis: A case report and review of the literature. World J Clin Cases. 2021;9(4):951-959. [DOI: 10.12998/wjcc.v9.i4.951] [PMID: 33585644]

35. Lerche D, Schmidt R, Zoellner K, Meier W, Paulitschke M, Distler B, et al. Rheology in whole blood and in red blood cells under recombinant human erythropoietin therapy. Contrib Nephrol. 1989;76:299-303. [DOI: 10.1159/000417906] [PMID: 2684529]

36. Mendonça-Reis E, Guimarães-Nobre C, Teixeira-Alves LR, Miranda-Alves L, Berto-Junior C. TSH Receptor Reduces Hemoglobin S Polymerization and Increases Deformability and Adhesion of Sickle Erythrocytes. Anemia. 2024; 2024:7924015. [DOI: 10.1155/2024/7924015] [PMID: 38596654] .

37. Keshavarz H, Meintsl L, Geiger M, Zinn K, Spence D. Specific binding of Leptin to Red Blood Cells Delivers a Pancreatic Hormones and Stimulates ATP Release. Mol Pharmaceutics 2021;18(6): 2438–2447. [DOI: 10.1021/acs.molpharmaceut.1c00300]

38. Özdemir S, Yücel R, Dariyerli N, Toplan S, Akyolcu M, Yigit G, et al. The effects of experimental hyperthyroidism on hemorheology and plasma fibrinogen concentration. Endocrine 2006;30,203-205. [DOI:10.1385/ENDO:30:2:203] [PMID: 17322580]

39. Hotić S, Kovačević P, Mrkobrada N. Incidence of anemia in patients hospitalized in the coronary unit of the Clinical Center Banja Luka. Scientific Journal of Emergency Medicine Halo 94, 2003;24-25(5),15-18.

40. Nikolic I, Tasic G, Bogosavljevic V, Nestorovic B, Jovanovic V, Kojic Z, Djoric I, Djurovic B. Predictable morphometric parameters for rupture of intracranial aneurysms - a series of 142 operated aneurysms.Turk Neurosurg. 2012;22(4):420-6. [DOI: 10.5137/1019-5149.JTN.4698-11.1] [PMID: 22843457]

41. Chapman F, Maguire J, Newby D, Davenport A, Dhaun N. Targeting the apelin system for the treatment of cardiovascular diseases. Cardiovasc Res. 2023; 119(17):2683-2696. [DOI: 10.1093/cvr/cvad171] [PMID: 37956047]

42. Yerer M, Yapislar H, Aydogan S, Yalcin O, Baskurt O. Lipid Peroxidation and Deformability of Red Blood Cells in Experimental Sepsis in Rats: The Protective Effects of Melatonin. Clin Hemorheol Microcirc. 2004;30(2):77-82. [PMID: 15004332]

43. Berker M, Dikmenoglu N, Bozkurt G, Ergonul Z, Ozgen T. Hemorheology, melatonin and pinealectomy. What's the relationship? An experimental study. Clin Hemorheol Microcirc. 2004;30(1):47-52. [PMID: 14967883]

44. Tokay A, Raymondjean M, Alicigüzel Y. The Effect of Thyroid Hormones on Erythrocyte 2,3-Diphosphoglycerate. The Endocrinologist 2006;16(2):57-60. [DOI: 10.1097/01.ten.0000202690.88807.11]

45. Sokanovic S, Baburski A, Kojic Z, Medar M, Andric S, Kostic T. Aging-Related Increase of cGMP Disrupts Mitochondrial Homeostasis in Leydig Cells. J Gerontol A Biol Sci Med Sci. 2021;76(2):177-186. [DOI: 10.1093/gerona/glaa132] [PMID: 32459846]

46. Medar M, Marinkovic D, Kojic Z, Becin A, Starovlah I, Kravic-Stevovic T, et al. Dependence of Leydig Cell's Mitochondrial Physiology on Luteinizing Hormone Signaling. Life 2021;11(1):19. [DOI: 10.3390/life11010019] [PMCID: PMC782461]

47. Bentzen P, Lang F. Effect of anandamide on erythrocyte survival. Cell Physiol Biochem. 2007;20(6):1033-1042. [DOI: 10.1159/000110714] [PMID: 17975305]

48. Lang P, Kempe D, Akel A, Klarl B, Eisele K, Podolski M, et al. Inhibition of erythrocyte "apoptosis" by catecholamines. Naunyn Schmiedebergs Archives Pharmacology 2005;3:228–235. [DOI:10.1007/s00210-005-0009-2] [PMID: 16247607]

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

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

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

