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EFFECT OF HISTAMINE AND HISTAMINE RECEPTOR BLOCKERS ON THE CONTENT OF ENDOGENIC HISTAMINE AND SORPTION CAPACITY OF RAT BLOOD ERYTHROCYTES

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Histamine is synthesized from histidine in mast cells and basophils. Upon release, it acts on histamine receptors H1, H2, H3, and H4 located on plasma membranes. However, the presence of histamine receptors on erythrocyte membranes has not been thoroughly investigated. The aim of this study was to detect histamine in erythrocytes and determine the presence of H1–H4 receptors on erythrocyte membranes using specific receptor blockers. These were assessed via changes in endogenous histamine levels and in the sorption capacity of erythrocytes. In the experiment, histamine was added to erythrocytes at a concentration of 5.4 μM; histamine receptor blockers: desloratadine (blocks the H1 receptor), ranitidine (blocks the H2 receptor), betahistine (blocks the H3 receptor) so that the final concentration was 0.1; 1; 10 μM. Groups were also created, to whose erythrocytes were added both the indicated blockers and histamine. To analyze the presence of the H4 receptor on the erythrocyte membrane, all three blockers (desloratadine, ranitidine, betahistine) were added to the cells simultaneously, since there is currently no freely available blocker of the H4 receptor for histamine. Histamine was found in rat erythrocytes, with higher levels in females than in males. Combined administration of histamine and the H1 receptor blocker desloratadine altered endogenous histamine levels in female erythrocytes compared to desloratadine alone and affected sorption capacity. Ranitidine (H2 blocker) increased endogenous histamine content in male erythrocytes. The H3 receptor blocker betahistine, combined with histamine, caused an increase in endogenous histamine content in both sexes and altered sorption capacity. Blocking H1–H3 receptors and introducing histamine decreased sorption capacity in male erythrocytes (at high blocker concentrations, 10 μM) and altered it in females (depending on concentration). These findings may suggest that erythrocyte membranes in both sexes contain H3 receptors involved in regulating endogenous histamine content and sorption capacity.

Keywords: erythrocytes, histamine, histamine receptors, receptor blockers, sorption capacity

Erythrocytes are highly specialized red blood cells that lose their nucleus and virtually all cytoplasmic organelles during development, yet retain many elements of molecular signaling pathways. The red blood cell membrane contains receptors for various biologically important substances, interactions with which lead to metabolic changes in erythrocytes that affect their functions [19, 26].

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Histamine is a biogenic amine produced by tissue basophils and circulating blood basophils. In these cells, histamine is stored in specialized granules in a bound state. Histamine has been shown to act against a T cell-dependent antigen (SRBC), as observed in studies comparing histamine to H2 receptor antagonist-treated and control rabbits. Jutel et al. demonstrated that tripelennamine (an H1 receptor antagonist) inhibited histamine binding in Th1 but not in Th2 cells, showing predominant H1 receptor expression on Th1 cells. Neither ranitidine (an H2 receptor antagonist) nor clobenpropit (an H3 receptor antagonist and H4 receptor partial agonist) had any impact on histamine binding. Histamine is synthesized by the enzyme histidine decarboxylase. There is also evidence that histamine can be absorbed by eosinophils and is present in platelets. It exerts its effects by binding to histamine receptors – H1, H2, H3, and H4 [17, 20, 29]. Histamine regulates dendritic cells, T lymphocytes, B lymphocytes, and related antibody isotype responses. Its immunosuppressive and immunomodulatory effects on both humoral and cell-mediated immunity (HI and CMI, respectively) have been documented. Immunomodulation studies in rabbit models have shown that histamine has a short-term effect on antibody generation, and that the in vivo production of antibodies (IgM and IgG) is influenced by histamine concentration. Histamine receptors H1R and H2R have been shown to enhance delayed-type hypersensitivity and antibody-mediated immune responses, regulating several key events in allergies and autoimmune diseases in experimental models, especially in knockout mice deficient in either H1R or H2R. Histamine and its receptor agonists (H1R and H2R) enhance antibody production by activating these receptors, whereas both H1R and H2R antagonists can positively or negatively modulate the antibody profile. Anti-IgM levels increased in H2R antagonist-treated rabbits and diminished in H1R antagonist-treated rabbits. H1R antagonist-treated rabbits also show diminished antibody production by Th1 cells [31]. The histamine H4 receptor, in biological systems, modulates immunological functions and stimulates antibody production only in response to exogenously administered agonists, not endogenous histamine [31].

Basophil granules contain several key components, including histamine, heparin, and peroxidase. Basophils are capable of synthesizing and storing histamine as well as eosinophil chemotactic factors of anaphylaxis. These leukocytes can also synthesize and release slow-reacting substances of anaphylaxis and, likely, platelet-activating factors upon stimulation; however, these substances are not stored.

Basophils (like mast cells) are believed to play a role in immediate hypersensitivity reactions, such as allergic asthma. Immunoglobulin E (IgE) binds readily to the membranes of basophils and mast cells. Degranulation occurs when a specific antigen interacts with membrane-bound IgE, leading to the release of mediators of immediate hypersensitivity reactions (e.g., histamine, anaphylaxis-associated substances, platelet-activating factor, heparin, and eosinophil chemotactic factors of anaphylaxis) [24].

Significant changes in circulating blood cell numbers following allergen exposure have been reported in patients with seasonal and perennial allergic rhinitis. When comparing blood cell counts taken immediately before and several hours after allergen exposure, a rapid mobilization of segmented neutrophils and a significant decline in circulating erythrocytes were observed in otherwise healthy allergic rhinitis subjects. A similar reduction in erythrocyte numbers was also observed in an animal model of allergic airway disease. Notably, this erythrocyte decline did not occur upon airway challenge with a nonspecific antigen or a placebo (saline buffer), indicating that the underlying mechanism was directly related to allergic inflammation triggered by the specific allergen. This allergen-induced erythrocyte declines and neutrophil increase persisted even after successful allergen-specific immunotherapy, as demonstrated in house dust

mite-sensitized allergic rhinitis patients. Therefore, even in allergic rhinitis patients who show significant symptom improvement following allergen-specific immunotherapy, exposure to the relevant allergen still triggers an acute inflammatory response involving both erythrocytes and neutrophils in sensitized individuals [23].

Little is known about the sex-specific effects of antihistamines on inflammatory responses and blood cell counts. However, a recent study demonstrated that cetirizine (an H1 receptor antagonist) reduces the clinical side effects of monoclonal antibody therapy targeting CD20+ B cells in a sex-specific manner [23]. Cetirizine inhibited the mobilization of neutrophils and lymphocytes, as well as the decline in erythrocyte numbers, but did not affect the allergen-induced increase in thrombocytes. It also attenuated gender-specific variations in blood cell dynamics. Overall, as reflected in a standard complete blood count (CBC), cetirizine significantly reduced both the immediate and late phases of the innate immune response following allergen exposure [23].

In recent years, genetically attenuated Plasmodium parasites have been developed in rodent models. These parasites cause self-resolving blood-stage infections and confer strong protective immunity. All genetically attenuated parasites developed thus far harbor mutations in housekeeping genes essential for parasite development within red blood cells. In one study using a Plasmodium berghei model compatible with long-term tracking of anti-blood-stage immune responses, researchers reported a novel blood-stage genetically attenuated parasite lacking a secreted factor related to histamine-releasing factor. The absence of this factor leads to increased IL-6 production, which enhances T and B cell responses, enabling infection resolution and providing cross-stage, cross-species, and long-lasting immunity. The protection induced by the mutant involves a combination of antiparasitic IgG2c antibodies and FcγR(+) CD11b(+) phagocytic cells, particularly neutrophils, which are sufficient to confer protection. This immune-enhancing genetically attenuated parasite highlights the critical role of opsonized parasite-mediated phagocytosis, which may be central to the protection induced by all self-resolving blood-stage genetically attenuated Plasmodium infections [18].

After reviewing the scientific literature, no information has been found regarding the presence of histamine in erythrocytes, nor the presence of histamine receptors H1, H2, H3, or H4 on erythrocyte plasma membranes. If such receptors do exist, their role in erythrocyte function remains unknown. It is also unclear how potential histamine is neutralized within erythrocytes, or whether histamine is taken up from plasma or synthesized within these cells. Although the scientific literature lacks information on the potential expression of histamine receptors by erythrocyte precursors, studying erythrocytes in relation to histamine is important. This is because histamine is involved in a wide range of physiological and pathological body functions, and erythrocytes perform numerous functions beyond just gas transport.

Objective: To detect histamine the presence in erythrocytes and to determine whether histamine receptors H1, H2, H3, H4 receptors are expressed on erythrocyte membranes, using specific histamine receptor blockers. The study aims to asses potential changes in endogenous histamine levels and alterations in the sorption capacity of erythrocytes.

Materials and Methods

Nonlinear male white rats (Rattus norvegicus f. domesticus) weighing 180–220 g were used for the experimental studies. Chloroform was used for euthanasia. All procedures involving animals were conducted in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, France, 1986), and in accordance with the General Principles for the Use of Animals in Research approved by the First National Congress on Bioethics (Kyiv, Ukraine, 2001).

Following decapitation, blood was collected into a container with heparine. The heparinized blood was centrifuged at 3000 rpm for 15 minutes. Plasma was discarded, and erythrocytes were washed three times with saline. The control group of erythrocytes was incubated with saline only.

To evaluate whether erythrocytes are capable of absorbing histamine through the plasma membrane, histamine dihydrochloride was added to erythrocytes at a final concentration of 5.4 μM. Samples were incubated for 5 minutes. A 0.01 % solution of histamine dihydrochloride (used as a stock solution) was obtained from Limited Liability Company "Immunolog", Ukraine (Vinnytsia).

To assess the presence of H1, H2, and H3 histamine receptors on erythrocyte membranes, specific pharmacological blockers were used:

- Desloratadine (commercial name Edem, manufacturer Farmak, 5 mg/tablet) as an H1 receptor blocker;
- Ranitidine (commercial name Ranitidine-Darnitsa, manufacturer Pharmaceutical Firm "Darnitsa", 150 mg/tablet) as an H2 receptor blocker;
- Betahistine (commercial name Betaserc, manufacturer Mylan Laboratories SAS, France, 8 mg/tablet) as an H3 receptor blocker.

To assess the potential presence of the H4 receptor, a mixture of desloratadine, ranitidine, and betahistine was used. Since there are currently no specific pharmaceutical drugs to block the H4 receptor, this combined approach was employed to indirectly evaluate its presence.

The experiment used the indicated pharmacological preparations. These also contained the usual excipients specified in the product's instructions for use.

Each blocker or the combination of blockers was added to erythrocyte suspensions to reach final concentrations of 0.1, 1, and 10 μM. Samples were incubated for 5 minutes at room temperature. Additional experimental groups were created in which erythrocytes were first incubated with receptor blockers for 5 minutes, followed by the addition of histamine (final concentration 5.4 μM) and a second 5-minute incubation. These groups were designed to investigate the specific effects of histamine under conditions of receptor blockade, particularly on the levels of endogenous histamine and the sorption capacity of erythrocytes. After incubation, erythrocytes were washed three times with saline. Each experiment was repeated at least five times (n=5).

To measure endogenous histamine content, erythrocyte hemolysis was performed using distilled water in a 3:1 ratio (three parts erythrocytes to one part water). Histamine content was determined using the method of Voronina L.M., based on the reaction between histamine and diazotized p-nitroaniline, which forms an orange-red complex [4]. Protein content was determined according to the method of Lowry [25]. To assess the sorption capacity of erythrocytes, hemolysis was not performed. This parameter was evaluated based on changes in the intensity of reduced methylene blue coloration in response to the presence of acidic metabolic products in the cells [5]. To determine the content of histamine in erythrocytes, glass test tubes were used. To determine the sorption capacity of erythrocytes, centrifuge tubes were used. In all experiments, mechanical mixing of substances (manual mixing) was used. In the experiment to determine the content of endogenous histamine, the volume of the incubation mixture was 9 ml. In the experiment to determine the sorption capacity of erythrocytes, the volume of the incubation mixture was 4 ml.

All data were analyzed using Microsoft Excel 2010 for Windows. Results are expressed as mean (M) ± standard error of the mean (m). Statistical significance was assessed using Student's t-test. Differences were considered significant at confidence levels of $p \geq 0.95$; $p \geq 0.99$; $p \geq 0.999$.

Results and Discussion

Experiments were conducted on isolated erythrocytes from male and female rats. We confirmed the presence of histamine in rat erythrocytes (Fig. 1). The results demonstrated that erythrocytes from female rats contain significantly more histamine – 2.26 times higher – than those from males. Histamine functions as a biogenic amine, neurotransmitter, and tissue hormone [2]. Systemic hormonal fluctuations in females may contribute to this disparity. The histamine content in erythrocytes may be associated with regulating cellular functions and maintaining a certain level of histamine in the bloodstream. Erythrocytes could potentially act as a histamine depot, similar to eosinophils. Previous studies have shown that histamine is primarily localized in blood basophils, eosinophils, and platelets [11]. Eosinophils are capable of absorbing exogenous histamine, which is either stored or degraded by histaminase. Histamine in platelets is thought to participate in blood coagulation, although the mechanisms remain unclear. The function of histamine in erythrocytes is still not well understood. Some literature reports suggest that histamine alters the agglutination behavior of erythrocytes in pregnant women, potentially through interaction with phytohemagglutinin, implying an indirect role in parturition. This could be mediated by H1 and H2 receptors on erythrocyte membranes, although this remains speculative.

Histamine also plays a role in ovulation and is known to increase vascular permeability, facilitating implantation of the fertilized ovum. However, it is not involved in oocyte maturation. Use of H1 and H2 receptor blockers in rabbits has been shown to inhibit this process. Furthermore, histamine enhances uterine contractility in both rats and humans, particularly during pregnancy, suggesting its involvement in labor. Conversely, when applied to the chorioallantoic membrane in chick embryos, histamine does not appear to affect embryonic development or induce congenital abnormalities in rodents [2, 22, 33].

Thus, histamine is indeed present in rat erythrocytes, with a higher concentration observed in females. The origin of histamine in these cells remains unclear – whether it enters from plasma or is synthesized de novo via histidine decarboxylase activity.

A slight decrease in histamine content may occur due to histamine receptor binding, which facilitates the release of this biogenic amine from the cell, or as a result of increased activity of histaminase, an enzyme responsible for histamine neutralization.

Methylation is an important metabolic pathway involved in the biotransformation of numerous drugs, neurotransmitters, and xenobiotic compounds. Histamine N-methyltransferase (HNMT) catalyzes the Nτ-methylation of histamine and structurally related molecules. Measurement of HNMT activity in erythrocytes allows for the assessment of enzyme activity variations, which may reflect differences in less accessible tissues such as the brain [27]. This evidence confirms the presence of histamine in erythrocytes, which can be neutralized by HNMT.

In a subsequent experiment, histamine receptor blockers used to investigate changes in endogenous histamine content (i.e., histamine present within erythrocytes) and the sorption capacity of these cells when receptors were blocked, and histamine was added exogenously. Desloratadine used as an H1 receptor antagonist, ranitidine as an H2 receptor antagonist, and betahistine as an H3 receptor antagonist. Since H4 receptor blockers are currently not commercially available, a combination of desloratadine, ranitidine, and betahistine was applied simultaneously to block H1, H2, and H3 receptors in washed erythrocyte suspensions. The results were compared to the independent effects of histamine alone and the blockers or their combination alone.

Exogenous addition of histamine to rat erythrocyte suspensions caused a decrease in endogenous histamine content (by 15 % in males and 24 % in females), although these changes were not statistically significant (Fig. 1). This suggests that elevated extracellular histamine levels may induce the release of endogenous biogenic amines from erythrocytes. These findings

imply the presence of histamine H receptors that signal for the release of this biogenic amine, like mechanisms observed in eosinophils, tissue basophils, and blood basophils. Alternatively, this effect may indicate the presence of histaminase (also known as diamine oxidase) [32]. Histamine can also be degraded by histamine N-methyltransferase; however, reports in the scientific literature suggest that in rats, histamine degradation within erythrocytes occurs solely via histaminase. In this case, erythrocytes must first absorb histamine, after which histaminase is activated – a process in which histamine receptors likely do not participate. Currently, there is no definitive evidence confirming the presence of histaminase in red blood cells. Its presence requires further experimental investigation, which we plan to undertake in future studies. Diamine oxidase is the principal enzyme involved in histamine catabolism, and its deficiency has been proposed as a potential cause of histamine intolerance [21].

When desloratadine, an H1 receptor antagonist, was added to the erythrocytes of male rats followed by histamine, no significant changes were detected in the content of the biogenic amine compared to the effect of desloratadine alone (Fig. 1). It was important to observe changes relative to the independent action of the blocker to confirm true receptor blockade rather than nonspecific effects of the chemical compound, which could induce cellular side effects.

In contrast, the addition of desloratadine at all tested concentrations to erythrocyte suspensions from female rats caused a significant decrease in endogenous histamine content (Fig. 1). This effect differs from that observed in males, where no significant changes in endogenous histamine levels were found.

Furthermore, we demonstrated that under the influence of the H1 receptor blocker at 10 μM, exogenous histamine administration led to a 2.5-fold increase in histamine accumulation within erythrocytes of female rats compared to desloratadine treatment alone at the same concentration. Notably, at 1 μM desloratadine, in the presence of histamine, endogenous histamine content decreased by 32 % relative to desloratadine alone (Fig. 1). These findings suggest that blocking a substantial number of H1 receptors with desloratadine at 10 μM may facilitate the uptake of exogenous histamine, resulting in increased intracellular histamine levels. Thus, the H1 receptor on the erythrocyte membrane appears to be involved in regulating endogenous histamine content in female rat erythrocytes. The differential effects of low (0.1 μM) versus high (10 μM) desloratadine concentrations in combination with histamine may reflect varying degrees of H1 receptor blockade, ranging from partial to complete. Moreover, it should be considered that when H1 receptors are blocked, other histamine receptors (H2, H3, and H4) remain active and can be influenced by exogenously administered histamine.

Importantly, the distinct responses observed in male and female erythrocytes suggest sex-dependent differences in the number or functionality of histamine receptors. Male erythrocytes may possess significantly fewer H1 receptors compared to females, or there may be differences in the distribution or involvement of H2, H3, and H4 receptors. Alternatively, H1 receptors may play a lesser role in regulating endogenous histamine content in male erythrocytes.

Thus, histamine is present in the erythrocytes of both male and female rats, with females exhibiting higher histamine levels compared to males. Desloratadine at all tested concentrations caused a decrease in histamine content in erythrocytes of female rats, whereas no significant changes were observed in males relative to controls. These results indicate a sex-dependent difference in erythrocytes regarding histamine content and sensitivity to H1 receptor blockade. In female rat erythrocytes, in the presence of histamine, low concentrations of the H1 receptor blocker induce a decrease in endogenous histamine, while high concentrations cause an increase. These findings support the hypothesis that the erythrocyte plasma membrane contains a limited number of H1 histamine receptors, the expression or functionality of which may depend on sex.

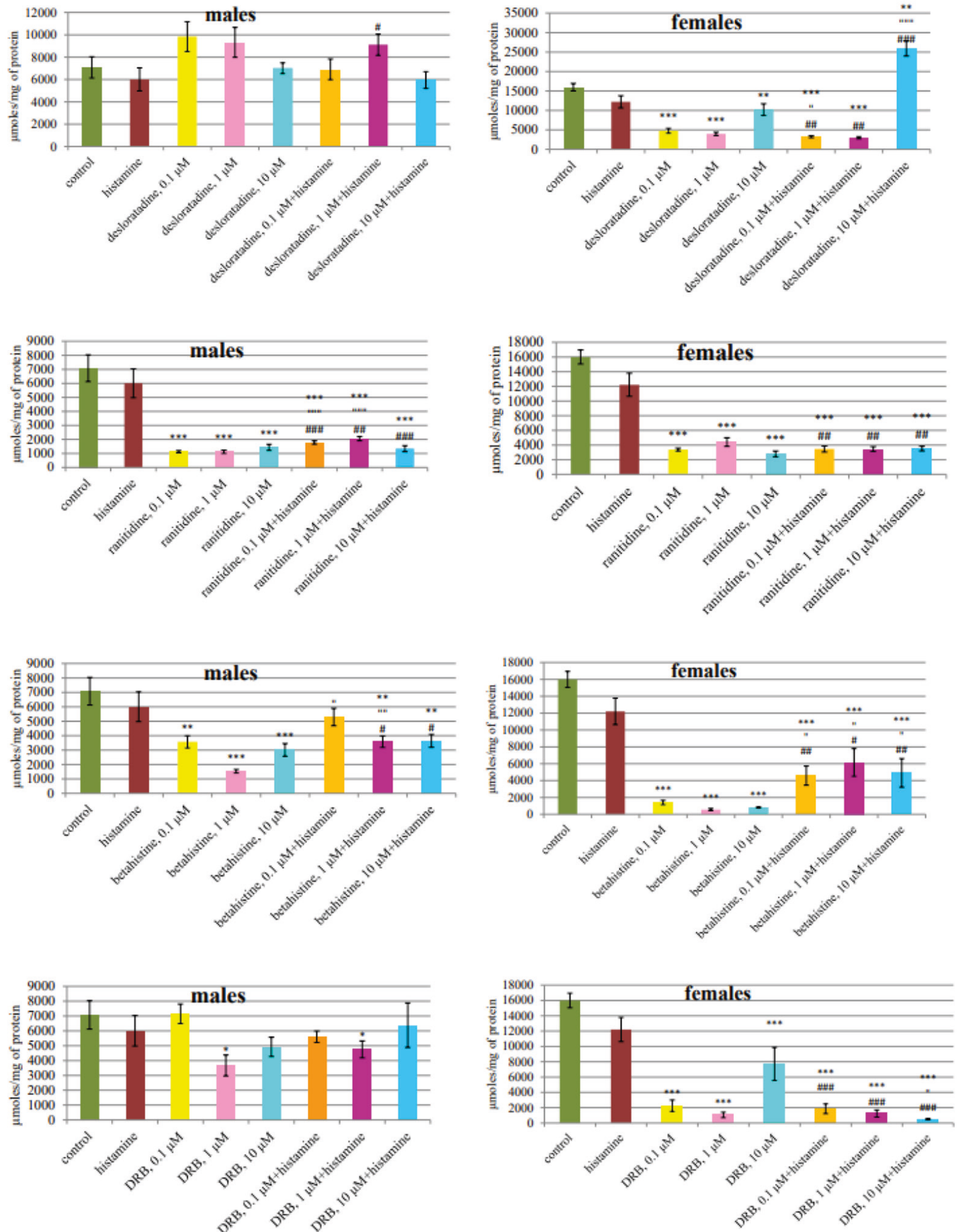

Fig. 1. Endogenous histamine content in rat erythrocytes under the action of exogenous histamine, desloratadine, ranitidine, betahistine, the combined effect of these three substances (DRB) and the combined action of histamine receptor blockers with histamine (* – p≥0,95; ** – p≥0,99; *** – p≥0,999; * – the difference is significant compared to intact cells; ′′ – the difference is significant compared to the group of erythrocytes to which the corresponding blocker or mixture of blockers was added; # – the difference is significant compared to the group of erythrocytes to which histamine was added)

Incubation of erythrocytes from both male and female rats with ranitidine at all concentrations studied (0.1, 1, and 10 μM) resulted in a significant reduction of endogenous histamine content (Fig. 1). The addition of histamine to male rat erythrocytes treated with ranitidine at 0.1 and 1 μM led to increases in endogenous histamine content by 58 % and 84 %, respectively, compared to ranitidine treatment alone. It is known that ranitidine reduces degranulation of tissue basophils and suppresses histamine release [13]. Ranitidine acts as an H2 receptor antagonist, primarily targeting histamine receptors in the stomach. However, in our experiments, other histamine receptors (H1, H3, and H4) remained active. Given these observations, we suggest that ranitidine also influences histamine release in erythrocytes. Therefore, we conclude that erythrocytes of male rats express functional H2 histamine receptors.

Incubation of male rat erythrocytes with 10 μM ranitidine followed by histamine addition did not alter endogenous histamine levels compared to ranitidine treatment alone (Fig. 1). Conversely, the addition of histamine to erythrocytes from female rats under ranitidine treatment resulted in endogenous histamine levels similar to those observed with ranitidine alone. This suggests that the potential H2 receptor on the plasma membrane of female rat erythrocytes does not regulate histamine content, is absent, or that the regulation of endogenous histamine in female erythrocytes follows sex-specific mechanisms (Fig. 1).

Thus, ranitidine causes a significant decrease in the content of endogenous histamine in erythrocytes of male rats, while the combined effect of ranitidine at concentrations of 0.1 and 1 μM together with histamine leads to an increase in biogenic amine content, although these values do not reach the control level. It is possible that ranitidine at a concentration of 10 μM is too high for *in vitro* experiments, potentially causing damage to the erythrocytes themselves, thereby increasing membrane permeability to histamine. Under such conditions, the receptor-specific effect of ranitidine may be masked. In erythrocytes of female rats, the combined effect of ranitidine and histamine does not alter the endogenous histamine level compared to the independent effect of ranitidine.

The decrease in histamine content in rat erythrocytes is likely due to the release of this biogenic amine from erythrocyte cells via the activation of potential histamine receptors on the plasma membrane, initiating exocytosis.

Ranitidine is a histamine H2 receptor blocker. However, this drug was temporarily withdrawn throughout the European Union in April 2020 due to the detection of low levels of N-nitrosodimethylamine, a probable carcinogen. Additionally, ranitidine may cause allergic reactions [16]. Considering these side effects, ranitidine might affect plasma membrane permeability by increasing it, which corresponds to the significant decrease in endogenous histamine observed in rat erythrocytes. The reduction in endogenous histamine content under the combined treatment of ranitidine and exogenous biogenic amine likely results from the toxic effects of ranitidine as a chemical compound.

Therefore, although the H2 receptor is present on the erythrocyte membrane of female rats, it does not appear to regulate the uptake of exogenous histamine or the removal of endogenous histamine, while a similar regulatory effect is observed in male rat erythrocytes.

The addition of the histamine H3 receptor blocker, betahistine, to erythrocytes of both male and female rats caused a decrease in endogenous histamine content. Notably, the decrease was more pronounced in female rat erythrocytes than in males. The most significant decrease occurred at a betahistine concentration of 1 μM. It is known that histamine can be released from cells via several mechanisms, including mechanical damage, exposure to chemical compounds

(e.g., polyglucin, tubocurarine), immune reactions, and through histamine receptor activation. The reduction in endogenous histamine in erythrocytes may be due to betahistine's action as a histamine-releasing agent. However, betahistine's prescribing information indicates that it increases histamine metabolism and release by blocking presynaptic H3 receptors and inducing their downregulation.

When betahistine at concentrations of 0.1 and 1 μM was added to washed erythrocytes of male rats followed by histamine incubation for 5 minutes, endogenous histamine content increased by 48 % and 133 %, respectively, compared to samples treated with betahistine alone (Fig. 1). Importantly, in female rat erythrocytes, all tested concentrations of betahistine combined with exogenous histamine significantly increased endogenous histamine levels. These results support the presence of H3 receptors on the plasma membrane of rat erythrocytes.

At the highest studied betahistine concentration (10 μM), combined treatment with histamine tended to increase endogenous histamine in male rat erythrocytes by 21 % relative to betahistine alone, although this increase was not statistically significant. This may reflect the need for a higher histamine concentration to detect effects at this betahistine level. The most robust increase in histamine content occurred with betahistine at 1 μM combined with histamine, although endogenous histamine did not reach control values. Thus, 1 μM betahistine appears to be the optimal concentration for these experiments.

In summary, betahistine reduces endogenous histamine in rat erythrocytes, with the greatest effect at 1 μM. Combined betahistine and histamine treatments increase endogenous histamine levels, confirming H3 receptor involvement in erythrocyte histamine regulation. Besides H3, other histamine receptors (H1, H2, and H4) may also be present and should be considered when interpreting results. H receptors are known to exist on tissue and blood basophils (histamine-synthesizing cells) and eosinophils (histamine-absorbing cells), regulating histamine release. Thus, the H3 receptor on erythrocyte membranes likely contributes to endogenous histamine regulation.

Histamine effects on cells, including erythrocytes, are pleiotropic, with activation of different histamine receptors (H1-H4) causing opposing outcomes. Betahistine has a slight agonistic effect on the H1 receptor [3, 6, 14], possibly enhancing histamine release from erythrocytes through partial H1 activation.

Previous studies showed that subcutaneous administration of exogenous histamine (1 μg/kg) in rats sharply decreases blood histamine by 72 % on day 1, normalizes by day 7, then decreases again on day 14 [3]. These fluctuations likely reflect histaminase activity neutralizing histamine and uptake by other blood cells, such as eosinophils, with erythrocytes potentially contributing to the decline.

To investigate the H4 receptor on erythrocytes, endogenous histamine levels were measured following simultaneous addition of desloratadine (H1 blocker), ranitidine (H2 blocker), betahistine (H3 blocker), collectively referred to as DRB, and exogenous histamine. Addition of DRB at 1 μM alone, or combined with histamine, reduced endogenous histamine compared to control, possibly by increasing membrane permeability and causing receptor-independent histamine release.

Thus, when H1, H2, and H3 receptors are blocked, only the H4 receptor remains active, with exogenous histamine inhibiting endogenous histamine release and promoting sorption. Only DRB at 1 μM significantly decreased endogenous histamine.

H3 receptors regulate histamine secretion in the central nervous system, whereas H4 receptors modulate histamine retention and release in erythrocytes. The H4 receptor is found on

immune and spleen cells, but its role is not fully understood. Evidence suggests the H4 receptor plays a key role in allergic diseases.

In male rat erythrocytes, combined DRB and histamine treatment reduced endogenous histamine only at 1 μM DRB. In female rat erythrocytes, DRB significantly decreased endogenous histamine across concentrations, with maximal reduction (93 %) at 1 μM and least reduction at 10 μM. The unexpected lesser effect at 10 μM may result from chemical interactions between blockers or erythrocyte detoxification mechanisms neutralizing DRB compounds. Partial receptor blockade at low DRB concentrations may explain differences between low and high dose effects.

Blocking H1, H2, H3 receptors with DRB (10 μM) plus exogenous histamine decreased endogenous histamine compared to DRB alone, indicating H4 receptor involvement in histamine release from female rat erythrocytes.

In conclusion, erythrocyte plasma membranes possess H3 receptors regulating endogenous histamine content, as evidenced by changes upon H3 receptor blockade and histamine addition. Presence of H1, H2, and H4 receptors is possible but likely sex-dependent and less directly involved in histamine regulation. H4 receptors appear least sensitive to histamine content regulation.

Histamine increased sorption capacity of male rat erythrocytes by 55 % (Fig. 2), indicating enhanced protective function but also increased erythrocyte membrane damage and altered surface potential, leading to decreased deformability and clearance from circulation. Sorption capacity reflects erythrocyte endogenous intoxication levels [8]. Histamine also influences blood rheology by increasing vascular permeability and tissue swelling, redistributing fluid from blood to interstitial space.

Desloratadine addition to male rat erythrocytes did not affect sorption capacity (Fig. 2). Combined histamine and desloratadine at 1 μM caused a small but significant 6 % decrease compared to desloratadine alone. Other desloratadine concentrations combined with histamine showed no difference from desloratadine alone.

Histamine addition to female rat erythrocytes decreased sorption capacity by 51 %. Sorption capacity reflects plasma membrane integrity; a decrease suggests impaired erythrocyte function in binding and removing harmful substances. This suggests that the number of potential H1, H2, H3, and H4 histamine receptors on the membranes of female rats is different from that on the membranes of erythrocytes of male rats.

The decrease in the sorption capacity of erythrocytes from female rats indicates that histamine affects cell membranes, reducing their ability to interact with methylene blue. Histamine interacts with various types of receptors on cell membranes. A significant decrease in the sorption capacity of erythrocytes may reflect alterations in the surface charge of the erythrocyte plasma membrane.

It was found that the addition of desloratadine at a concentration of 0.1 μM reduced the sorption capacity of female rat erythrocytes by 62 %. In contrast, desloratadine at higher tested concentrations did not significantly alter this capacity. Desloratadine contains an NH-group in its structure, which may affect the sorption capacity of erythrocytes. It is known that erythrocyte sorption of compounds occurs via Van-der-Waals interactions. Generally, desloratadine is expected to bind to histamine H1 receptors. Desloratadine is classified among highly toxic substances [9]. Therefore, the observed decrease in the sorption capacity of female rat erythrocytes was unexpected.

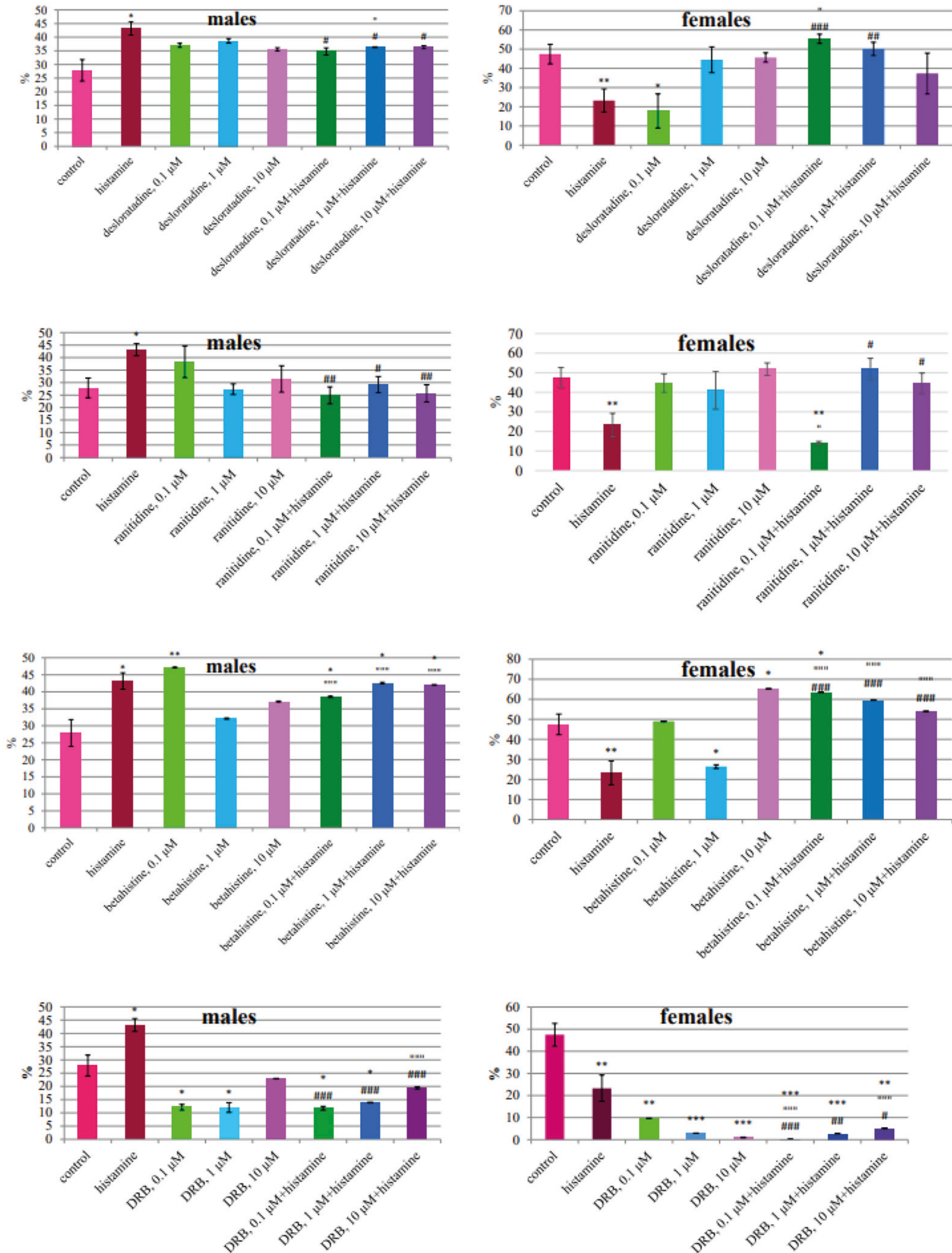

Fig. 2. Sorption capacity of rat erythrocytes under the action of exogenous histamine, desloratadine, ranitidine, betahistine, the combined effect of these three substances (DRB) and the combined action of histamine receptor blockers with histamine (* – p≥0,95; ** – p≥0,99; *** – p≥0,999; * – the difference is significant compared to intact cells; ´´ – the difference is significant compared to the group of erythrocytes to which the corresponding blocker or mixture of blockers was added; # – the difference is significant compared to the group of erythrocytes to which histamine was added) female rats is different from that on the membranes of erythrocytes of male rats

We observed that histamine, when applied in the presence of desloratadine at 0.1 μM, caused an increase in the sorption capacity of female rat erythrocytes by 211 % compared to erythrocytes treated solely with desloratadine at the same concentration. These results indicate that the combined effect of desloratadine and histamine counteracts the effect of desloratadine alone. When desloratadine is added to the erythrocyte suspension, it should bind to potential histamine H1 receptors on the erythrocyte membranes, thus blocking these receptors. Addition of exogenous histamine to erythrocytes with blocked H1 receptors does not result in histamine binding to these receptors. Therefore, it can be concluded that the H1 receptor is directly or indirectly involved in regulating the sorption capacity of erythrocytes. Both desloratadine at 0.1 μM and histamine alone reduced erythrocyte sorption capacity. We noted that desloratadine might affect Van-der-Waals interactions due to the presence of NH-groups in its structure. Histamine also contains NH groups. Thus, adding histamine to erythrocytes with blocked H1 receptors could lead to its binding to other histamine receptors, such as H2, H3, or H4, which may explain the observed changes in sorption capacity.

It should be noted that desloratadine at concentrations of 1 and 10 μM, when combined with histamine, did not induce significant changes in the sorption capacity of female rat erythrocytes compared to erythrocytes treated with desloratadine alone at the respective concentrations.

Scientific literature reports that desloratadine at doses of 1/500 DL50, 1/100 DL50, and DL50 affects bull sperm, characterized by a reduced intensity of oxidative processes, likely due to impaired mitochondrial respiratory chain function and ATP resynthesis, resulting in decreased motility and survival time [1]. The desloratadine penetrates the plasma membrane of cells, inducing functional changes. The toxicity of desloratadine, causing 50 % mortality in Daphnia magna Straus, ranges from 5.7 to 19.2 mg/dm3, depending on exposure time and concentration. A concentration of 2.9 mg/dm3 is moderately toxic (toxicity class 3), while concentrations from 5.7 to 19.2 mg/dm3 belong to toxicity classes 4–5. A concentration of 0.57 mg/dm3 shows no acute lethal toxicity. The threshold concentration affecting aquatic organisms is 0.5 mg/dm^3 [1]. Considering these data, it can be concluded that desloratadine concentrations of 1 and 10 μM penetrate erythrocytes and thus do not alter their sorption capacity in our experiments.

Therefore, histamine exerts opposite effects on the sorption capacity of erythrocytes from male and female rats, indicating a sex-dependent difference in histamine's impact on this parameter. Desloratadine decreases the sorption capacity only at 0.1 μM and only in female erythrocytes. Histamine in the presence of desloratadine at 1 μM reduces the sorption capacity of male rat erythrocytes. Combined administration of desloratadine at 0.1 μM and histamine increases the sorption capacity of female rat erythrocytes compared to desloratadine alone.

Importantly, the addition of ranitidine at all tested concentrations to erythrocyte suspensions from both male and female rats did not significantly affect their sorption capacity (Fig. 2). This result was unexpected, since ranitidine is a chemical compound foreign to erythrocytes. These findings suggest a positive effect of ranitidine on erythrocyte plasma membranes. Sorption capacity serves as a protective reaction of erythrocytes to harmful substances sorbed onto their plasma membrane surfaces. Therefore, the absence of changes in this parameter is considered beneficial. Ranitidine is a histamine antagonist, specifically targeting histamine H2 receptors.

Erythrocytes play a direct role in sensitization mechanisms to medicinal substances, involving changes in cytometric parameters, plasma membrane structure and function, and sorption capacity [12]. However, no changes in erythrocyte sorption capacity were observed under ranitidine exposure in our study. It is known that erythrocyte plasma membranes possess

high sorption capacity, mediating transport of amino acids, lipids, and toxins, thus participating in body metabolism. Erythrocytes can carry antigens, mitogens, mediators, hormones, and other biologically active compounds, transferring them to lymphocytes and regulating lymphoproliferation [10]. Sorption processes involving molecular attachment to membranes occur via Van-der-Waals interactions [28]. Ranitidine is rapidly absorbed in the gastrointestinal tract and easily crosses histohematological barriers, including the placental barrier, indicating it does not bind to the membrane surface but penetrates it readily. Therefore, no changes in the sorption capacity of erythrocytes under the influence of ranitidine were observed in our study.

The combined effect of ranitidine at all tested concentrations with histamine did not alter erythrocyte sorption capacity in male and female rats, except for ranitidine at 0.1 μM combined with histamine, which caused a 69 % decrease in sorption capacity of female rat erythrocytes compared to ranitidine alone. This suggests that the H2 receptor may not directly regulate erythrocyte sorption capacity or exert only indirect effects. The enhanced decrease in sorption capacity under combined histamine and ranitidine (0.1 μM) exposure may be related to their interaction, altering physicochemical properties of erythrocyte membranes. Ranitidine possibly potentiates histamine action by modulating receptor activity or membrane permeability.

Thus, ranitidine does not affect sorption capacity in erythrocytes of male and female rats, and its combination with histamine alters sorption capacity only in female erythrocytes. It is probable that the H2 receptor is indirectly involved in regulating erythrocyte sorption capacity. Mature erythrocytes adsorb circulating immune complexes and interact with antibodies via membrane C-receptors for immunoglobulins and complement components C3b and C4b, as well as surface antigens. Approximately 90 % of these receptors in the vascular bed are located on erythrocytes [12]. Given this, histamine and its H2 receptor may be involved in modulating erythrocyte sorption capacity. Sorption is immunologically important, and its modulation by histamine warrants further investigation.

Addition of betahistine at 0.1 μM to male rat erythrocytes increased sorption capacity by 69 % (Fig. 2). Combined exposure to betahistine at 0.1 μM and histamine decreased sorption capacity by 18 % compared to betahistine alone, suggesting histamine may regulate this parameter via H3 receptors. Co-administration of betahistine at 1 and 10 μM with histamine increased sorption capacity by 32 and 13 %, respectively, compared to betahistine alone.

Therefore, histamine and betahistine at minimal tested concentrations enhance sorption capacity of male rat erythrocytes. Histamine modulates sorption capacity in a concentration-dependent manner under betahistine influence. Literature indicates erythrocytes participate in drug sensitization mechanisms involving changes in sorption capacity [12], although these mechanisms remain undefined. Our findings and others suggest histamine may serve as a regulatory factor in erythrocyte sorption capacity, consistent with its key role in allergic disease development. The marked increase in sorption capacity at minimal betahistine concentration highlights dose-dependent compensatory-adaptive cellular responses, where low doses exert protective effects while higher doses may harm erythrocytes.

Under combined betahistine and histamine exposure, male rat erythrocyte sorption capacity shifts toward levels observed with histamine alone, indicating the presence of H3 receptors on erythrocyte membranes involved in sorption regulation.

Scientific literature reports that increase in mean corpuscular volume and membrane function alterations leading to elevated sorption capacity reduce erythrocyte deformability and mobility, causing cellular aggregation and microcirculatory disturbances [15]. Therefore, increased erythrocyte sorption capacity induced by histamine, betahistine, and their combination may represent a negative phenomenon. Sorption analysis provides insights into erythrocyte

regenerative capacity linked to plasma membrane barrier properties. Elevated sorption capacity indicates membrane damage and cellular disorganization, serving as a clinical marker of endogenous intoxication severity.

Betahistine at 1 μM reduced sorption capacity of female rat erythrocytes by 44 %, whereas 10 μM increased it by 37 %. Betahistine at 0.1 and 1 μM combined with histamine increased sorption capacity by 30 and 126 %, respectively, relative to betahistine alone, suggesting H3 receptor involvement. Betahistine at 10 μM followed by histamine reduced sorption capacity by 17 % compared to betahistine alone.

Thus, betahistine modulates sorption capacity in erythrocytes of both sexes. Betahistine exhibits weak H1 receptor agonism and strong H3 receptor antagonism [14]. The observed effects likely reflect redistribution of histamine and betahistine actions on erythrocytes. Combined betahistine and histamine treatment altered sorption capacity, supporting the presence of H3 receptors on rat erythrocyte membranes and their role in regulating sorption.

Adsorption is a reversible process achieving equilibrium when adsorption and desorption rates are equal [7]. Physical adsorption involves Van-der-Waals forces and is spontaneous, reversible, and nonspecific, unlike generally irreversible chemical adsorption. Betahistine may promote Van-der-Waals interactions, increasing erythrocyte sorption capacity. Histamine addition following betahistine treatment likely modifies membrane surface charge, enhancing sorption. Van-der-Waals interactions include dispersion forces and dipole–dipole interactions between neutral/nonpolar and polar groups, respectively.

Under desloratadine, ranitidine, and betahistine (DRB) at 0.1 and 1 μM, male rat erythrocyte sorption capacity decreased by 57 % (Fig. 2). The addition of these compounds, containing cationic groups, is expected to reduce sorption. However, the lack of effect at 10 μM was unexpected, possibly indicating synergistic drug effects.

Blocking H1, H2, and H3 receptors with DRB at 10 μM followed by histamine exposure decreased sorption capacity by 15 % compared to DRB alone (Fig. 2).

It is known that histamine accumulates in blood eosinophils and neutrophils and is produced by basophils; its synthesis by erythrocytes remains unknown. Allergen exposure in the respiratory tract cross-links IgE on basophils, triggering release of histamine, lipid mediators, and cytokines. Antigens also activate dendritic cells and macrophages, leading to T helper cell presentation and local cytokine release. Histamine acts on multiple cells via H1 and H4 receptors, mediating chemotaxis, inflammation, vascular permeability, and smooth muscle tone, contributing to asthma pathophysiology [30]. The mechanism of histamine action on erythrocytes is unknown but likely complex and receptor mediated.

Comparing our male erythrocyte results with females, similar effects were observed.

DRB at 0.1, 1, and 10 μM decreased female erythrocyte sorption capacity by 80, 94, and 98 %, respectively (Fig. 2). Sorption capacity relates to receptor presence on erythrocyte surfaces [12]. Blocking H1, H2, H3 receptors with DRB at 0.1 μM followed by histamine addition decreased female erythrocyte sorption by 98 %, whereas DRB at 10 μM with histamine increased sorption fivefold.

Erythrocytes have significant detoxification function due to glutathione transferase and glutathione content and likely neutralize some drugs (DRB). Alternatively, H4 receptor activity on erythrocyte membranes may regulate sorption capacity. Therefore, DRB reduces erythrocyte sorption capacity in both sexes, while combined DRB and histamine exposure modulates this parameter compared to DRB alone.

Analyzing the results of the study on the effect of histamine on rat erythrocytes, it can be concluded that blocking the potential H3 receptor with betahistine on the membranes

of erythrocytes from both females and males leads to changes in the content of endogenous histamine within erythrocytes and their sorption capacity. This indicates the presence of the H3 histamine receptor on the plasma membranes of red blood cells and its involvement in regulating these parameters. It should be emphasized that the addition of other blockers targeting H1 and H2 receptors induces only slight changes in endogenous histamine levels in erythrocytes from either male or female rats, suggesting the presence of these receptors and a modest influence of their activation on histamine regulation, which may also be sex-dependent. When H1, H2, and H3 receptors are blocked, only the H4 receptor remains active, which causes changes in the sorption capacity of erythrocytes in both male and female rats at the highest tested blocker concentrations. Therefore, the H4 receptor may also participate in the regulation of erythrocyte sorption capacity.

Notably, male and female erythrocytes respond differently to the addition of exogenous histamine to the cell suspension without prior receptor blockade, indicating a differential quantitative distribution of H1, H2, H3, and H4 receptors. It is known that H1 and H2 receptors are activating, whereas H3 and H4 receptors are inhibitory. Consequently, depending on the concentration of both blockers and histamine, the effects of these compounds on erythrocyte sorption capacity differ.

Histamine, when the H3 receptor is blocked, acts through the remaining H1, H2, and H4 receptors, leading to activation of phospholipase C and protein kinase C, as well as alterations in adenylyl cyclase activity. These signaling events result in changes to the biophysical properties of the membrane and modify its permeability to histamine. Moreover, such membrane alterations affect the sorption capacity of erythrocytes. Van der Waals interactions play a role in sorption processes. While an increase in sorption capacity can be considered beneficial, it may also reduce cell deformability, which is a negative effect. Literature reports indicate that increased activity of adenylyl cyclase and protein kinase C negatively affects erythrocyte deformability.

It should also be noted that although betahistine is primarily an H3 receptor antagonist, it acts as a minor agonist of the H1 receptor. Thus, it is noteworthy that when desloratadine, ranitidine, and betahistine are added to erythrocyte suspensions – thereby leaving only the H4 receptor active – the exogenously administered histamine exerts effects on sorption capacity that are opposite to those observed otherwise.

In conclusion, we propose that all four types of histamine receptors may be present on the erythrocyte plasma membrane; however, only the H3 receptor demonstrates high specificity (direct or indirect) in regulating endogenous histamine content and modulating erythrocyte sorption capacity. The potential presence of H1, H2, and H4 receptors suggests, they likely exhibit lower specificity in these processes.

Thus, betahistine, an H3 receptor antagonist, followed by histamine administration, induces an increase in the endogenous histamine content in erythrocytes of both male and female rats, as well as alters the sorption capacity of these cells compared to the independent effect of betahistine. This suggests the presence of H3 histamine receptors on the plasma membrane of red blood cells and their role in regulating histamine content and sorption capacity. Simultaneous blockade of potential H1, H2, and H3 receptors by desloratadine, ranitidine, and betahistine, leaving only the H4 receptor functional, followed by histamine administration, causes changes in the sorption capacity of erythrocytes from male and female rats compared to the independent effects of these blockers. This may be indicates the presence of H4 histamine receptors. Administration of desloratadine or ranitidine alone to erythrocyte suspensions, followed by histamine, leads to isolated sorption capacity. changes in endogenous histamine content

and sorption capacity, dependent on substance concentration and sex. These results suggest the presence of H1 and H2 receptors; however, their involvement in regulating endogenous histamine levels and erythrocyte sorption capacity appears to be indirect or limited. Thus, H1 and H2 receptors likely do not play a primary role in regulating these parameters.

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ВПЛИВ ГІСТАМІНУ І БЛОКАТОРІВ ГІСТАМІНОВИХ РЕЦЕПТОРІВ НА ВМІСТ ЕНДОГЕННОГО ГІСТАМІНУ ТА СОРБЦІЙНУ ЗДАТНІСТЬ ЕРИТРОЦИТІВ КРОВІ ЩУРІВ

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Відомо, що гістамін синтезується з гістидину в тканинних базофілах і базофілах крові. Після вивільнення з клітин гістамін діє на Н1, Н2, Н3, Н4 рецептори до гістаміну, які містяться на плазматичних мембранах. Невивченим є питання наявності на плазматичних мембранах еритроцитів рецепторів до гістаміну. Мета дослідження - виявити гістамін в еритроцитах і визначити наявність Н1–Н4 рецепторів на мембранах еритроцитів, застосовуючи блокатори гістамінових рецепторів, через зміну рівня потенційного ендогенного гістаміну та зміну сорбційної здатності еритроцитів. У досліді до еритроцитів додавали гістамін у концентрації 5,4 мкМ, блокатори гістамінових рецепторів (дезлоратадин, який блокує Н1 рецептор; ранітидин, який блокує Н2 рецептор; бетагістин, який блокує Н3 рецептор) таким чином, щоб кінцева концентрація становила 0,1; 1; 10 мкМ. Було також створено групи, до еритроцитів яких додавали і зазначені блокатори, і гістамін. Для аналізу наявності Н4 рецептора на мембрані еритроцитів до клітин одночасно додавали усі три блокатори (дезлоратадин, ранітидин, бетагістин), оскільки на сьогодні немає у вільному доступі блокатора Н4 рецептора до гістаміну. Встановлено, що в еритроцитах міститься гістамін, причому в еритроцитах самок щурів рівень гістаміну вищий, ніж в еритроцитах самців. Поєднане додавання до крові блокатора Н1 рецептора (дезлоратадину) та гістаміну змінює вміст ендогенного гістаміну в еритроцитах самок порівняно з незалежною дією дезлоратадину, а також впливає і на сорбційну здатність. Ранітидин, блокатор Н2 рецептора, за вказаних умов досліду веде до підвищення вмісту ендогенного гістаміну в еритроцитах самців. Поєднане додавання до суспензії еритроцитів блокатора Н3 рецептора, бетагістину та гістаміну спричиняє підвищення вмісту ендогенного гістаміну в еритроцитах самок і самців щурів порівняно з незалежною дією бетагістину, а також зумовлює зміну сорбційної здатності. За блокування Н1, Н2, Н3 рецепторів до гістаміну та подальшого введення до суспензії еритроцитів відбувається зниження сорбційної здатності клітин самців (за використання високих концентрацій блокаторів; 10 мкМ) та зміна сорбційної здатності еритроцитів самок щурів (за окремих концентрацій) порівняно з незалежною дією суміші блокаторів. Отже, можна зробити висновок, що на мембранах еритроцитів самок і самців щурів наявний Н3 рецептор до гістаміну, функція якого полягає в регуляції вмісту ендогенного гістаміну та сорбційної здатності цих клітин.

Ключові слова: еритроцити, гістамін, гістамінові рецептори, блокатори гістамінових рецепторів