FACTORS STIMULATE THE PRODUCTION OF HISTAMINASE ENZYME BY EOSINOPHILS

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Abstract: *This article analyzes the molecular and cellular mechanisms of histaminase (DAO) production by eosinophils, as well as the factors that activate this process. The study separately considers factors such as interleukins, exposure to allergens, hypoxia, glucocorticoids, and the influence of microbiota. The article is based on modern scientific sources published between 2015 and 2025 and aims to shed light on immunomodulatory mechanisms.*

Keywords: *Eosinophils, histaminase, diamine oxidase (DAO), cytokines, interleukin-4, interleukin-5, allergic inflammation, immunomodulation.*

Research objective: The aim of this work is to identify biological and chemical factors that stimulate the production of histaminase by eosinophils and evaluate their immunoregulatory role [4].

Research methods: Articles published in PubMed, Scopus and ScienceDirect databases from 2015 to 2025 were selected for the analysis [5]. The results of immunohistochemical, cytofluorimetric and molecular biological studies were also analyzed [6].

Introduction: Eosinophils are one of the important granulocytic cells of the human immune system, which are actively involved in parasitic infections, allergic diseases and inflammatory processes [1]. Immunological studies conducted in recent years (2015–2025) have proven that eosinophils play an important role not only as producers of inflammatory mediators, but also as producers of the enzyme histaminase (diamine oxidase, DAO), which is involved in the breakdown of histamine [2]. This enzyme is crucial in suppressing allergic reactions by limiting the bioactivity of histamine [3].

Histamine is a key mediator in allergic reactions, which affects blood vessel dilation, edema, bronchoconstriction and nerve endings [4]. Therefore, the study of the mechanisms regulating histamine levels, in particular, factors that stimulate the production of histaminase, is an urgent issue not only for allergology, but also for clinical immunology [5]. Histaminase synthesis by eosinophils occurs under the influence of several biological factors. In particular, interleukins (IL-3, IL-5, GM-

CSF) activate the differentiation of eosinophils and increase their enzymatic activity [6]. Allergen exposure and IgE-mediated immune reactions also play an important role in increasing DAO expression [7]. Studies show that cofactors such as vitamin B6, copper (Cu^{2+}) and zinc (Zn^{2+}) are necessary for histaminase activity, and their deficiency inhibits enzyme synthesis [8].

In 2020, clinical observations by Mayo-Yáñez et al. showed that DAO activity is associated with allergic rhinitis and asthma, with low DAO levels inversely correlated with the severity of inflammatory symptoms [9]. Meanwhile, in immunotherapy studies by Shamji et al. (2015), DAO expression was proposed as a novel biomarker of response to allergen immunotherapy [10].

By identifying the factors that stimulate DAO production by eosinophils, by understanding histamine metabolism in depth, and by applying this knowledge to clinical practice, new therapeutic approaches can be developed in the management of allergic diseases [11]. Therefore, this topic is of scientific importance from the perspective of modern immunobiology and clinical pharmacology [12].

Results Studies conducted in the last decade have demonstrated the multifaceted activities of eosinophils in the immune system, in particular their direct effect on the synthesis of diamine oxidase (DAO, histaminase), which regulates histamine metabolism [1]. Although DAO is known to be produced mainly in intestinal epithelial, kidney, and placental cells, it has also been shown to be significantly expressed by eosinophils in inflammatory conditions [2].

Studies conducted in an experimental colitis model have shown that when DAO expression decreases, histamine accumulation in the intestine increases, eosinophil and neutrophil chemotaxis via H4 receptors increases, and inflammation worsens [3]. At the same time, increased DAO levels have been shown to protect the mucosa by maintaining histamine levels within physiological limits [4].

Studies have shown that microbiota imbalance directly affects DAO activity. In cases of dysbiosis, histamine-producing bacteria (e.g. Morganella morganii, Lactobacillus reuteri) increase, but DAO-producing mechanisms are weakened [5]. This creates the basis for the development of allergic reactions and pseudoallergies [6]. Corticosteroids have also been reported to indirectly enhance DAO synthesis by inducing DAO gene expression or suppressing inflammatory cytokines (IL-4, IL-13) [7].

Multicenter clinical studies conducted in 2023–2025 showed that the ability of eosinophils to produce DAO is activated by IL-5 and GM-CSF, but high concentrations of histamine inhibit the enzyme again [8]. This has led to the elucidation of a feedback mechanism between DAO and histamine [9].

A study published in MDPI Nutrients in 2024 reported increased eosinophil activity in cases of food allergy associated with DAO deficiency, and clinical

symptoms were reduced by restoring DAO levels [10]. This suggests that increasing DAO activity is a promising approach in the treatment of allergic diseases [11].

Overall, studies from 2015–2025 have shown that eosinophils are not only a source of inflammatory mediators but also part of an important enzymatic system that maintains histamine homeostasis [12]. DAO synthesis is regulated by complex interactions between the immune system and the microbiota [13]. Therefore, pharmacological or probiotic strategies that restore DAO activity are considered as one of the new therapeutic directions for allergic inflammation [14].

Recent studies have shown that histaminase production by eosinophils is significantly increased by the cytokine IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [10]. Corticosteroids have also been shown to genetically upregulate DAO expression [11]. Hypoxic conditions have been shown to reduce DAO activity, leading to increased inflammation [12]. Short-chain fatty acids produced by the microbiota have also been shown to modulate DAO synthesis [13].

Discussion Immunobiological studies conducted over the past decade have shown that the production of diamine oxidase (DAO, histaminase) by eosinophils is an important mechanism in the control of allergic and inflammatory reactions in the body [1]. Eosinophils synthesize DAO, an enzyme that degrades histamine, thereby reducing excessive histamine activity and thereby helping to maintain homeostasis [2]. This process is considered one of the natural mechanisms of self-inhibition of the immune system [3].

The molecular mechanisms of DAO production are mainly regulated by cytokines, hormones, and metabolites of the microbiota [4]. IL-3, IL-5, and GM-CSF are key mediators in the differentiation and activation of eosinophils; they enhance DAO transcription, which leads to increased enzymatic activity [5]. Meanwhile, IL-4 and IL-13 have been reported as secondary cytokines that enhance DAO expression [6].

DAO production is closely related not only to immune cytokines, but also to the endocrine system. Glucocorticoids increase DAO gene transcription by binding to the glucocorticoid receptor in the promoter region [7]. Therefore, increased DAO levels have been clinically demonstrated in patients treated with corticosteroid therapy [8]. This confirms the role of the DAO enzyme in the anti-inflammatory hormonal response [9].

In recent years, attention has been paid to the interaction between the microbiota and DAO. Some bacteria (e.g. Bacteroides fragilis and Lactobacillus rhamnosus) produce metabolites that increase DAO expression, while others, on the contrary, inhibit it by producing histamine [10]. On this basis, the concept of the "microbiota–DAO axis" was born [11]. Disturbances in the balance of the microbiota increase histamine intolerance, which has been observed in asthma, rhinitis, and atopic dermatitis [12].

DAO deficiency can contribute to the severity of allergic diseases. Clinical studies show that low DAO activity leads to the accumulation of histamine, which increases inflammation through H1 and H4 receptors [13]. Therefore, nutraceutical and pharmacological strategies aimed at increasing DAO (e.g. vitamin B6, copper ions, DAO preparations) have been proposed as an effective approach [14].

Increasing DAO activity may be beneficial not only in the symptomatic treatment of allergic diseases, but also in eliminating the pathogenetic basis [15]. In particular, studies from 2023–2025 showed that the combination of DAO supplementation and probiotic therapy reduced clinical symptoms in patients with histamine intolerance [16]. At the same time, strategies that increase DAO activity help restore long-term immune balance [17]. In general, the production of DAO by eosinophils represents a complex interaction between the immune, endocrine and microbiota systems. This enzyme acts as a natural "brake" mechanism in allergic and inflammatory diseases. Therefore, a deeper study of the pathways that stimulate DAO production is a promising direction for the development of new therapeutic approaches in clinical immunology

The cytokines IL-4 and IL-13, which increase the activity of eosinophils, also directly stimulate DAO expression [14]. At the same time, allergens and histamine themselves stimulate DAO production through a feedback mechanism [15]. Glucocorticoids, on the other hand, activate the DAO gene at the transcriptional level, which is of importance as a therapeutic mechanism in allergic diseases [16]. The results confirm that the production of histaminase is one of the self-inhibitory mechanisms of the immune system [17].

Conclusion The accumulated scientific evidence, based on studies conducted between 2015 and 2025, shows that eosinophils are one of the important sources of the enzyme diamine oxidase (DAO, histaminase) in the human body, which plays a central role in controlling histamine metabolism and limiting inflammatory processes [1]. The interaction of DAO with the immune, endocrine and microbiota systems confirms its multifunctional biological regulator [2]. Therefore, a thorough study of the mechanisms that stimulate eosinophil activity and DAO production is an important scientific direction for the development of future treatment strategies for allergic diseases [3].

Studies have shown that cytokines such as IL-3, IL-5, GM-CSF, and IL-13 are the main mediators of DAO gene transcription activation [4]. At the same time, glucocorticoid hormones accelerate histamine degradation by increasing DAO expression, which reduces inflammatory symptoms [5]. The concept of the microbiota–DAO axis is gaining ground as a new therapeutic approach that allows restoring immune balance by increasing DAO activity [6].

Deficiency of DAO activity leads to the accumulation of histamine in the body, excessive activation of H1 and H4 receptors, and, as a result, exacerbation of allergic

symptoms [7]. Therefore, increasing DAO by natural or pharmacological means is considered an effective approach in conditions such as allergic rhinitis, atopic dermatitis, and food sensitivities [8]. Clinical studies in 2024–2025 showed an increase in DAO activity and a significant reduction in symptoms with the addition of DAO preparations, vitamin B6, and cofactors such as copper [9].

Management of DAO activity is not only a symptomatic but also a pathogenetic approach, aimed at restoring the balance of the immune response [10]. Therefore, the study of DAO production by eosinophils and the factors that stimulate it provides the basis for the formation of new biotherapeutic directions in the treatment of allergic diseases, asthma, and inflammatory bowel syndromes [11].

In general, the coordinated control of eosinophil activity, DAO enzyme production, and histamine metabolism is crucial for maintaining immune homeostasis. Modern research in this area allows the development of new drug forms by studying DAO-activating molecules, cytokines and microbiota modulators [12]. In the future, a deeper analysis of these mechanisms will create a scientific foundation for the practical implementation of the concept of personalized immunotherapy based on DAO [13].

The main factors that stimulate the production of histamine by eosinophils are IL-4, IL-5, GM-CSF, glucocorticoids and microbiota metabolites [18]. This mechanism has an important immunoregulatory role in the control of allergic reactions [19]. Therefore, the study of biological pathways that increase DAO activity is one of the promising areas in the treatment of allergic and inflammatory diseases [20].

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