# Histamine

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Histamine [2-(4-imidazolyl)-ethylamine] is a biogenic amine that was first synthesized in the early 1900s. Histamine is a biogenic amine with numerous effects on many cell types, mediated by the activation of its four different histamine receptors (H1–H4Rs).

Keywords: histamine ; histamine receptors ; histamine intolerance

## 1. Histamine

Histamine [2-(4-imidazolyl)-ethylamine] is a biogenic amine that was first synthesized in the early 1900s. Since then, its functions have started to be discovered and more well-described [1][2]. Histamine, which is found in many cell types, seems to be the most pleiotropic molecule in the human body [3]. The best known action of histamine is to induce contraction of smooth muscle cells (including bronchi and intestines) as well as dilate blood vessels and increase their permeability. Histamine causes heart rhythm disturbances and influences blood pressure, increases mucous secretion, gastric acid secretion, and irritation of nociceptive nerve fibers [4][5]. Histamine may also play a role in neurotransmission, immunomodulation, hemopoiesis, wound healing, intestinal ischemia, day–night rhythm regulation, and angiogenesis in tumor models [6].

## 2. Synthesis and Degradation of Histamine

Histamine is formed by oxidative decarboxylation from the amino acid L-histidine with the enzyme histidine decarboxylase (HDC). Histamine is degraded as a result of the cyclopentyl action of histamine N-methyltransferase (HNMT) and by oxidative deamination of diaminoxidase (DAO). HNMT is mainly responsible for the degradation of intracellular histamine. The highest expression of HNMT occurs in the kidneys and liver as well as in the spleen, colon, prostate, ovary, cells in the spinal cord, bronchi, and trachea [7]. A small part of histamine is converted into N-methylhistamine by the action of HNMT. In its original form, approximately 2–3% of histamine is excreted [8][9]. DAO, which is a secreted protein, is responsible for the degradation of extracellular histamine. The greatest activity of DAO is recorded in the small intestine, colon, placenta, and kidneys. The vast majority of histamine is converted into imidazole acetic acid by DAO [9].

## 3. Sources of Histamine in the Body

The main cellular source of histamine are mast cells and basophils [10]. In the Golgi apparatus of the cell, the amino acid L-histidine is decarboxylated with the enzyme L-histidine decarboxylase, whose co-factor is pyridoxal phosphate (vitamin B6). The result of this reaction is the formation of histamine, which is later stored in the cytoplasmic granules along with other amines (e.g., serotonin), proteases, proteoglycans, cytokines/chemokines, and angiogenic factors and released after sensitization and degranulation of the cell [11][12]. The degranulation of mast cells and the release of histamine occur mainly as the result of binding a specific antigen to the FcRI receptor as well as in response to non-immune stimuli (e.g., neuropeptides, parts of the complement system, cytokines, platelet activation factor). IgE antibodies are mediators of mast cell degranulation during allergic diseases. The binding of IgE to its high-affinity IgE receptor on mast cell surfaces is called “sensitization” and precedes the development of clinical allergy. Histamine released from mast cells and basophils exerts its biological activities by activating four G protein-coupled receptors, namely H1R, H2R, H3R (expressed mainly in the brain), and H4R. While H1R and H2R activation mainly accounts for some mast cell and basophil-mediated allergic disorders, the selective expression of H4R on immune cells is uncovering new roles for histamine (possibly derived from mast cells and basophils) in allergic, inflammatory, and autoimmune disorders [12]. Histamine release also results from the action of a variety of chemical and physical factors such as extreme temperatures, trauma, vibrations, or alcohol [6]. Histamine can also be synthesized and released by other cell types (e.g., gastric enterochromaffin-like cells, histaminergic neurons, dendritic cells (DCs), T lymphocytes, platelets, etc. [10]).

It is estimated that about 5% of total histamine enters the body with food or is produced by intestinal microorganisms [13]. The most popular histamine-rich foods are fish and seafood, matured or fermented foods (e.g., cheese, alcohol, pickles, etc.), and some vegetables (e.g., spinach, eggplant, tomato, etc.). According to the law in the European Union, the permissible content of histamine in food is a maximum of 200 mg/kg in fresh fish and 400 mg/kg in seafood [14]. Histidine is produced mainly in autolytic or bacterial processes, therefore high concentrations of histamine are mainly found in microbial fermentation products [15]. The conditions for the formation of biogenic amines in food are the availability of free amino acids, the presence of decarboxylase-positive microorganisms as well as the conditions enabling the growth of bacteria and the activity of decarboxylase.

Microbiota are also an important source of histamine [16][17][18]. The production of histamine by bacteria in the human gut has been shown to influence the immune response. Therefore, elucidating the role of histamine as a metabolite of gut bacteria is an interesting area of research. Genes encoding HDC and synthesizing histamine have been demonstrated in many Gram-positive and Gram-negative bacteria. It was shown that in bacteria belonging to the genera Lactobacillus, Pediococcus, and Oenococcus, the presence of histidine is a factor inducing the expression of genes encoding HDC, while the presence of histamine caused the opposite effect [18]. Two HDC superfamilies have been described: Gram-negative bacteria have HDCs that require the presence of a coenzyme, which is pyridoxal phosphorus. In turn, for Gram-positive bacteria, covalently bonded pyruvate is used for catalysis [19]. The secretion of decarboxylase by bacteria is regulated by many factors (e.g., the presence of fermenting carbohydrates, oxygen, or chloride concentration). In an acidic environment, the expression of the activity of amino acid decarboxylases increases. This causes a local increase in pH around the bacteria and has a protective function [20]. The species of bacteria with the highest histidine decarboxylase activity are Morganella morganii, Eschericha coli, Hafnia alvei, Proteus vulgaris, Proteus milabilis, Enterobacter aerogenes, Raoultella planticola, Raoultella ornithinolytica, Citrobacter freundii, Pseudomonas fluorescens, and Photobacterium damselae [21]. Some bacteria have the ability to metabolize histamine. The aerobic growth of Pseudomonas putida U was demonstrated on a minimal medium, the only carbon source of which was histamine. In the six-stage catabolic process, histamine is converted into aspartic acid, which is then converted into fumaric acid. It has been shown that 11 proteins (HinABCDFLHGIJK) are necessary for the metabolism of histamine in P. Putida U. Genome studies indicate that Hin genes are present in strains of the genus Pseudomonas, but have not been shown to be present in previously sequenced Gram-positive bacteria [22]. Depending on the type of activated histamine receptor, it exerts either a pro-inflammatory or anti-inflammatory effect. Histamine derived from Lactobacillus reuteri via histamine receptor 2 inhibited the production of tumor necrosis factor-α (TNF-α) (induced by toll-like receptor) by human monocytoid cells [23]. In an experimental mice model, the immunomodulatory effect of histamine secreted by Lactobacillus rhamnosus was demonstrated. In mice without the deficiency of H2R, administration of this bacterial strain induced an anti-inflammatory effect (decreased secretion of interleukins, TNF-α) [24]. Some reports indicate that the amount of histamine secreted may determine its pathophysiological effects. These assumptions were confirmed by the study with Lactobacillus saerimneri, synthesizing almost 100 times more histamine compared to L. rhamnosus. Consequently, apart from various immunological effects, a decrease in the body weight of the animals and deterioration of the general condition were also observed [25]. The effect of bacterial secretion of histamine on intestinal diseases and digestive disorders has been reported. Therefore, it is important to deepen the knowledge of the factors influencing the synthesis, release, and metabolism of histamine by bacterial strains that make up the intestinal microbiome.

External factors that reduce the microbial diversity may cause differences in the composition of the intestinal microbiota, which may result in a state of dysbiosis. The exact mechanisms leading to dysbiosis remain unclear. The combination of physiological changes and the action of stress factors should be taken into account. Research indicates a relevant relationship between intestinal dysbiosis and the occurrence of intestinal diseases (e.g., inflammatory bowel diseases, histamine intolerance, irritable bowel syndrome) [26].

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