Histamine and antihistamines

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Learning objectives

After reading this article, you should be able to:

- describe the role of histamine in health and disease
- describe the four classes of histamine receptors
- understand the current and future clinical application of antihistamines

Abstract

Histamine is one of the most extensively studied biological amines in medicine. It stimulates smooth muscle contraction and gastric acid secretion, increases vascular permeability, functions as a neurotransmitter, and plays various roles in immunomodulation, allergy, inflammation, haematopoiesis and cell proliferation. Histamine exerts its effects through four receptors, designated H1–H4. H1 and H2 receptors are widely distributed, H3 receptors are mainly presynaptic, and H4 receptors are mainly haematopoietic. H1 antihistamines are classified as first- and second-generation compounds. First-generation compounds lack specificity and cross the blood–brain barrier causing sedation. Second-generation compounds are less sedating and highly specific. H1 antihistamines have well-documented anti-allergic and anti-inflammatory effects and are well established in the treatment of a variety of allergic disorders. First-generation antihistamines are also used in the treatment of vestibular disorders and can be used as sedatives, sleeping aids and anti-emetics. H2 antihistamines are widely used in the treatment of gastric acid-related disorders; however, proton pump inhibitors are becoming the drugs of first choice in some of these disorders. H3 antihistamines are expected to be of potential value in the treatment of some cognitive disorder. H4 antihistamines could be of potential therapeutic benefit in the management of various immune and inflammatory disorders.

Keywords Antihistamines; histamine; histamine receptors

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Histamine, 2-(4-imidazole)-ethylamine, was chemically synthesized for the first time by Windaus and Vogt in 1907; however, it was not until 1910 that Henry Dale and Patrick Laidlaw characterized its biological effects. Since that date histamine has become one of the most extensively studied biological amines in medicine.

In addition to its well-known three functions (smooth muscle contraction, increased vascular permeability and stimulation of gastric acid secretion), histamine plays various roles in immunomodulation, inflammation, regulation of cell proliferation and differentiation, haematopoiesis, embryonic development, regeneration and wound healing. Moreover, as a neurotransmitter, histamine is involved in the regulation of sleep and wakefulness, cognition, memory, and energy and endocrine homeostasis. It also modulates the release of several neurotransmitters through presynaptic receptors located on histaminergic and non-histaminergic neurones of the central and peripheral nervous system.

Histamine also plays a pivotal role in the pathogenesis of allergic inflammation. In response to an antigen, reaginic antibodies of the immunoglobulin (Ig)E type are generated. These antibodies bind to specific receptors expressed on the surface of mast cells and basophils. The binding triggers a complex chain of intracellular reactions leading to exocytosis and release of histamine along with tryptase, leukotrienes and prostaglandins as well as other mediators. Alternatively, histamine can be directly displaced and released from its storage granules upon exposure to certain organic bases, including drugs such as morphine and tubocurarine. Subsequent binding of histamine to central and peripheral histamine receptors leads to immediate, concentration-dependent smooth muscle contraction in the respiratory and gastrointestinal tracts, vasodilatation and sensory nerve stimulation. These actions of histamine manifest clinically as erythema, pruritus, nasal congestion, flushing, headache, hypotension, tachycardia and bronchoconstriction. Moreover, in addition to its role in the early allergic response, histamine acts as a stimulatory signal for the production of cytokines and the expression of cell adhesion molecules and class II antigens, thereby contributing to the late allergic response.

Histamine is formed by decarboxylation of the amino acid L-histidine in a reaction catalysed by the enzyme histidine decarboxylase (HDC). Mast cells, basophils, enterochromaffin-like cells of the gastric mucosa, and histaminergic neurones synthesize considerable amounts of histamine and store the mediator in special storage granules inside the cells. Upon appropriate stimulation, these cells can rapidly release relatively large amounts of histamine and thereby efficiently activate suitable effector mechanisms. Apart from these histamine-storing cell types, many other cells including epithelial cells and lymphocytes can express HDC and synthesize histamine. However, in these cells, histamine is immediately released and is not stored.

In humans, histamine is metabolized by histamine N-methyltransferase to N-methylhistamine, which can be further metabolized to N-methyl-imidazole acetic acid by the enzyme monoamine oxidase. Alternatively, histamine can be metabolized by diamine oxidase (DAO) to imidazole acetic acid, which can be further conjugated to form imidazole acetic acid ribose. In the gut wall, DAO is responsible for metabolizing dietary histamine present in considerable amounts in certain foods, preventing its

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uptake into the circulation. However, the DAO pathway is not active in the central nervous system.

Histamine receptors

Histamine exerts its diverse biologic effects through four types of receptors; H1, H2, H3 and H4 receptors (Table 1). Additionally, low-affinity intracellular non-H1, -H2, -H3, or -H4 receptors, have been recently described in cell nuclei and microsomes, although biologic functions at these receptors is still somewhat unclear.

The H1 receptor is widely distributed throughout the body, with well-documented expression in the CNS, smooth muscle, sensory nerves, heart, adrenal medulla, and immune, endothelial, and epithelial cells. The H1 receptor mediates most of the postsynaptic effects of histamine within the central nervous system. Moreover, through its activity at H1 receptors, histamine stimulates smooth muscle contraction in the respiratory and gastrointestinal tract, stimulates sensory nerves leading to pruritus and sneezing, and increase vascular permeability leading to oedema. Simultaneous activation of H1 and H2 receptor can also result in hypotension, tachycardia, flushing, and headache.

The H2 receptor is also widely expressed and can be found in gastric mucosal cells, heart, CNS, immune cells, and smooth muscles of the airway, vasculature, and uterus. H2 receptor activation stimulates hydrochloric acid secretion from the acid-secreting parietal cells of the gastric mucosa, leads to smooth muscle relaxation in the vasculature and airways, increases cardiac rate and contractility, and mediates some of the immunomodulatory effects of histamine.

The histamine H3 receptor is found mainly in the central nervous system (basal ganglia, hippocampus and cortical areas), but can also be found in the peripheral nervous system, airways, the cardiovascular system, and the gastrointestinal tract. Acting through presynaptic H3 receptor, histamine regulates its own release as well as the release of other neurotransmitters such as noradrenaline, dopamine, serotonin, acetylcholine, and gamma-amino-butyric acid. In the lower airways, H3 receptors are located on postganglionic cholinergic nerves and defend against excess bronchoconstriction and in the upper airways, histamine may play a role in nasal congestion through its activity at H3 receptors.

The H4 receptor has been detected in bone marrow, peripheral blood, spleen, thymus, lung, gastrointestinal tract, liver, peripheral nerves, and central neurones. Nevertheless, cells that clearly express functional H4 receptors are mainly haematopoietic and include: mast cells, eosinophils, basophils, dendritic cells, and T cells. H4 receptor activation induces calcium mobilization in mast cells and mediates mast cells migration towards histamine. Moreover the receptor plays a significant role in regulating dendritic and T-cell function.

In general terms, the four histamine receptors can be described as heptahelical G-protein coupled receptors. They transduce extracellular signals through various G proteins, which function as mediators between the cell surface receptors and the intracellular second messenger systems.

Histamine receptors exist in an equilibrium between two conformational states (Figure 1), active (R*) or inactive (R).

Histamine receptor subtypes along with their selective agonists, inverse agonists/antagonists, G-protein coupling and signal transduction

Receptor subtype	H1	H2	H3	H4
G-protein coupling	$G_{q/11}$	G_s	$G_{i/o}$	$G_{i/o}$
Signal transduction	• Phospholipase C activation → ↑ IP3 and DAG → ↑ Intracellular Ca and protein kinase C activation • Phospholipase A2 activation → ↑ Arachidonic acid • NOS activation • Phospholipase D activation	• Adenylate cyclase activation → ↑ cAMP → Protein kinase A activation	• Adenylate cyclase inhibition → ↓ cAMP • MAPK pathway activation • Phospholipase A2 activation → ↑ Arachidonic acid • Inhibition of Na/H exchanger • ↓ Intracellular Ca	• Adenylate cyclase inhibition → ↓ cAMP • MAPK pathway activation
Selective agonists	Histaprodifen	Amthamine Dimaprit Impromidine	Alpha-Methyl-histamine Imetit Immepip	Clobenopropit (partial agonist) Imetit Immepip 4-Methylhistamine
Antagonists/ inverse agonists (examples)	Chlorphenamine Promethazine Loratidine Fexofenidine	Cimetidine Ranitidine Famotidine Nizatidine	Thioperamide Pitolisant (ABT-288) MK-0249 JNJ-17216498	JNJ-7777120 VUF-6002

IP3, inositol triphosphate; DAG, diacylglycerol; NOS, nitric oxide synthase; cAMP, cyclic adenosine monophosphate; MAPK, mitogen-activated protein kinase.

Table 1

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