

HISTAMINE AND ITS EFFECTS MEDIATED VIA H₃ RECEPTOR – POTENTIAL CLINICAL APPLICATIONS OF H₃ ANTAGONISTS

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Abstract

Histamine is one of the most important biogenic amines and it mediates numbers of physiological processes. It is also involved in majority of inflammatory diseases via its receptors H₁, H₂, H₃ and H₄. The role of histamine had been recognized as substantial in many allergic diseases including bronchial asthma, thus the histamine receptor antagonists (H₁) are frequently used in the clinical practice as potent anti-allergic and anti-inflammatory drugs.

However, first generation of antihistamines have also adverse effects, predominantly sedation, changes in appetite and many more, and they are still not fully effective in all patients. Attention is now focused mainly on H₃ and H₄ receptor antagonists and their potential clinical applications. This review focuses basically on the H₃ receptor, its expression pattern and some effects which are mediated by H₃, discussing its clinical relevance.

Key words: histamine – histamine receptor – expression – allergies - neurons

INTRODUCTION

Histamine plays a prominent role in the pathophysiology of allergic diseases, asthma, rhinitis and urticaria (1, 2, 3). In human pathology, histamine triggers acute symptoms via its very rapid action on vascular endothelium and bronchial smooth muscle cells, leading to the development of acute symptoms such as nasal discharge, nasal congestion, bronchoconstriction, abdominal cramps, diarrhoea or skin wheal and a flare response. Moreover, in addition to these effects on the immediate-type response, histamine also significantly modulates chronic phase of inflammatory processes (4).

In fact, these data would be shared probably by majority of medical students, or health care professionals, because the role of the histamine in inflammation and allergies is well recognized and described. However, there is still a potential in further research of histamine action, mainly in central nervous system. The role of histaminergic neurons, their function and relevance are not well established. Except of central nervous system, H₃ receptors are involved in many processes outside of it, for example mast cell-neuron loop in the tissues, where H₃ receptors regulate intensity of neurogenic inflammation. Histamine H₃ receptor and its antagonists may have clinical applications in treatment of diseases induced or influenced by the action of histaminergic neurons, thus leading to limited availability of certain neuromediators. The aim of this short review is to focus on less known histamine receptor H₃ and its relevance for human physiology and pathophysiology.

HISTAMINE AND ITS ACTION

Histamine (2-[4-imidazolyl] ethylamine), is a biogenic amine, that was isolated from the mould ergot in 1910 by Sir Henry Dale and his colleagues at the Wellcome Laboratories. Afterward they found that it stimulated smooth muscle from the gastrointestinal and respiratory tract, it induced vasodilatation and stimulated cardiac contractility. Finally, it

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induced a shock-like syndrome when injected into animals (5, 6). In 1920, Popielski demonstrated that histamine has a marked stimulating effect on the secretion of acid from the stomach of dogs (7). In 1924, Lewis described the classic 'triple response' to histamine consisting of a red spot due to vasodilatation, a wheal which was the consequence of increased permeability and a flare due to an axon reflex (8). Histamine was identified as a mediator of anaphylactic reactions in 1932 (9). In 1927, Best et al. (10) isolated histamine from samples of liver and lungs, and later from other tissues, hence, the name histamine was given after the Greek word for tissue, *histos*. Since that time there has been a growing pool of data about the action of histamine, histamine receptors, their intracellular signaling pathways and potent antagonists with clinical application.

Histamine is synthesized by the pyridoxal phosphate-containing L-histidine decarboxylase (HDC) from the amino acid histidine (11). Gastric enterochromaffin-like cells, histaminergic neurons as well as mast cells and basophils are classical cellular sources of histamine, where it is stored in intracellular vesicles and released on stimulation. Several haematopoietic cell lines have been shown to synthesize histamine, but 100–1000-fold less than mast cells and basophils. *De novo* histamine synthesis has also been shown in other cell types, such as platelets, monocytes/macrophages, dendritic cells, neutrophils and lymphocytes (12, 13, 14).

The major routes of histamine inactivation in mammals are methylation of the imidazole ring, catalyzed by histamine N-methyltransferase (HNMT), and oxidative deamination of the primary amino group, catalyzed by diamine oxidase (DAO) also known as histaminase (15). The DAO protein is stored in plasma membrane-associated vesicular structures in epithelial cells and is secreted into the circulation on stimulation (16, 17). In mammals, DAO expression is restricted to specific tissues; the highest activities are shown for small intestine, ascending part of colon (18, 19) and for placenta and kidney (16, 20). Conversely, HNMT is a cytosolic protein (21), which can convert histamine only in the intracellular space of the cells (20, 22). HNMT is widely expressed in human tissues; the greatest expression is in kidney and liver, followed by spleen, colon, prostate, ovary, spinal cord cells, bronchi, and trachea (23). HNMT is regarded as the key enzyme for histamine degradation in the bronchial epithelium (24).

Histamine is a potent mediator of numerous biologic reactions. Besides the well-known triggering of mast cells degranulation by crosslinking of the Fc RI receptor by specific allergens, several other non-immunologic stimuli, such as neuropeptides, substance P, complement factors (i.e., C3a and C5a), cytokines (IL-1, IL-3, IL-8, GM-CSF), platelet-activating factor (PAF), hyperosmolarity, lipoproteins, adenosine, superoxidases (25), hypoxia, chemical and physical factors (e.g., extreme temperatures, traumas, vibration) (26), or alcohol and certain food and drugs, may activate mast cells too (27, 28). The pleiotropic effects of histamine are triggered through one or several histamine receptors on different cells. Four subtypes of receptors (histamine 1 receptor (H_1R), histamine 2 receptor (H_2R), histamine 3 receptor (H_3R), and histamine 4 receptor (H_4R)) have been described. All these receptors belong to the G-protein-coupled receptor family. They are heptahelical transmembrane molecules that transduce the extracellular signal by using G-proteins and intracellular second messenger systems (29, 30). Differences in the affinities of these receptors are highly decisive on the biological effects of histamine and agents that target.

HISTAMINE RECEPTORS

Histamine has diverse actions in the human body, and those are influenced by several factors. One of the determining factors governing the histamine action is the type of receptor mediating the signal transduction. Basically, the knowledge on histamine receptors classifies four types of them with different expression pattern within the body and main actions they are capable to induce (Table 1).

The active and inactive states of HRs exist in equilibrium. However, it has been shown in recombinant systems that HRs can trigger downstream events in the absence of receptor occupancy by an agonist, which accounts for constitutive spontaneous receptor activity (31).

HR agonists stimulate the active state in the receptor and inverse agonists stimulate the inactive one. An agonist with a preferential affinity for the active state of the receptor stabilizes the receptor in its active conformation leading to a continuous activation signal. An inverse agonist with a preferential affinity for the inactive state stabilizes the receptor in this conformation and consequently induces an inactive state, which is characterized by blocked signal transduction via the HR (32). HR antagonists block receptor sites causing no action at that receptor since agonists can't bind.

HRs form dimers and even oligomers, which allow cooperation between HRs and other G-protein-coupled receptors. The affinity of histamine to different HRs varies significantly, with K_i values ranging from 5–10 nM for the H_3 and H_4 receptors to 2–10 mM for the H_1 and H_2 receptors (11, 33). Specific activation or block of HRs showed that they differ in expression, signal transduction or function and improved the understanding of the role of histamine in physiology and disease mechanisms (4). Histamine can act not only on cell surface receptors (H_1 , H_2 , H_3 and H_4 receptors), but may also bind to some "intracellular receptors" such as cytochrome P450 and cytochrome c (34, 35) and high-affinity lipocalins isolated from the saliva of ticks (36).

Table 1 Pattern of histamine receptors distribution and main actions they mediate (37)

Abbreviations: AV – atrioventricular, CNS - central nervous system, GI – gastrointestinal, NK – natural killer

receptor	location	responses
H1	blood vessels, sensory nerves (smooth muscle bronchi, GI tract, cardiac tissue, endothelium, CNS)	increase vascular permeability, vasodilation, stimulation of airway sensory nerves, eosinophil chemotaxis, smooth muscle contraction in bronchi and GI tract, stimulation of vagal nerves inducing reflex smooth muscle contraction in airways, decrease AV node conduction time, enhance release of histamine and arachidonic acid derivatives from platelets, increase nitric oxide production via iNOS
H2	vascular bed, nasal epithelium, nasal submucosal glands, mucosa of stomach, CNS, cardiac tissue, uterus, smooth muscle	stimulate mucous glands in airways, increase vascular permeability, direct chronotropic effect on atrium and inotropic action on ventricle, relaxation of lower esophageal sphincter stimulation of suppressor T cells, decrease in neutrophil and basophil chemotaxis and activation, proliferation of lymphocytes, activity of NK cells
H3	presynaptic nerves in the peripheral sympathetic adrenergic system, nasal submucosal glands, CNS (histaminergic nerves), airways, GI tract	suppression of norepinephrine release at presynaptic nerve ending, stimulate nasal submucosal gland secretion, opposes bronchoconstriction and gastric acid secretion
H4	eosinophils, mast cells, basophils, neutrophils, nasal turbinates (nerves), lung, colon, epicantus, bone marrow, spleen, liver	chemotaxis and chemokinesis of mast cells and eosinophils, enhancement of the activity of other chemoattractants (e.g. chemokines) on eosinophils, up-regulation of adhesion molecules

H₃ - HISTAMINE RECEPTOR

The histamine H₃ receptor (H₃R) was first identified by Arrang and colleagues in 1983 using a functional assay. It was found that histamine inhibits its own synthesis and release (38). The cloning of the histamine H₃ receptor (H₃R) cDNA in 1999 by Lovenberg et al. (39) allowed detailed studies of its molecular aspects and indicated that the H₃R can activate several signal transduction pathways (Figure 2) including G_{i/o}-dependent inhibition of adenylyl cyclase, activation of phospholipase A₂, Akt and the mitogen activated kinase as well as the inhibition of the Na⁺/H⁺ exchanger and inhibition of K⁺-induced Ca²⁺ mobilization.

Moreover, cloning of the H₃R has led to the discovery of several H₃R isoforms produced by alternative splicing of the H₃R mRNA (40). The human and rat H₃ receptors exhibit a 97% homology in the transmembrane domains, but surprisingly they display a significant difference in the affinity for some H₃ ligands (e.g. thioperamide shows a tenfold preference for the rat receptor). Single form of the H₃ gene can give rise to multiple mRNA isoforms, named H_{3A}, H_{3B} and H_{3C} in the rat (41) and H_{3L} and H_{3S} in the guinea pig (42).

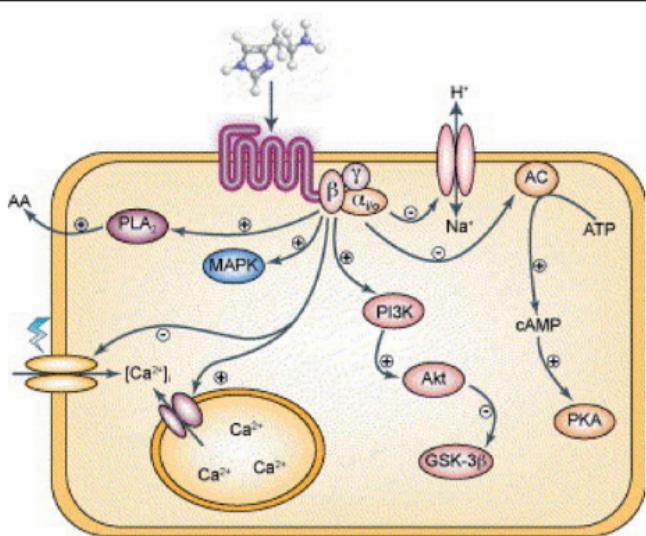


Fig. 1. Schematic representation of the H₃R-mediated signal transduction. The H₃R has been shown to modulate several signal transduction pathways including the inhibition of adenylyl cyclase (AC), activation of mitogen-activated protein kinase (MAPK), activation of phospholipase A₂ (PLA₂), intracellular calcium mobilization, activation of the Akt/GSK-3 axis and inhibition of the Na⁺/H⁺ exchanger (40).

NEURONAL H₃R

H3R is expressed in many brain areas including cerebral cortex, hippocampus, amygdala, nucleus accumbens, globus pallidus, striatum and hypothalamus. The H3R acting as presynaptic autoreceptor on the neurons (inhibits release of histamine from histaminergic neurons) and heteroreceptor expressed in non-histamine-containing neurons in the central and peripheral nervous systems, where it inhibits release of other neurotransmitters such as acetylcholine, noradrenaline, dopamine, and serotonin (Figure 3) (39, 43).

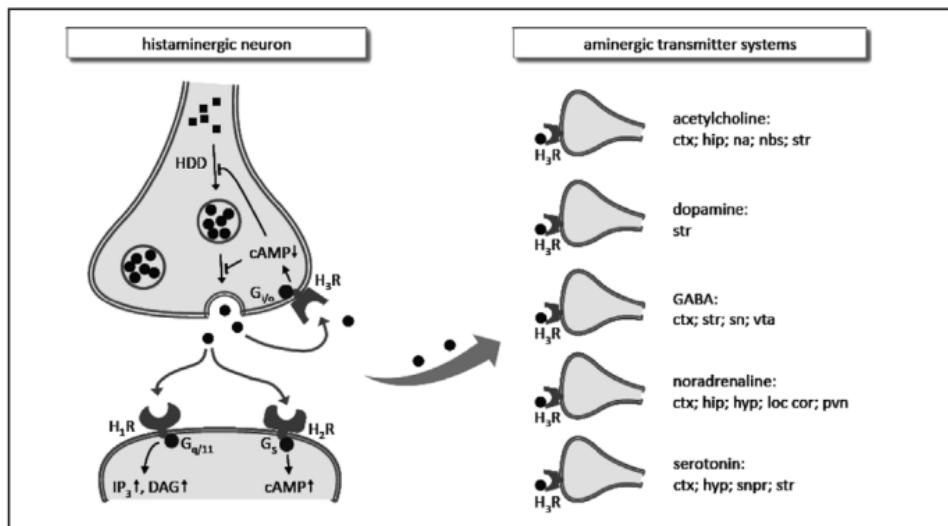


Figure 2. H_3R auto- and heteroreceptors – mechanisms of histamine action on different neurons and neuromediators (44). Presynaptic H_3 autoreceptor (histaminergic neuron), postsynaptic H_3 heteroreceptor (aminergic transmitter systems)

Abbreviations: H_1R - histamine H_1 receptor, H_2R - histamine H_2 receptor; H_3R - histamine H_3 receptor, G-G protein, cAMP - cyclic adenosine monophosphate, ctx - cortex, HDD - histamine decarboxylase, hip - hippocampus, hyp - hypothalamus, IP_3 - inositol triphosphate, DAG - diacyl glycerol, loccor - locus coeruleus, - na - nucleus accumbens, nbs - nucleus basalis magnocellularis, pvn - paraventricular nucleus, sn(pr) - substantia nigra (pars reticulata), str - striatum, vta - ventral tegmental area.

Both histamine and the neurotransmitters regulated by it participate in many important physiological functions. Histamine synthesizing neurons are located in the tuberomammillary nucleus of the hypothalamus and project widely throughout the brain to regions that include the cortex, the hippocampus, amygdala and striatum (45). The central histaminergic system is involved in many central nervous system functions: sleep-wake cycle, arousal, anxiety, activation of the sympathetic nervous system, cognition, learning, memory, the stress-related release of hormones from the pituitary and of central aminergic neurotransmitters, antinociception, water retention and suppression of eating, through the four receptors subtypes: H_1 , H_2 , H_3 and H_4 (45, 46). Acetylcholine plays an important role in cognitive functions, and noradrenaline has become recognized as playing a large role in attention and focus. Since the H_3R regulates the levels of these important neuronal agents, it has become an attractive target for developing treatments for variety of neurological disorders (47).

H_3 antagonists are potential drugs for the treatment of disorders connected to cognitive processes and alertness, such as, excessive daytime sleepiness with Parkinson patients, narcolepsy, Alzheimer's disease, attention-deficit hyperactivity disorder, epilepsy, and schizophrenia (44, 48). Moreover, histamine via H_3 receptors can also decrease blood brain barrier permeability and mitigate against early phase neuroinflammation (49). Examples of histamine H_3R antagonists and agonist are summarized in Table 2, documenting huge research in this area, and availability of many H_3R relevant molecules for research purposes.

Table 2 Histamine H₃R agonists and antagonists

H ₃ R antagonists	H3R agonists	H ₃ R inverse agonists
A-431404, A-424835, A-349821, A-320436, A-331440, A-417022, A-423579, A-688057, A-687136, A-698418, ABT-834, ABT-239, Betahistine, BF-2649, Burimamide, Clobenpropit, Ciproxifan, Conessine, GSK-189254, GSK-207040, GT-2227, GT-2394, Iodophenpropit, Impentamine, JB 98064, JNJ-17216498, JNJ-5207852, JNJ-7737782, JNJ-10181457, NNC-0038-1049, NNC-0038-1202, Proxyfan, SCH-79687, SCH-79876, Thioperamide, VUF-568,	BP-2.94, Histamine, Imetit, Immepip, Immethridine, Methimepip, (R)- α -methylhistamine, N α - methylhistamine, Cipralisant, Proxyfan	Ciproxifan, ST-889, BF2.649

ANTINOCICEPTIVE ACTION

Histamine H₃ receptors (H₃Rs), distributed within the brain, the spinal cord, and on specific types of primary sensory neurons, can modulate pain transmission by several mechanisms. In the skin, H₃Rs are found on certain A β fibers, and on keratinocytes and Merkel cells, as well as on deep dermal, peptidergic A δ fibers terminating on deep dermal blood vessels. Activation of H₃Rs on the latter in the skin, heart, lung, and dura mater reduces calcitonin gene-related peptide and substance P release, leading to anti-inflammatory (but not antinociceptive) actions. However, activation of H₃Rs on the spinal terminals of these sensory fibers reduces nociceptive responding to low-intensity mechanical stimuli and inflammatory stimuli such as formalin (50).

PRESYNAPTIC MODULATION IN AUTONOMIC NERVOUS SYSTEM

Visceral organs are widely innervated by the fibres of autonomic nerves with many ganglia located within the wall of dull organs such as esophagus or stomach. Functions of these organs are regulated by the way of neurotransmitter releases from the nerve fibers they have on target effectors – muscles, glands etc. There are numerous reports of presynaptic H₃ receptors in the autonomic nervous system controlling neurotransmitter release in the heart, the lung, and the gastrointestinal tract (39).

In the gastrointestinal tract H₃ receptors are located in cholinergic and non-adrenergic non-cholinergic (NANC) neurons of the myenteric plexus, in endocrine and/or paracrine cells of the gastric mucosa and, at least in rabbits, also in parietal cells (51). H₃ receptors are mainly located on histamine-producing cells, where they work as an endogenous inhibitory mechanism operated by histamine itself to control excess acid production. H₃ receptor agonists combine antiinflammatory properties with antisecretory and gastroprotective effects (52).

MODULATION OF ADRENERGIC RESPONSES IN THE HEART

H₃-receptors are present in sympathetic nerve endings in the human heart, where they modulate adrenergic responses by inhibiting noradrenaline release (53). In severe myocardial ischemia, H₃R activation affords cardioprotection by preventing excessive noradrenaline

release and arrhythmias; pivotal to this action is the inhibition of neuronal Na^+/H^+ exchanger (NHE). Conversely, angiotensin II, formed locally by mast cell-derived renin, stimulates NHE via angiotensin II type 1 (AT_1) receptors, facilitating noradrenaline release and arrhythmias. Ischemic dysfunction may therefore depend on a balance between the NHE-modulating effects of H_3 receptors and AT_1 receptors. Thus, H_3 receptor-mediated NHE inhibition in ischemia/reperfusion not only opposes the angiotensin II-induced stimulation of NHE in cardiac sympathetic neurons, but also down-regulates AT_3 receptor expression. Cardioprotection ultimately results from the combined attenuation of angiotensin II and noradrenaline effects and alleviation of arrhythmias (54).

UPPER AND LOWER AIRWAYS

It is well known that histamine plays an important role in eliciting the nasal symptoms of allergic rhinitis; i.e., pruritus, sneezing, rhinorrhea, and congestion (55). H_3R plays a role in mucus secretion in the nasal submucosal gland. H_3R plays a role in allergic rhinitis, and expression of H_3R increases during allergic rhinitis (56).

Nakaya et al. (57) used immunohistochemistry to examine distribution of histamine receptor subtypes in the human inferior turbinates, and reported that H_4R and H_3R were clearly expressed on nerves in the human inferior turbinates. They demonstrated that H_3R protein was expressed on the nerve bundle, rather than on the nerve terminals. Stimulation of H_3R expressed on sympathetic nerve terminals inhibits release of noradrenaline from those nerves. In the absence of histamine, noradrenaline released from sympathetic nerve terminals helps to maintain normal vascular tone. The presence of histamine decreases noradrenaline levels, causing vasodilatation leading finally to nasal obstruction (58). In the human lower airways, H_3R regulates cholinergic nerve transduction (59). In guinea pigs, H_3R is present on the vagus nerve, which modulates cholinergic neurotransmission in the airways (60).

H_3 -receptors presented in the vagal pathway inhibit acetylcholine release and could play a role in modulating neural bronchoconstriction in allergic disease when histamine is released from airway mast cells in the vicinity of airway ganglia and cholinergic nerves (60).

The control of mast cells by histamine acting on H_3R involves neuropeptide-containing nerves and might be related to a local neuron-mast cell feedback loop controlling neurogenic inflammation (61). Dysregulation of this feedback loop may lead to excessive inflammatory responses and suggests a novel therapeutic approach by using H_3R agonists (4).

CONCLUSIONS

As it could be seen from this short overview, there is a growing pool of data indicating that histamine and particularly histamine H_3 receptors are constantly under the scope and they are studied in relation to many aspects. Very strong aspect is the role of histaminergic neurons in onset, development and progression of certain neurologic disorders as they have been described above. Also interesting and very strong side of H_3R antagonists could be the field of antinociception. The fact they are abundant in autonomic nerves within visceral organs makes it possible targets for visceral pain, mechanisms of which are still not satisfactorily explained. Primary interest of our research is respiratory system, allergic rhinitis, asthma and cough. This is also the main reason we studied H_3 receptors to see possible involvement of H_3 antagonists in models of airway diseases. As long as we know, there are some H_4 antagonists at the very beginning of clinical trials but no H_3 antagonists so far.

We do believe that every single effort counts in the process of searching for effective enough but safe treatment for our patients and that is also the reason we will focus further attention on H_3 receptors in our future research.

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