

New Concepts of Histamine Receptors and Actions

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Histamine and antihistamines are so deeply woven into the fabric of allergic diseases that it is sometimes difficult to see how this field could advance beyond our current, potent histamine H1-receptor drugs. Investigations of other actions of histamine and the identification of H2, H3, and now H4 receptors have suddenly reignited the search for new mono- and multi-receptor-specific agonists and antagonists. There is great excitement due to preliminary findings that H3 receptors act as neural inhibitory autoreceptors, and H4 receptors might modulate immune cell functions.

Introduction

Histamine, also known as 2-(4-imidazolyl) ethylamine and 5b-amino-ethylimidazole, acts as a multifunctional hormone that regulates smooth muscle contraction in the airways and gut; vasodilatation and vascular permeability in the nose and other vascular beds; activation of itch-specific neurons; regulation of stomach acid; and acts as a neurotransmitter in the central nervous system (CNS). These effects are evident from histamine nasal provocations in which histamine causes itching, sneezing, nasal discharge, and mucosal swelling with increased nasal airway resistance [1,2]. These profound consequences make histamine the single most important mediator of acute or immediate phase allergic symptoms. Histamine can also have more long-lasting effects that might trigger immune responses. This potent vasodilator was discovered in 1911 by Dale and Laidlaw [3] and associated with tissue mast cells by Riley and West in 1953 [4]. Recent discoveries from molecular biology and genomics have identified histamine H1 receptors (H1-R), H2-R, H3-R, and the newest member of the family, the H4-R. The functions of histamine depend on the activation of these receptors, their localizations, and their interactions.

H1 Receptors

H1 receptors are present throughout the body and play an important role in allergy diseases. H1-R are distributed on bare endings of unmyelinated type C fibers, endothelial and other vascular cells, bronchial and other smooth muscle, and some glandular and epithelial cells. The ability to contract endothelial cells within the postcapillary venule basement membrane and to relax capacitance vessels makes these vessels a critical site for massive plasma extravasation that can lead to edema formation and mucosal exudation of a plasma-rich discharge. This is very evident as the watery rhinorrhea of acute allergic rhinitis and the massive vasodilation, plasma extravasation, and “third spacing” that lead to hypotension in anaphylaxis [5].

During acute exposures to allergens in allergic rhinitis, H1-R mediate eye, nose, throat, and palate itching; rhinorrhea; swelling of deep venous sinusoids that increases turbinate and mucosal thickness and reduces nasal patency (causes obstruction to airflow); as well as local axon responses, cholinergic parasympathetic reflexes responsible for glandular exocytosis, and complex systemic avoidance reflexes such as sneezing and the allergic salute [5]. H1-R antagonists can reduce these symptoms by approximately 40% to 50%. The complex mix of mast cell and other mediators account for the remainder of the effects.

It is likely that as allergic reactions progress or become persistent (“perennial”), the recruitment of many cells such as eosinophils and Th2 lymphocytes, and activation of other cells contribute mediators that cause a relative decrease in histamine’s influence, and, therefore, the apparent efficacy of antihistaminic drugs. The antihistamine might in fact be functioning maximally at blocking H1-R, but cytokines, leukotrienes, and other factors might be contributing to more of the symptoms, and to symptoms that are not mediated by H1-R. H1-R agonists might even act to modulate chemotactic and immunoregulatory actions of some of these inflammatory cells such as monocyte and dendritic cells [6]. However, if symptoms continue while taking one antihistamine, the patient and doctor might become dissatisfied and switch to an alternative antihistamine. When this drug also proves to have the same limited efficacy in the midst of mucosal mediator overload, patient frustration can become an important issue leading to noncompliance with all medications. This situation, which occurs during the cellular inflammatory

phase of persistent inflammation, is similar to the late-phase response in allergen challenge models and requires the addition of a topically inhaled nasal steroid to rebuke and rout the entrenched inflammation. This reality is reflected by recent changes in rhinitis diagnosis and treatment assessments and guidelines.

The H1-R was identified pharmacologically in 1966. After being cloned, the deduced protein of 487 amino acids showed similarity to G-protein-coupled receptors [7]. Members of this "rhodopsin receptor family" have seven transmembrane segments, an extracellular N-terminal, two extracellular loops, two intracellular loops, and a C-terminal tail. Recently, a subpopulation of H1-R was suggested when Chinese hamsters' ovary (CHO) cells transfected with cloned guinea pig and human H1-R showed atypical sensitivity to histamine provocations. These changes might be due to posttranslational modifications leading to heterogeneous H1-Rs [8].

Histamine-1 receptors generate intracellular messages by activating guanosine triphosphate (GTP)-binding protein ($\alpha\beta\gamma$ G-protein complexes). The $\beta\gamma$ subunits lead to activation of nuclear factor- κ B, a proinflammatory transcription factor [9].

The physical binding of histamine to the H1-R has been studied by site-directed mutagenesis and three-dimensional computer modeling of the receptor [10]. The histamine-binding site was defined by five amino acids. Two separately defined components of the binding site might exist, with one region responsible for rewinding the α -helix of the fifth transmembrane region. This in turn might lead to conformational changes in the third intracellular loop and other sites that promote binding of the intracellular G proteins and cellular activation. This mechanism differs from both β 2-adrenergic and H2-R ligand-binding models. H1-R activation leads to rapid transient cellular activation, suggesting that continued release of histamine is required for prolonged histamine-induced symptom production [11].

Histamine-1-receptor messenger RNA (mRNA) is upregulated in endothelial and mucosal epithelial cells in allergic rhinitis [12]. Allergic sensitization of guinea pigs increases H1-receptor density and vasodilator responses to histamine provocation [13]. In addition, the nasal hyperresponsiveness in chronic allergic rhinitis might be explained in part by an elevation of G-protein levels that might increase the binding affinity of histamine to its receptors, increase recycling of functional H1-R to the cell surface after activation, or promote H1-R-G-protein coupling. These mechanisms could augment histamine-induced nasal responses [14].

In addition to direct effects on endothelial and other cells, histamine has other, more indirect proinflammatory effects. Histamine nasal provocations lead to the expected plasma exudation, but also stimulate glandular exocytosis. This exocytosis does not occur with human nasal mucosa in vitro [15]. Instead, activation of histamine-sensitive itch nerves recruit cholinergic parasympathetic reflexes that mediate glandular exocytosis. Atropine, for example, totally blocks the

glandular secretion, but has no effect on histamine-induced itch or plasma extravasation. In allergic conjunctivitis, H1-Rs promote the eosinophil infiltration found during the late-phase reaction by upregulating expression of preformed and newly induced P selectin stored in the Weibel-Palade bodies of endothelial cells [16]. H1-R antagonists have been shown to attenuate cytokine secretion from conjunctival epithelial cells [11]. Inhibition of proinflammatory cytokine secretion provides a rationale for longer term use of topical or systemic H1-R antagonists in allergic disease.

H2 Receptors

The histamine H2 receptor (H2-R) also belongs to the heptahelical receptor family. This receptor is linked to a G protein that activates adenylyl cyclase and increases cyclic adenosine monophosphate (cAMP) formation [17]. Induction of cAMP causes a secondary rise in intracellular calcium that mediates calcium-calmodulin actions in gastric mucosa, vascular smooth muscle, brain, adipocytes, basophils, neutrophils, and other tissues [18]. Stimulation of H2-R leads to a slower onset but more sustained response than H1-R [19].

In human nasal mucosa, H1- and H2-receptor mRNA have been identified by reverse-transcriptase polymerase chain reaction (RT-PCR) [20]. H2-R mRNA is localized in the epithelium and the submucosal glands in the inferior turbinate mucosa, suggesting that H2-R might play some role in allergic rhinitis [21]. H2 antagonists alone do not affect allergy skin tests, which indicates that H2-R do not mediate itch, the flare response, or local vasodilatation, leading to the wheal. However, concomitant administration might increase the inhibitory effect of an H1 antagonist. Clinically, this has led to the combination of H1-R and H2-R antagonists to decrease nasal swelling. Clinical benefit has been difficult to reproduce.

Activation of H2-R stimulates tracheobronchial mucus secretion and suppressor T-cell activity but also inhibits basophil histamine release, neutrophil chemotaxis, and enzyme release [19]. H2-Rs play a major role in stomach parietal cell hydrogen ion production and in esophageal contraction.

H2-R stimulation might mediate a substantial portion of the negative chronotropic and ionotropic cardiac effects of histamine in conditions such as anaphylaxis. Although histamine plays little or no role in the control of vasomotor tone under normal conditions, a synergy between H1 and H2 antagonists has been demonstrated in the cardiovascular system. The combination significantly blunted the fall in diastolic blood pressure and pulse pressure associated with infusion of low-dose histamine [22].

An additional interaction is seen in cultured endothelial cells. Histamine causes a transient decrease in H1-R mRNA and a rapid and prolonged decrease in H2-R mRNA [23]. The latter effect might be mediated via an H1-R-mediated transduction pathway. This interaction has relevance to tachyphylaxis of H1-R and H2-R, because continuous exposure to histamine as an ongoing mast cell degranulation state might

lead to tachyphylaxis of H2-R-mediated events but continued expression of H1-R mRNA. These preliminary studies on gene expression must be followed by an examination of the function of H1-R and H2-R, because uncoupling from G-protein-transducing systems might occur for H1-R, despite the continued generation of H1-R mRNA.

H2-R might also play surprising roles in the pathology of other organs and diseases. For example, H2-R activation might ameliorate experimental allergic encephalomyelitis (EAE). H2-R agonists suppress the production of superoxide anions, tumor necrosis factor- α , and interleukin-12 from inflammatory cells, which have been implicated in the pathophysiology of multiple sclerosis, autoimmune diseases, and other demyelinating diseases. Dimaprit, an H2 agonist, might reduce symptom severity in EAE [24].

In the nervous system, evidence indicates the involvement of histamine in the generation and organization of defensive reactions. In the midbrain tectum, H2-R might be involved in the control of defensive behaviors organized by the dorsal periaqueductal gray matter and inferior colliculus following activation of the cortical, limbic, and other neural substrates of fear. CNS injection of ranitidine leads to fearful behaviors that can be prevented by prior injection of dimaprit [25].

Blockade of H2-R by cimetidine or ranitidine could be beneficial in a hyperthermic brain injury. Hyperthermia or other extreme stressors might cause histamine release as part of cerebrovascular autoregulatory vasodilatation responses. The increase in oxygen, arginine, and other substrates of free radicals such as superoxide anion and nitric oxide, respectively, might further damage physiologically stressed neurons. H2-R antagonists reduced cerebral blood flow, brain edema formation, and cell injury in rats [26]. More information is needed to determine if these would be beneficial in heat stroke, viral encephalitis, thromboembolic events, or other types of injury in humans.

Ito *et al.* [27••] were the first to postulate the role of dysfunctional histaminergic neuronal circuits in schizophrenia. New genomic data suggest a wide diversity of H2-R gene polymorphisms with no association of these allelic variations in this illness.

H3 Receptors

Histamine-3-receptor (H3-R) activity is still under intense investigation in humans. The H3-R also belongs to the G-protein-coupled receptor superfamily [28]. It was identified by Arrang *et al.* [29]. The H3-R is distinct from H1-R and H2-R based on its localization and pharmacology.

Histamine-3 receptors have been observed in neurons of the cerebral cortex, the amygdala, the hippocampus, the striatum, the thalamus, and the hypothalamus [30]. The bulk of CNS H3-R are localized to presynaptic sites on histaminergic nerve terminals. When activated by histamine release, these "inhibitory autoreceptors" inhibit histamine release and biosynthesis [31–33]. New H3-R antagonists that enter

the CNS can block these autoreceptors and thus increase histamine release. There might also be increased reuptake of histamine into the synaptic terminals because there is no change in methyl-histamine, the product of histamine methylation *in vivo* [33].

Presynaptic H3 receptors on peripheral afferent neurons reduce peripheral nerve depolarization and potentially axon response-mediated release of neurotransmitters. Roles for H3-R agonists have been proposed for treatment of nociceptive nerve involvement that might participate in the pathophysiology of headache, cardiac ischemia, and gastrointestinal and bronchial tract neural function [34].

Histamine-3-receptors have been detected in several vascular beds and might cause vasodilatation.

McLeod *et al.* [35] suggested that histamine might cause nasal congestion through activation of inhibitory presynaptic H3-R on sympathetic nerves. This would decrease release of the vasoconstrictor norepinephrine and cause subsequent "default" vasodilatation with nasal vascular engorgement. A combination of H1-R and H3-R antagonists could reduce nasal airflow resistance and increase nasal cavity airspace volumes (measured by acoustic rhinometry) in feline models. They proposed that a dual H1/H3 antagonist could provide relief for allergic nasal congestion.

H4 Receptors

Nakamura *et al.* [36••] recently cloned a fourth histamine receptor (H4-R) from a human leukocyte cDNA library. Its amino acid sequence was approximately 40% related to the human H3-R. While screening genomic databases for novel G-protein-coupled receptors, Liu *et al.* [37] identified a partial clone (GPCR105) with significant homology to H3-R. The overall sequence homology was 37.4% toward H3-R, its nearest genomic relative, but the H4-R and H3-R share 58% identity in the transmembrane regions [38•]. The porcine H4-R has 73% homology to the human receptor [39].

The distribution of H4-R mRNA suggests that it might play a role in the regulation of immune functions, particularly with respect to allergy and asthma [40]. It is highly expressed in the peripheral blood, leukocytes, spleen, lung, thymus, small intestine, colon, and bone marrow [41]. It was also detected in several human brain regions, but with low expression [42]. It can be activated by histamine, R- α -methylhistamine (H3-R agonist), and clozapine (neuroleptic), and antagonized by thioperamide and alobanpropit (H3-R antagonists) [41].

Conclusions

The discovery of these four histamine receptors have revealed much about the pathophysiology of atopic and many other diseases. Cloning of the receptors and investigation of the structure-function relationships with histamine will lead to novel agonist and antagonist drugs. These might be of value in diseases such as allergic rhinitis in which H1-R appear to be

Table 1. Summary of actions and antagonists of histamine at H1, H2, H3, and H4 receptors

	H1-receptor	H2-receptor	H3-receptor	H4-receptor
Vessels	Vasodilation	Vasodilation	Vasodilation?	Not yet known
Adhesion	Vascular permeability Leukocyte adhesion through multiple mechanisms	No permeability No significant effect	Indirect permeability No effect	Not yet known
Bronchial smooth muscle	Contraction	No effect	No effect	Not yet known
Glands	No effect on exocytosis of mucus	Possible bronchial mucus secretion	No effect	Not yet known
Neurons	Activate nociceptive "itch" nerves	No effect	Inhibit neural activation leading to reduced neurotransmitter release	Not yet known
Atrioventricular node conduction	Conduction time	Positive chronotropic and inotropic effects	Potential inhibitory autoreceptor effects on cardiac innervation	Not yet known
Transduction	PLC, guanylyl cyclase, cGMP, NO	Adenylyl cyclase and cAMP	Modulation of hyperpolarizing potassium channels?	PLC, inositolphosphates, diacylglycerol and [Ca ²⁺]
Antagonists	Acrivastine Astemizole Azatadine Azelastine Cetirizine Chlorpheniramine Diphenhydramine Ebastine Fexofenadine Hydroxycine Ketotifen Levocabastine Loratadine Mepyramine Mizolastine Oxatomide Promethazine Pyrilamine Terfenadine	Burimamide Cimetidine Dimaprid Famotidine Lafutidine Nizatidine Pibutidine Ranitidine Zolantidine	Alobenpropit Ciproxifan Clobenpropit Imoproxifan Thioperamide	Specific anti-H4 not yet known Alobenpropit (anti-H3) Thioperamide (anti-H3)

cAMP—cyclic adenosine 3',5' monophosphate; cGMP—cyclic guanosine 3',5' monophosphate; NO—nitric oxide; PLC—phospholipase C.

predominant, but in which other histamine receptors might also modulate the functions of inflamed tissues, nociceptive itch nerves, inflammatory cells, and CNS function. Examination of histamine receptor polymorphisms, interactions of these receptors, potential roles in determining an individual's spectrum of complaints, and the range of selectivity and efficacy of specific antihistamines in the atopic population are areas that remain largely unstudied. The role of the H3-R as an inhibitory autoreceptor is that it might modulate nasal obstruction, and potential roles for H4-R on immune cells are an exciting example that despite years of familiarity, the book on histamine is still open (Table 1).

Acknowledgments

Correspondence for Dr. Repka-Ramirez can be sent c/o Dr. James N. Baraniuk at the address provided.

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