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REGULATORY EFFECTS OF HISTAMINE AND HISTAMINE RECEPTOR EXPRESSION IN HUMAN ALLERGIC IMMUNE RESPONSES

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Acknowledgments: The authors laboratory is sponsored by Swiss National Science Foundation Grants and Global Allergy and Asthma European Network (GA2LEN)
Abstract

Histamine influences several immune/inflammatory and effector functions in addition to its dominant role in type I hypersensitivity reactions. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and other functions leading to chronic inflammation. Histamine also regulates monocytes, dendritic cells, T cells and B cells, as well as related antibody isotype responses. The diverse effects of histamine on immune regulation appear to be due to differential expression and regulation of 4 types of histamine receptors and their distinct intracellular signals. In addition, differences in affinities of these receptors for histamine is highly decisive for the biological effects of histamine and drugs that target histamine receptors.

Molecular Basis for Action

Histamine (2-[4-imidazole]-ethylamine) is a low-molecular-weight amine synthesized from L-histidine exclusively by histidine decarboxylase. It is produced by various cells throughout the body, including central nervous system neurons, gastric mucosa parietal cells, mast cells, basophils and lymphocytes (1-4). Since its discovery as an uterine stimulant more than 100 years ago it has become one of the most intensely studied molecules in medicine. The name histamine was given after the Greek word for tissue, histos after it was isolated first from liver and lung tissue and than from several other sites. Its smooth muscle stimulating and vasodepressor action was demonstrated in the first experiments by Dale and Laidlaw (5), who also found that the effects of histamine mimicked those occurring during anaphylaxis.

Histamine is involved in the regulation of many physiological functions including cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing. Within central nervous system it affects cognition and memory, the regulation of cycle of sleeping and waking, energy and endocrine homeostasis (6). In human pathology histamine triggers acute symptoms due to its very rapid activity on vascular endothelium and bronchial and smooth muscle cells.
leading to the development of such symptoms as acute rhinitis, bronchospasm, cramping, diarrhea or cutaneous wheal and flare responses. In addition to these effects on the immediate type response histamine significantly regulates the immune response and a number of chronic phase inflammatory events (1, 2). For example, histamine is increased in bronchoalveolar lavage fluid from patients with allergic asthma and this increase negatively correlates with airway function (7). An increase in histamine levels has been noted in the skin and plasma of patients with atopic dermatitis (8) and in chronic urticaria (9). Histamine levels are also increased in multiple sclerosis (10) and in psoriatic skin (11). Both plasma and synovial fluid of patients with rheumatoid arthritis and plasma of patients with psoriatic arthritis have increased histamine levels (12). Consequently the antihistamines should be viewed as systemic anti-allergic agents and immunoregulators.

**Histamine receptors**

The pleiotropic effects of histamine are triggered by activating on one or several of histamine membrane receptors on different cells. Four subtypes of receptors (histamine receptor (HR) 1, HR2, HR3, and HR4) have been described (Table 1). All of these receptors belong to the G-protein-coupled receptor family. They are heptahelical transmembrane molecules that transduce extracellular signal by using G-proteins and intracellular second messenger systems (1, 2). 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 (13).

HRs agonists stimulate the active state in the receptor and inverse agonists, 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 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 (13). In reporter gene assays, constitutive HR1-mediated nuclear factor (NF)-κB activation has been shown to be inhibited by many of the clinically used H1-antihistamines, indicating that these agents are inverse HR1-agonists (13). Constitutive activity has now been shown for all four histamine receptors (13).

Specific activation or blockade 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. It has long been recognized that most positive effects of histamine are mediated by HR1, while HR2 is mostly involved in its suppressive activities. The human Gq11-coupled HR1 is encoded by a single exon gene located on the distal short arm of chromosome 3p25b and contains 487 amino acids. The HR1 is expressed in numerous cells including airway and vascular smooth muscle cells, hepatocytes, chondrocytes, nerve cells, endothelial cells, dendritic cells, monocytes, neutrophils, T and B cells (1, 2). Histamine binds to transmembrane domains 3 and 5. Activation of the HR1-coupled Gq11 stimulates the inositol phospholipid signaling pathways resulting in formation of inositol-1,4,5-triphosphate (IP3) and diacylglycerol and an increase in intracellular calcium (14). The rise in intracellular calcium accounts for nitric oxide production, liberation of arachidonic acid from phospholipids increased cyclic AMP. The HR1 also activates phospholipase D and phospholipase A2 and the transcription factor NF-κB. through Gq/11 and Gpγ upon agonist binding. Constitutive activation of NF-κB occurs only through Gpγ (14). The HR1 is responsible for the development of many symptoms of allergic disease. Targeted disruption of the H1-receptor gene in mice results in the impairment of neurologic functions such as memory, learning, locomotion, and nociception, and in aggressive behavior. Immunologic abnormalities have also been described in HR1-deleted mice, with impairment of both T and B cell responses (15). Activation of HR1 is responsible for many symptoms of allergic disease.

In humans the intronless gene encoding HR2 is located on chromosome 5. The human HR2 is a protein of 359 amino acids coupled to both adenylate cyclase and
phosphoinositide second messenger systems by separate GTP-dependent
mechanisms including $G_\alpha_s$ and also induces activation of c-Fos, c-Jun PKC and
p70S6 kinase (16). Studies in different species and several human cells
demonstrated that inhibition of characteristic features of the cells by primarily cAMP
formation dominates in HR2-dependent effects of histamine.

Human HR3 encoded by a gene, which consists of four exons on chromosome
20 has been demonstrated in 1987 and cloned recently (17). HR3 has initially been
identified in the central and peripheral nervous system as pre-synaptic receptors
controlling the release of histamine and other neurotransmitters (dopamine,
serotonin, noradrenaline, GABA, and acetylcholine). HR3 signal transduction
involves $G_{i/o}$ of G proteins leading to inhibition of cAMP and accumulation of Ca$^{++}$ and
activation of mitogen-activated protein kinase (MAPK) pathway. R-$\alpha$-methyhistamine
and imetit are agonists, thioperamide and clobenpropit are antagonists of HR3. The
control of mast cells by histamine acting on HR3 involves neuropeptide-containing
nerves and might be related to a local neuron-mast cell feedback loop controlling
neurogenic inflammation. Dysregulation of this feedback loop may lead to excessive
inflammatory responses and suggests a novel therapeutic approach by using HR3
agonists. Probably more than one HR3 subtype exists, which differ in central nervous
system localization and signaling pathways.

Human HR4, which is encoded by a gene containing three exons, separated by
two large introns located in chromosome 18q11.2. It has 37-43% homology to HR3
(58% in the transmembrane region). HR4 is functionally coupled to G protein $G_{i/o}$,
inhibiting forskolin-induced cAMP formation like the HR3 [14]. HR4 shows high
expression in the bone marrow and peripheral hematopoietic cells, neutrophils,
eosinophils and T cells, basophils and mast cells and moderate expression in spleen,
thymus, lung, small intestine, colon, and heart (18). Until now relatively little is known
about the biological function of HR4. It seems to be involved in the immune
regulatory functions including chemotaxis and cytokine secretion (1, 2). H4 histamine
receptor is expressed in cells of the innate immune system, which include NK cells, monocytes, and dendritic cells (19).

HRs form dimers and even oligomers, which allow cooperation between HRs and other G protein-coupled receptors. Thus, the effects of histamine upon receptor stimulation can be very complex.

**Synthesis and metabolism of histamine**

The classical cellular sources of histamine are mast cells and basophils, gastric enterochromaffin-like cells, platelets and histaminergic neurons. Interestingly the cells in the immune system, which do not store histamine show high HDC activity and are capable of production of high amounts of histamine, which is secreted immediately after synthesis (20). These cells include platelets, monocytes/macrophages, dendritic cells, neutrophils, T and B lymphocytes.

Histamine is synthesized by decarboxylation of histidine by L-histidine decarboxylase (HDC), which is dependent on the cofactor pyridoxal-5′-phosphate (21). Mast cells and basophils are the major source of granule-stored histamine, where it is closely associated with the anionic proteoglycans and chondroitin-4-sulfate. Histamine is released when these cells degranulate in response to various immunologic and nonimmunologic stimuli. In addition, several myeloid and lymphoid cell types (dendritic cells [DCs] and T cells), which do not store histamine, show high HDC activity and are capable of production of high amounts of histamine (20). HDC activity is modulated by cytokines, such as IL-1, IL-3, IL-12, IL-18, GM-CSF, macrophage-colony stimulating factor, TNF-α and calcium ionophore, in vitro (22). HDC activity has been demonstrated in vivo in conditions such as LPS stimulation, infection, inflammation, and graft rejection (14). The generation of HDC-deficient mice provided histamine-free systems to study the role of endogenous histamine in a broad range of normal and disease processes. These mice show decreased numbers of mast cells and significantly reduced granule content, which suggests that
Histamine might affect the synthesis of mast cell granule proteins (23). IgE binding to the FcεRI on IL-3-dependent mouse bone marrow-derived mast cells induces the expression of HDC through a signaling pathway distinct to that operating during antigen-stimulated FcεRI activation (24). More than 97% of the histamine is metabolized in 2 major pathways before excretion (25). Histamine N-methyltransferase metabolizes the majority of histamine to N-methylhistamine, which is further metabolized to the primary urinary metabolite M-methylimidazole acetic acid by monoamine oxidase. Diamine oxidase metabolizes 15% to 30% of histamine to imidazole acetic acid.

**Histamine in chronic inflammatory responses**

Chronic inflammatory response is one of the hallmarks of allergic diseases. Over the course of pollen season, there might be even a 10-fold increase in numbers of nasal epithelial submucosal mast cells. Histamine released from these cells might not only induce acute allergic symptoms but also be crucial for sustaining this response into a chronic phase as increasing evidence suggests that it influences several immune/inflammatory and effector functions (Table 2) (2).

Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of proinflammatory cytokines like IL-1α, IL-1β, IL-6 as well as chemokines like RANTES or IL-8, both in several cell types and local tissues (26-29). Endothelial cells express functional HR1 and HR2 and increased adhesion molecule expression such as ICAM-1, VCAM-1 and P-selectin was demonstrated by histamine infusion via HR1 (30-32). Histamine regulates the expression of its own receptors on endothelial cells and influences the overall inflammatory reaction (33).

Histamine regulates granulocyte accumulation to tissues in distinct ways. Allergen-induced accumulation of eosinophils in the skin, nose and airways is potently inhibited by H1-antihistamines (34). The effect of histamine on eosinophil migration may differ according to the dose. Whereas high doses inhibit eosinophil
chemotaxis via HR2, low doses enhance eosinophil chemotaxis via HR1 (35). Recently, it has been shown that the histamine receptor responsible for the selective recruitment of eosinophils, is HR4 (36). Histamine possesses all the properties of a classical leukocyte chemoattractant (i.e., agonist-induced actin polymerization, mobilization of intracellular calcium, alteration in cell shape, and upregulation of adhesion molecule expression). The eosinophils chemoattractive ability of histamine is weak, when compared to the potent CCR3-binding chemokines, eotaxin and eotaxin-2 (36-39). Histamine possesses all the properties of a classical leukocyte chemoattractant, including: agonist-induced actin polymerization, mobilization of intracellular calcium, alteration in cell shape, and up-regulation of adhesion molecule expression. In vivo, allergen-specific wild-type, but not histamine H$_1$ receptor-deficient CD4+ T cells were recruited to the lungs of naive recipients following inhaled allergen challenge (40). Histamine inhibits neutrophil chemotaxis due to histamine H$_2$ receptor-triggering, which is mimicked by impromidine (histamine H$_2$ receptor agonist), but not by betahistine (histamine H$_1$ receptor agonist) (41).Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of proinflammatory cytokines such as IL (interleukin)-1$\alpha$, IL-1$\beta$, IL-6 as well as chemokines such as RANTES or IL-8, in several cell types and local tissues (27, 28, 42, 43). Histamine induces the CC chemokines, monocyte chemotactic protein 1 and 3, RANTES, and eotaxin in explant cultures of human nasal mucosa via histamine H$_1$ receptor, suggesting a prolonged inflammatory cycle in allergic rhinitis between the cells that release histamine and their enhanced migration to nasal mucosa (44).

However, histamine upon activation of the HR4 induces enhanced migration of eosinophils towards eotaxin and eotaxin-2 (45). On the other hand, the potential of histamine alone to act as an eosinophil chemoattractant in vivo, might be augmented by other factors, such as growth factors or cytokines like IL-5, the cytokine specific for the differentiation, activation, and survival of eosinophils (46). Triggering of HR4 also induces chemotaxis of mast cells (47). Experiments in mice showed that mast cells
from wild type and HR3- receptor-deleted mice migrated in response to histamine, while mast cells from the HR4-deleted mice did not. Thus, chemotaxis of eosinophils and mast cells via histamine is triggered mainly through the HR4. The HR4-mediated chronic inflammatory effects of histamine may be aborted by administration of HR4 antagonists and combination therapies with the HR1 antagonists are a promising approach.

Histamine inhibits neutrophil chemotaxis due to HR2 triggering, which is mimicked by impromidine (HR2 agonist), but not by betahistine (HR1 agonist). In addition, histamine inhibits neutrophil activation, superoxide formation and degranulation via HR2 (48). Down regulation of NF-κB, which acts as a potent transcription factor in initiating inflammation may represent a possible mechanism for H1-antihistamines to inhibit inflammatory cell accumulation (49). Low concentrations of H1-antihistamines, cetirizine and azelastine have been demonstrated to down-regulate NF-κB expression in parallel to inhibition of pro-inflammatory cytokines (50). A recent study with HDC-deficient and mast cell-deficient mice demonstrated that histamine mainly derived from non-mast cells plays an essential role in angiogenesis and the generation of inflammatory granulation (51). The pretreatment of the nasal mucosa and the conjunctivae with topical H 1-antihistamines has been shown to down-regulate the inflammation locally after an allergen challenge (52). Decreased macrophage IL-6 production and in dendritic cells decreased expression of CD86 and decreased IL-8 production was shown (53, 54).

These findings open a new therapeutic window for antihistamines as systemic antiallergic agents. Although the use of H1-antihistamine in persistent asthma is currently not recommended some recent evidence might finally lead to reevaluation of this approach. Histamine has been found in the airways of asthma patients even during asymptomatic periods (55, 56). Increased number of degranulated mast cells and basophils has been detected in biopsies of asthmatic airways long after an acute asthma attack (57). The level of histamine in bronchoalveolar lavage fluid (BALF) has
been found to correlate with the severity of asthma and airway hyperresponsiveness (58).

Inhaled and intravenous histamine causes bronchoconstriction as one of the first recognized properties of histamine, which is inhibited by H1-antihistamines. As a manifestation of airway hyper-responsiveness, asthmatic individuals are more sensitive to the bronchoconstrictor effect of histamine than normal individuals. In addition in vitro studies have shown increased histamine release in basophils and mast cells obtained from asthmatic subjects compared with cells obtained from persons without asthma (55). In lavage fluid of the patients treated with H1-antihistamines decreased levels of proinflammatory cytokines, and mediators (e.g., histamine, leukotrienes, prostaglandin, cell adhesion molecules (e.g., intercellular adhesion molecules and vascular cell adhesion molecules), cells (e.g., eosinophils and neutrophils), plasma exudation along with reduced symptom score has been found (59).

The potential efficacy of H1 antihistamines in asthma has been intensively investigated (59). It has been shown that inhalation, intravenous or oral administration of clemastine or chlorpheniramine induced significant bronchodilatation. However, second generation H1-antihistamines induce only a very limited increase of FEV1 (5-10 % over baseline) by recommended doses (60, 61). There is variable effect on allergen challenge or exercise-induced bronchospasm. Only terfenadine with 3 times recommended dose inhibited early and late bronchoconstrictor response (61). Terfenadine, cetirizine and loratadine with 2 to 5 times the usual dose appeared to improve asthma symptoms in mild seasonal or perennial asthma, but did not block development of bronchial hyperresponsiveness in seasonal pollen asthma nor show apparent benefit in patients with more severe asthma (60, 61). In patients with concurrent symptoms of allergic rhinitis and asthma, treatment with H1-antihistamine results in significant decrease in symptoms of both rhinitis and asthma, decrease in use of β2-agonists, and some improvement of
airway function (62). Montelukast sodium – a leukotriene receptor antagonist showed similar effect as desloratadine (62).

The mechanisms of the beneficial effect of HR1-antihistamines in asthma have been investigated in a mice model. Fexofenadine was found to suppress allergic immune/inflammatory responses in sensitised mice (63). Treatment with fexofenadine diminished Th2-like response that typically follows sensitisation and challenge with allergen. Decreased secretion of IL-4, IL-5, prevention of allergen-specific IgE increase and reduced eosinophilia in lung tissue and BALF as well as normalization of airway response to metacholine was observed.

Importantly, in an adoptive transfer model it was demonstrated that the target mechanism was T cell-mediated. Lung T cells from sensitised mice when transferred to naïve recipient mice triggered airway hyperresponsiveness and allergic inflammatory features after allergen challenge. In contrast naïve mice which received T cells from sensitised mice treated before with fexofenadine showed no such responses to allergen challenge (63). The inability of T cells from HR1 antihistamine-treated allergen-sensitised mice to transfer allergic sensitivity to naïve recipients resulted from an alteration in the cytokine production profile of the transferred cells.

Consistently, histamine-induced concentration-dependent release of IL-6 and β-glucuronidase from macrophages isolated from the human lung parenchyma was inhibited by fexofenadine but not by ranitidine, an H₂-receptor antagonist (64). Thus long-term treatment with H1 antihistamines can alter disease progression in patients with respiratory allergy associated with tissue damage/remodeling mediated by macrophage and Th2 cell activation. It has been shown that treatment with cetirizine over period of 18 months delayed the onset of asthma in some young children with atopic dermatitis (65). Although H1-antihistamines clearly show weaker antiinflammatory effects than corticosteroids but they may in a subtle way modulate the immune response by modulating the balance between Th1, Th2 and Treg cells and suppressing the accumulation of inflammatory cells. Although previous studies suggested a basal tone of smooth muscle mediated by histamine binding to HR1,
currently constitutive intrinsic activity of the HR1 without any occupation by histamine could be more relevant. Histamine also induces proliferation of cultured airway smooth muscle cells (66).

Difference in histamine response between species has been reported indicating a role for HR2-mediated bronchodilatation in cat, rat, rabbit, sheep and horse (67). However, in humans, H2-antihistamines such as cimetidine and ranitidine do not cause bronchoconstriction in normal or asthmatic individuals (68). Although there is no direct evidence that it plays a role in disease pathogenesis, HR2-mediated gastric secretion is impaired in asthma (69). Histamine may play an important role in the modulation of the cytokine network in the lung via HR2, HR3 and HR4 that are expressed in distinct cells and cell subsets. Apparently, due to the same signal transduction patterns, β2 adrenergic receptors may function similar to HR2 in humans. The role of histamine and other redundant G-protein-coupled receptors in the regulation of immune/inflammatory pathways in the lung remain to be intensely focused in future studies.

Role of histamine in the regulation of immune response

*Antigen-presenting cells*

Dendritic cells (DC) are often located in the vicinity of various histamine sources such as connective tissue mast cells. They are potent antigen-presenting and cytokine-producing cells. Therefore, histamine may effectively influence the immune response through DC. These professional antigen-presenting cells mature from monocytic and lymphoid precursors and acquire DC1 and DC2 phenotypes, which in turn facilitate the development of Th1 and Th2 cells, respectively. Endogenous histamine is actively synthesized during cytokine-induced DC differentiation, which acts in autocrine and paracrine fashion and modifies DC markers (70). Histamine actively participates in functions and activity of DC precursors as well as their immature and mature forms (Figure 1). Immature and mature DCs express all four HR, however comparison of their levels of expression has not yet been studied. In
the differentiation process of DC1 from monocytes, HR1 and HR3 act as positive stimulants that increase antigen-presentation capacity and proinflammatory cytokine production and Th1 priming activity. In contrast, HR2 acts as a suppressive molecule for antigen-presentation capacity, enhances IL-10 production and induces IL-10-producing T cells or Th2 cells (Table 2) (71)(72).

In monocytes stimulated with Toll-like receptor-triggering bacterial products histamine inhibits the production of pro-inflammatory IL-1-like activity, TNFα, IL-12 and IL-18, but enhances IL-10 secretion, through HR2 stimulation (26) (72). Histamine also downregulates CD14 expression via H2 receptors on human monocytes (73). The inhibitory effect of histamine via H2-receptor appears through the regulation of ICAM-1 and B7.1 expression, leading to the reduction of innate immune response stimulated by LPS (74).

Histamine induces intracellular Ca\(^{++}\) flux, actin polymerization, and chemotaxis in immature DCs due to stimulation of HR1 and HR3 subtypes. Maturation of DCs results in loss of these responses. In maturing DCs, however, histamine dose-dependently enhances intracellular cAMP levels and stimulates IL-10 secretion, while inhibiting production of IL-12 via HR2 (16). Interestingly, although human monocyte-derived dendritic cells (MoDC) have both histamine H1 and H2 receptors and can induce CD86 expression by histamine, human epidermal Langerhans cells express neither H1 nor H2 receptors (75).

Effect of histamine on T cells and antibody isotypes

Histamine has been shown to intervene in the Th1, Th2, Treg cell balance and consequently antibody formation. Differential patterns of histamine receptor expression on Th1 and Th2 cells determine reciprocal T cell responses following histamine stimulation (Table 2) (Figure 1) (76). Th1 cells show predominant, but not exclusive expression of HR1, while Th2 cells show increased expression of HR2. Histamine enhances Th1-type responses by triggering the HR1, whereas both Th1- and Th2-type responses are negatively regulated by HR2, due to activation of
different biochemical intracellular signals (76). In mice, deletion of HR1 results in suppression of IFN-γ and dominant secretion of Th2 cytokines (IL-4 and IL-13). HR2-deleted mice show upregulation of both Th1 and Th2 cytokines. Bphs a non-major histocompatibility complex-linked gene involved in the susceptibility to many autoimmune diseases has been identified as HR1 gene in mice. HR1-deleted mice showed delayed disease onset and decreased disease severity when immunized to develop experimental allergic encephalomyelitis (77). It has also been shown that histamine stimulation induced IL-10 secretion through HR2 (1, 2). Increased IL-10 production in both DC and T cells may account for an important regulatory mechanism in the control of inflammatory functions through histamine. Various cytokines regulate the production of histamine and its receptor expression. IL-3 stimulation significantly increases HR1 expression on Th1, but not on Th2 cells (76).

In mice, histamine enhances anti-IgM-induced proliferation of B cells, which is abolished in HR1-deleted mice. In HR1-deleted mice, antibody production against a T cell-independent antigen-TNP-Ficoll is decreased (15), suggesting an important role of HR1 signaling in responses triggered from B cell receptors. Antibody responses to T cell-dependent antigens like ovalbumin (OVA) show a different pattern (15). HR1-deleted mice produced high OVA-specific IgG1 and IgE in comparison to wild type mice. In contrast, HR2-deleted mice showed decreased serum levels of OVA-specific IgE in comparison to wild type mice and HR1-deficient mice. Although T cells of HR2-deficient mice secreted increased IL-4 and IL-13, OVA-specific IgE was suppressed in the presence of highly increased IFN-γ. Thus, HR1 and related Th1 response may play a dominant role in the suppression of humoral immune response.

The role of histamine and H1 antihistamines during allergen-SIT

The rationale for the use of H1-antihistamines during SIT is diverse and may include both the reduction of side effects, which may develop immediately after the shots of vaccine and providing help in the long term induction of allergen tolerance induced by vaccination. Pretreatment with antihistamines has been proposed as
early as in 1980s as the effective approach to reduce the side effects of allergen immunotherapy (78) It has been confirmed in a number of studies that administration of high doses of second generation H1R antihistamines before vaccine shots of insect venom or grass pollen is effective in reduction of local allergic reactions and generalized symptoms of the urticaria and angioedema type (79-81). Unfortunately, this modality is much less effective in the reduction of more severe systemic symptoms (79-81).

The effect of pre-treatment with terfenadine on the long-term protection from honeybee stings during rush immunotherapy with honeybee venom was analyzed in a double-blind, placebo-controlled trial (82). After an average of 3 years, 41 patients were re-exposed to honeybee stings. Surprisingly, none of 20 patients, who had been given HR1-antihistamine premedication, but 6 of 21 given placebo, had a systemic allergic reaction to the re-exposure by either a field sting or a sting challenge. This highly significant difference suggests that H1-antihistamine premedication during the initial dose-increase phase may have enhanced the long-term efficacy of immunotherapy. This indicates a positive role of histamine in immune regulation during SIT (83). Similarly in the ETAC (early treatment of the atopic child) study - a double-blind placebo-controlled trial aiming at the determination of the preventative effect of cetirizine on the development of asthma which included 830 children with atopic dermatitis aged 12–24 months it has been shown that treatment with cetirizine reduced relative risk of developing asthma for the children sensitized to grass pollen or house dust mite (84). These findings indicate the immunoregulatory and anti-inflammatory effects of H1 antihistamines. The underlying mechanisms are not fully elucidated. On one side treatment with H1R antagonists also results in H2R predominance. Moreover the expression of HR1 on T lymphocytes is strongly reduced during ultra rush immunotherapy, which may lead to a dominant expression of HR2.

Peripheral T cell tolerance characterized by immune deviation to regulatory/suppressor T cells represents a key event in the control of specific immune
response during allergen-specific immunotherapy (85). Although, multiple suppressor factors including contact dependent or independent mechanisms might be involved, IL-10 and TGF-β predominantly produced by allergen-specific T cells play an essential role (86, 87). Histamine interferes with the peripheral tolerance induced during SIT in several pathways. Histamine induces the production of IL-10 by dendritic cells (88). In addition, histamine induces IL-10 production by Th2 cells (89). Furthermore, histamine enhances the suppressive activity of TGF-β on T cells (90). All three of these effects are mediated via HR2, which is relatively highly expressed on Th2 cells and suppresses IL-4 and IL-13 production and T cell proliferation. Apparently, these recent findings suggest that HR2 may represent an essential receptor that participates in peripheral tolerance or active suppression of inflammatory/immune responses. Although the selective activation of H2R might be a more promising approach as compared to the use of H1 antihistamines, so far it has not been investigated in vivo.

However, selective HR2 antagonists, have attracted interest because of their potential immune response-modifying activity (91). Most data suggest that cimetidine has a stimulatory effect on the immune system, possibly by blocking the receptors on subsets of T-lymphocytes and inhibiting HR2-induced immune suppression. Cimetidine has also been used successfully to restore immune functions in patients with malignant disorders, hypogammaglobulinemia and AIDS-related complexes.

The use of H1 antihistamines in asthma

Histamine administered intravenously or by inhalation causes bronchoconstriction, which is inhibited by HR1 antihistamines. Individuals with asthma are more sensitive to the bronchoconstrictor effect of histamine than healthy individuals are. Although current evidence does not support the use of H1-antihistamines in persistent asthma, some investigators have shown a significant decrease in asthma symptoms and improvement in pulmonary function after H1-antihistamine treatment (3, 92-95). Treatment with the H1-antihistamine cetrizine
over a period of 18 months was reported to delay the onset of asthma in some young children with atopic dermatitis who were at high risk for the disease, however, this observation requires confirmation (3, 92-95). In sensitized mice, treatment with the H1-antihistamine fexofenadine before allergen challenge prevented airway hyperresponsiveness. Decreases in bronchoalveolar lavage fluid and tissue eosinophilia, lymphocyte numbers, and TH2 cytokine production were also observed in this model (96). Another HR1 antihistamine, desloratadine, given at the time of allergen exposure, inhibited the induction of allergic inflammation in the airways and bronchial hyperresponsiveness (97).

Histamine-induced, concentration-dependent release of IL-6 and β-glucuronidase from macrophages isolated from human lung parenchyma can be consistently inhibited by fexofenadine but not by ranitidine, an H2-antihistamine (98). Thus, long-term treatment with HR1 antihistamines might potentially alter disease progression in patients with respiratory allergy associated with tissue damage/remodeling mediated by macrophage and Th2 cell activation.

Although previous studies suggested a basal tone of smooth muscle mediated by histamine binding to HR1, constitutive intrinsic activity of the HR1 without any occupation by histamine might be more relevant. Histamine also induces proliferation of cultured airway smooth muscle cells (66).

Species differences in the response to histamine have been reported. HR2-mediated bronchodilation occurs in cats, rats, rabbits, sheep and horses (67); however, in healthy and asthmatic humans, H2-antihistamines such as cimetidine and ranitidine do not cause bronchoconstriction (99, 100). Although there is no direct evidence that it plays a role in disease pathogenesis, HR2-mediated gastric secretion may be impaired in asthma (101). H2-antihistamines, given for the treatment of gastroesophageal reflux, improve asthma symptoms (102); whether this is an indirect effect due to down-regulation of gastric acid secretion, or whether it is a direct effect remains to be elucidated. In addition, recent studies suggest that histamine may play an important role in the modulation of the cytokine network in the lung via HR2, HR3
and HR4 that are expressed in distinct cells and cell subsets (103, 104). Apparently, due to the same signal transduction patterns, β2 adrenergic receptors may function similar to HR2 in humans (105). Future research should focus on the role of histamine and other redundant G-protein-coupled receptors in the regulation of immune/inflammatory pathways in the lung.

In particular, the discovery of a fourth histamine receptor (H4) and its expression on numerous immune and inflammatory cells has prompted a re-evaluation of the actions of histamine, suggesting a new potential for H4-receptor antagonists and a possible synergy between H1 and H4-receptor antagonists in targeting various inflammatory conditions (106).

**Conclusions**

The emerging pattern of immune regulation by histamine is very complex and calls for further investigation. Histamine and 4 different histamine receptors constitute a multifaceted system with distinct functions of receptor types due to their differential expression, which changes according to the stage of cell differentiation and influences of the microenvironment. The diverse effects of histamine on immune regulation appear to be due to differential expression and regulation of 4 types of histamine receptors and their distinct intracellular signals. In addition, differences in affinities of these receptors for histamine is highly decisive for the biological effects of histamine and drugs that target histamine receptors. The cells involved in the regulation of immune response and hematopoiesis express histamine receptors and also secrete histamine. Histamine can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization, and other functions leading to chronic inflammation. Histamine also regulates dendritic cells, T cells and B cells, as well as related antibody isotype responses. Although contrasting findings have been reported, HR1 stimulates the immune system cells by potentiating their proinflammatory activity for increased migration to the area of inflammation as well as increased effector functions. In addition, acting through its receptor 2, histamine
positively interferes with the peripheral antigen tolerance induced by T regulatory cells in several pathways. The data on the role of HR3 and HR4 in immune regulation are limited. The observation that H4R activation promotes the accumulation of inflammatory cells at sites of allergic inflammation opens a new window of therapeutic opportunity based on concurrent H1-antihistamine and H4-antihistamine administration, or development of selective dual H1-/H4-antihistamines. Whether such treatment will provide additional suppression of allergic inflammatory responses compared with that observed after H1-antihistamine treatment alone remains to be elucidated.
### Table 1. Histamine receptors, expression, activated intracellular signals, and coupled G proteins.

<table>
<thead>
<tr>
<th>Histamine receptors</th>
<th>Expression</th>
<th>Activated intracellular signals</th>
<th>Coupled G proteins</th>
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<tbody>
<tr>
<td>Histamine H₁ receptor</td>
<td>nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, DC, T and B cells</td>
<td>Ca²⁺, cGMP, phospholipase D, phospholipase A₂, NFκB</td>
<td>Gq/11</td>
</tr>
<tr>
<td>Histamine H₂ receptor</td>
<td>nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, DC, T and B cells</td>
<td>adenylate cyclase, cAMP, c-Fos, c-Jun, PKC, p70S6K</td>
<td>Gαs</td>
</tr>
<tr>
<td>Histamine H₃ receptor</td>
<td>histaminergic neurons, eosinophils, DC, monocytes low expression in peripheral tissues</td>
<td>enhanced Ca²⁺, MAP kinase, inhibition of cAMP</td>
<td>Gi/o</td>
</tr>
<tr>
<td>Histamine H₄ receptor</td>
<td>High expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DC, T cells, basophils, mast cells, low expression in nerve cells, hepatocyte peripheral tissues, spleen, thymus, lung, small intestine, colon and heart</td>
<td>Enhanced Ca²⁺, Inhibition of cAMP</td>
<td>Gi/o</td>
</tr>
<tr>
<td>Table 2. Histamine receptors in allergic inflammation and immune modulation</td>
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<tr>
<td><strong>Histamine function in allergic inflammation and immune modulation</strong></td>
<td><strong>histamine H₁ receptor</strong></td>
<td><strong>histamine H₂ receptor</strong></td>
<td><strong>histamine H₃ receptor</strong></td>
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<tr>
<td>increases release of histamine and other mediators; increases cellular adhesion molecule expression and chemotaxis of eosinophils and neutrophils; increases antigen-presenting cell capacity, co-stimulatory activity on B cells; increases cellular immunity (Th1), IFN-γ, autoimmunity. decreases humoral immunity and IgE production.</td>
<td>decreases eosinophil and neutrophil chemotaxis; decreases IL-12 by dendritic cells; increases IL-10 and induces development of Th2 or tolerance-inducing dendritic cells; increases humoral immunity; decreases cellular immunity; suppresses Th2 cells and cytokines; role in allergy, autoimmunity, malignancy, graft rejection.</td>
<td>probably involved in control of neurogenic inflammation through local neuron-mast cell feedback loops; increases pro-inflammatory activity and APC capacity.</td>
<td>increases calcium flux in human eosinophils; increases eosinophil chemotaxis; increases IL-16 production (H₂-receptor also involved).</td>
</tr>
</tbody>
</table>
References


103. Gantner F, Sakai K, Tusche MW, Cruikshank WW, Center DM, and Bacon KB: Histamine h(4) and h(2) receptors control histamine-induced interleukin-16 release from human CD8(+) T cells. J Pharmacol Exp Ther 2002;303:300-307.
Legend to the figure

Figure 1

Histamine regulates monocyte, dendritic cell, T cells and B cell functions. Monocytes and dendritic cells express all four HRs. Activation of HR1 and HR3 triggers proinflammatory events and increases APC capacity. HR2 plays a suppressive role on monocytes and monocyte-derived dendritic cells (DC). Th1 cells show predominant, but not exclusive, expression of HR1, whereas Th2 cells show upregulation of HR2. Histamine induces increased proliferation and IFN-γ production in Th1 cells. Th2 cells express predominant HR2, which acts as the negative regulator of proliferation, IL-4 and IL-13 production. Histamine enhances Th1-type responses by triggering the HR1, whereas both Th1- and Th2-type responses are negatively regulated by HR2, showing an essential role for immune regulation for this receptor. Distinct effects of histamine suggest roles of HR1 and HR2 on T cells for autoimmunity and peripheral tolerance, respectively. Histamine also modulates antibody production. Histamine directly effects B cell antibody production as a co-stimulatory receptor on B cells. HR1 predominantly expressed on Th1 cells may block humoral immune responses by enhancing Th1 type cytokine IFN-γ. In contrast, HR2 enhances humoral immune responses. Allergen-specific IgE production is differentially regulated in HR1- and HR2-deficient mice. HR1-deleted mice show increased allergen-specific IgE production, whereas HR2-deleted mice show suppressed IgE production.
Th1 cells:
HR1 enhances IFN-γ production and Th1 cell proliferation, HR2 antagonizes this effect.

Th2 cells:
HR2 suppresses IL-4 and IL-13 production and Th2 cell proliferation.

Histamine enhances the production of IL-10 and the suppressive effect of TGF-β is potentiated via HR2.

Dendritic cells:
HR1 increases antigen-presenting capacity and Th1 priming. HR2 induces IL-10 production, suppresses antigen-presentation and aids development of IL-10-secreting T cells.

B cells:
HR1 blocks humoral immunity, induces cellular immunity. HR2 blocks cellular immunity. HR1-deficient mice show increased specific IgE, HR2-deficient mice show suppressed specific IgE.

Treg cells:
HR1 blocks humoral immunity, induces cellular immunity. HR1-deficient mice show increased specific IgE, HR2-deficient mice show suppressed specific IgE.

Figure 1