

Histamine in Allergic Inflammation and Immune Modulation

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Abstract

Histamine, originally considered as a mediator of acute inflammatory and immediate hypersensitivity responses has also been demonstrated to affect chronic inflammation and regulate several essential events in the immune response. On the other hand, various cytokines control histamine synthesis, release and expression of histamine receptors (HRs). The cells involved in the regulation of immune response and hematopoiesis express HRs and also secrete histamine, which can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization and effector functions leading to chronic inflammation. Histamine, acting through its receptor type 2, positively interferes with the peripheral antigen tolerance induced by T regulatory cells in several pathways. Histamine also regulates antigen-specific Th1 and Th2 cells, as well as related antibody isotype responses. The diverse effects of histamine on immune regulation are due to differential expression and regulation of four HRs and their distinct intracellular signals. In addition, differences in affinities of these receptors are highly decisive on the biological effects of histamine and agents that target HRs. This article highlights the findings leading to a change of perspective in histamine immunobiology.

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Introduction

Histamine, 2-(4-imidazole)-ethylamine, is one of the most intensely studied molecules in medicine. It is a low-molecular-weight amine synthesized from *L*-histidine exclusively by histidine decarboxylase. Histamine is produced by various cells throughout the body, including central nervous system neurons, gastric mucosa parietal cells, mast cells, basophils and lymphocytes. It was discovered as the uterine stimulant in different extracts approximately 100 years ago. Its smooth muscle-stimulating and vasodepressor action was demonstrated in the first experiments by Dale and Laidlaw [1], who also found that the effects of histamine mimicked those occurring during anaphylaxis.

Histamine plays an important role both in normal human physiology as well as in various pathologies. It is involved in the cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration and wound healing [2–6]. Within the central nervous system, histamine is involved in cognition and memory, the regulation of the cycle of sleeping and waking, energy and endocrine homeostasis [7–9]. Histamine released from mast cells and basophils triggers acute symptoms due to its very rapid activity on vascular endothelium and bronchial and smooth muscle cells. This results in the development of symptoms such as acute rhinitis, bronchospasm, cramping, diarrhea or cutaneous wheal and flare responses.

In addition to its role in the early allergic response, histamine significantly affects chronic inflammatory re-

Table 1. Histamine receptors, expression, coupled G proteins and activated intracellular signals

Histamine receptors	Expression	Activated intracellular signals	G proteins
HR1	nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, DCs, T and B cells	Ca ⁺² , cGMP, phospholipase D, phospholipase A ₂ , NF-κB	G _{q/11}
HR2	nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, DCs, T and B cells	adenylate cyclase, cAMP, c-Fos, c-Jun, PKC, p70S6K	G _{as}
HR3	histaminergic neurons, eosinophils, DCs, monocytes, low expression in peripheral tissues	enhanced Ca ⁺² , MAP kinase, inhibition of cAMP	G _{i/o}
HR4	high expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DCs, T cells, basophils, mast cells, low expression in nerve cells, hepatocytes, peripheral tissues, spleen, thymus, lung, small intestine, colon and heart	enhanced Ca ⁺² , inhibition of cAMP	G _{i/o}

sponses as well. It can influence numerous functions of macrophages, dendritic cells (DCs), T lymphocytes, B lymphocytes, epithelial and endothelial cells including proliferation, production of cytokines, the expression of cell adhesion molecules or MHC class II antigens [2–6]. Although substantial evidence has been accumulated for histamine metabolism, receptors, signal transduction, physiological and pathological effects, the complex inter-relationship and crosstalk by histamine, its receptors and other G protein-coupled receptors remain to be understood.

Histamine Receptors

The pleiotropic effects of histamine are triggered by activating one or several histamine membrane receptors on different cells. Four subtypes of histamine receptors (HRs), HR1, HR2, HR3 and HR4, have been described (table 1). All of these receptors belong to the G protein-coupled receptor family. They are heptahelical trans-membrane molecules that transduce extracellular signals by using G proteins and intracellular second messenger systems [10, 13]. 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 [14].

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 [15]. 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 [15]. Constitutive activity has now been shown for all four HRs [15]. In addition to the four membrane receptors, histamine binds to some intracellular receptors, such as cytochrome p450 and cytochrome c, and high-affinity lipocalins isolated from saliva of ticks [16].

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. HR1 and HR2 were first distinguished by Ash and Schild in 1966 [17]. 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 G_{q/11}-coupled HR1 is encoded by a single exon gene located on the distal short arm of chromosome 3p25b and contains 487 aminoacids. HR1 is expressed in numerous cells, including airway and vascular smooth muscle cells, hepa-

toocytes, chondrocytes, nerve cells, endothelial cells, DCs, monocytes, neutrophils and T and B cells [18–20]. Histamine binds to transmembrane domains 3 and 5. Activation of the HR1-coupled $G_{q/11}$ stimulates the inositol phospholipid signaling pathways resulting in the formation of inositol-1,4,5-triphosphate and diacylglycerol and an increase in intracellular calcium [21]. The rise in intracellular calcium accounts for nitric oxide production, liberation of arachidonic acid from phospholipids and increased cyclic AMP (cAMP). HR1 also activates phospholipase D and phospholipase A_2 . More recently, HR1 has also been shown to activate the transcription factor NF- κ B [22] through $G_{q/11}$ and $G\beta\gamma$ upon agonist binding. Constitutive activation of NF- κ B occurs only through $G\beta\gamma$ [21]. HR1 is responsible for the development of many symptoms of allergic disease. HR1 polymorphisms have been described, although it is not yet clear how they influence the clinical response to H_1 antihistamines [23]. Targeted disruption of the HR1 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 [24, 25]. Activation of HR1 is responsible for many symptoms of allergic disease.

In humans, the intronless gene-encoding HR2 is located on chromosome 5. Human HR2 is a protein of 359 aminoacids 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 [26]. 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 recently cloned [27]. 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, nor-adrenaline, γ -aminobutyric acid and acetylcholine). HR3 signal transduction involves $G_{i/o}$ of G proteins leading to inhibition of cAMP, accumulation of Ca^{2+} and activation of mitogen-activated protein kinase pathway. R- α -methylhistamine 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 in-

flammation [28]. 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 exist, which differ in central nervous system localization and signaling pathways.

Human HR4 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 HR3 [13]. HR4 shows high expression in the bone marrow and peripheral hematopoietic cells, neutrophils, eosinophils and T cells, and moderate expression in the spleen, thymus, lung, small intestine, colon and heart [13]. Both basophils and mast cells express HR4 mRNA [29]. Related to high homology between the two receptors, presently available HR3 agonists and antagonists are also recognized by HR4 [13]. However, clobenpropit, an HR3 antagonist, exerts agonistic activity on HR4. 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 [30–34].

It was reported that the H_1 antagonists, doxepin, cinnarizine and promethazine, exhibit high affinity binding to HR4 [35]. HRs form dimers and even oligomers, which allow cooperation between HRs and other G protein-coupled receptors. The affinity of histamine binding to different HRs varies significantly, with K_i values ranging from 5–10 nM for HR3 and HR4 to 2–10 μ M the HR1 and HR2 [34, 36]. Thus, the effects of histamine upon receptor stimulation can be very complex.

Cellular Sources of Histamine

Mast cells and basophils, gastric enterochromaffin-like cells, platelets and histaminergic neurons are the classical sources of histamine. Remarkably, other cells in the immune system which do not store histamine show high histidine decarboxylase activity and are capable of production of high amounts of histamine, which is secreted immediately after synthesis [37, 38]. These cells include platelets, monocytes/macrophages, DCs, neutrophils and T and B cells [39, 40].

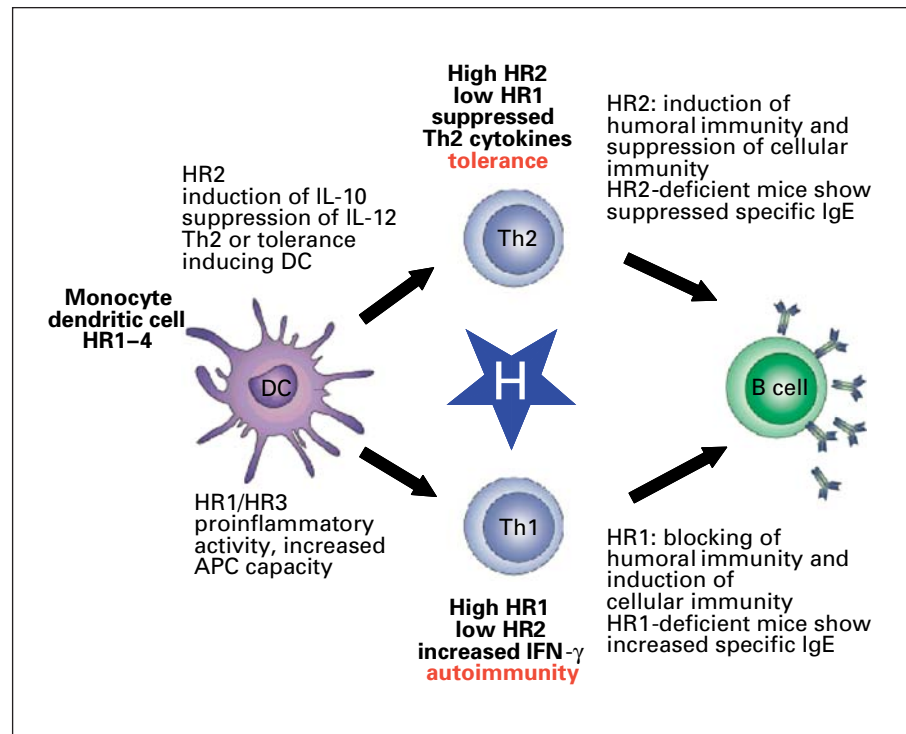


Fig. 1. In lymphatic organs and subepithelial tissues of allergic inflammation, histamine regulates monocytes, DCs, T cells and B cells. Monocytes and DCs express all known HRs. HR1 and HR3 induce proinflammatory activity and increased anaphase-promoting complex capacity, whereas HR2 plays a suppressive role on monocytes and monocyte-derived DCs. 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. These distinct effects may 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 costimulatory 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.

Regulation of Immune Response

Antigen-Presenting Cells

DCs 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 DCs. 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 modi-

fies DC markers [41]. Histamine actively participates in functions and activity of DC precursors as well as their immature and mature forms (fig. 1). Immature and mature DCs express all four HRs; however, a comparison of their levels of expression has not yet been studied [31, 42–44]. In the differentiation process of DC1 from monocytes, HR1 and HR3 act as positive stimulants that increase antigen presentation capacity, 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 [45–47].

In monocytes stimulated with Toll-like receptor-triggering bacterial products, histamine inhibits the produc-

tion of proinflammatory IL-1-like activity, TNF α , IL-12 and IL-18, but enhances IL-10 secretion through HR2 stimulation [48, 49]. Histamine also downregulates CD14 expression via HR2 on human monocytes [50]. The inhibitory effect of histamine via HR2 appears through the regulation of ICAM-1 and B7.1 expression, leading to the reduction of innate immune response stimulated by LPS [51].

Histamine induces intracellular Ca²⁺ 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. However, in maturing DCs, histamine dose-dependently enhances intracellular cAMP levels and stimulates IL-10 secretion, while inhibiting production of IL-12 via HR2 [46]. Interestingly, although human monocyte-derived DCs have both HR1 and HR2 and can induce CD86 expression by histamine, human epidermal Langerhans cells do not express either HR1 or HR2 [52].

T Cells and Antibody Isotypes

Histamine has been shown to intervene in the Th1, Th2 and T regulatory cell balance and consequently in the antibody formation. Differential patterns of HR expression on Th1 and Th2 cells determine reciprocal T cell responses following histamine stimulation (fig. 1) [53]. 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 HR1, whereas both Th1- and Th2-type responses are negatively regulated by HR2, due to activation of different biochemical intracellular signals [53]. 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. Recently, *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 [54]. It has also been shown that histamine stimulation induced IL-10 secretion through HR2 [55]. Increased IL-10 production in both DCs 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 and GM-CSF are enhancers of histamine release from basophils, while stem cell factor stimulates

mast cells [4]. In addition, IL-3 stimulation significantly increases HR1 expression on Th1, but not on Th2 cells [53].

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 [25], 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 [25]. HR1-deleted mice produced high OVA-specific IgG1 and IgE in comparison with wild-type mice. In contrast, HR2-deleted mice showed decreased serum levels of OVA-specific IgE in comparison with wild-type 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.

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 [56]. 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 [56, 57]. Histamine interferes with the peripheral tolerance induced during specific immunotherapy in several pathways. Histamine induces the production of IL-10 by DCs [46]. In addition, histamine induces IL-10 production by Th2 cells [55]. Furthermore, histamine enhances the suppressive activity of TGF- β on T cells [58]. All of these three 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 [53]. Apparently, these recent findings suggest that HR2 may represent an essential receptor that participates in peripheral tolerance or active suppression of inflammatory/immune responses.

The long-term protection from honeybee stings by terfenadine premedication during rush immunotherapy with honeybee venom in a double-blind, placebo-controlled trial was analyzed [59]. After an average of 3 years, 41 patients were reexposed to honeybee stings. Surprisingly, none of the 20 patients who had been given HR1-antihistamine premedication, but 6 of 21 patients who had been given placebo, had a systemic allergic reaction to the reexposure 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. Expression of HR1 on T lymphocytes is strongly reduced during ultrarush immunotherapy, which may lead to a dominant expression and function of tolerance-inducing HR2. This indicates a positive role of histamine in immune regulation during specific immunotherapy [60].

Selective HR2 antagonists have attracted interest because of their potential immune response-modifying activity [61]. 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. On the other hand, HR2 agonists such as dimaprit significantly reduce disease severity in experimental allergic encephalomyelitis mice [62].

Histamine and Chronic Inflammatory Responses

Over the course of the pollen season, there might even be 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 [2, 3].

Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of proinflammatory cytokines like IL-1 α , IL-1 β , IL-6, as well as chemokines like RANTES or IL-8, both in several cell types and local tissues [63–66]. Histamine induces the CC chemokines, monocyte chemoattractant protein 1 and 3, RANTES and eotaxin in explant cultures of human nasal mucosa via HR1, suggesting a prolonged inflammatory cycle in allergic rhinitis between the cells that release histamine and their enhanced migration to nasal mucosa [67]. 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 [68–70]. Histamine regulates the expression of its own receptors on endothelial cells and influences the overall inflammatory reaction [71].

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 [72]. 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 [73]. Recently, it has been shown that the HR responsible for the selective recruitment of eosinophils is HR4 [33]. 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 eosinophil chemoattractive ability of histamine is weak, when compared with the potent CCR3-binding chemokines, eotaxin and eotaxin-2 [30, 33, 73, 74]. However, histamine upon activation of HR4 induces enhanced migration of eosinophils towards eotaxin and eotaxin-2 [30, 74]. 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 [33]. Triggering of HR4 also induces chemotaxis of mast cells [32]. Experiments in mice showed that mast cells from wild-type and HR3-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 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 betahistidine (HR1 agonist). In addition, histamine inhibits neutrophil activation, superoxide formation and degranulation via HR2 [75]. Downregulation of NF- κ B, which acts as a potent transcription factor in initiating inflammation, may represent a possible mechanism for H₁ antihistamines to inhibit inflammatory cell accumulation [21]. Low concentrations of H₁ antihistamines, cetirizine and azelastine have been demonstrated to downregulate NF- κ B expression in parallel with inhibition of proinflammatory cytokines [76]. A recent study with histidine decarboxylase-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 [77]. The pretreatment of the nasal mucosa and the conjunctivae

with topical H₁ antihistamines has been shown to locally downregulate the inflammation after an allergen challenge [78, 79]. Decreased macrophage IL-6 production and in DCs, decreased expression of CD86 and decreased IL-8 production were shown [45, 80, 81].

Effects of Histamine and Antihistamines on Airway Function

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 [82–84]. Increased numbers of degranulated mast cells and basophils have been detected in biopsies of asthmatic airways long after an acute asthma attack [85, 86]. The level of histamine in bronchoalveolar lavage fluid has been found to correlate with the severity of asthma and airway hyper-reactivity [87].

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 hyperreactivity, 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 [82]. In the lavage fluid of the patients treated with H₁ antihistamines, decreased levels of proinflammatory cytokines, 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) and plasma exudation along with a reduced symptom score have been found.

The potential efficacy of H₁ antihistamines in asthma has been intensively investigated [88].

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 [89–93]. There are variable effects on allergen challenge or exercise-induced bronchospasm. Only terfenadine with a 3 times recommended dose inhibited early and late bronchoconstrictor response [89]. Terfenadine, cetirizine and loratadine with 2–5 times the usual dose

appeared to improve asthma symptoms in mild seasonal or perennial asthma, but did not block the development of bronchial hyperresponsiveness in seasonal pollen asthma or show apparent benefit in patients with more severe asthma [89–93]. 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 β_2 -agonists and some improvement of airway function [94–98]. Montelukast sodium, a leukotriene receptor antagonist, showed an effect similar to desloratadine [96]. However, an additive efficacy was observed when loratadine was used together with montelukast [97].

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 sensitized mice [98]. Treatment with fexofenadine diminished a Th2-like response that typically follows sensitization and challenge with allergen. Decreased secretion of IL-4 and IL-5, prevention of allergen-specific IgE increase and reduced eosinophilia in lung tissue and bronchoalveolar lavage fluid as well as normalization of airway response to methacholine were observed.

Importantly, in an adoptive transfer model, it was demonstrated that the target mechanism was T cell-mediated. Lung T cells from sensitized mice when transferred to naive recipient mice triggered airway hyperresponsiveness and allergic inflammatory features after allergen challenge. In contrast, naive mice which received T cells from sensitized mice previously treated with fexofenadine showed no such responses to allergen challenge [98]. The inability of T cells from HR₁ antihistamine-treated allergen-sensitized mice to transfer allergic sensitivity to naive recipients resulted from an alteration in the cytokine production profile of the transferred cells. Similar observations were made using desloratadine [99].

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 HR₂ antagonist [80]. 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 a period of 18 months delayed the onset of asthma in some young children with atopic dermatitis [100]. Although H₁ antihistamines clearly show weaker anti-inflammatory effects than corticosteroids, they may in a subtle way

modulate the immune response by modulating the balance between Th1, Th2 and T regulatory 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 [101].

A difference in histamine response between species has been reported, indicating a role for HR2-mediated bronchodilatation in cat, rat, rabbit, sheep and horse [102]. However, in humans, H₂ antihistamines such as cimetidine and ranitidine do not cause bronchoconstriction in normal or asthmatic individuals [103]. Although there is no direct evidence that it plays a role in disease pathogenesis, HR2-mediated gastric secretion is impaired in asthma [104]. Rather, a beneficial effect of H₂ antihistamines given for the treatment of gastritis was observed in asthma [105]. 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 [106]. Apparently, due to the same signal transduction patterns, β_2 -adrenergic receptors may function similar to HR2 in humans [107]. 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 on in future studies.

Conclusion

The recent developments in histamine research have led to a change in the approach to the role of this mediator and its receptors in the allergic inflammatory reactions. Histamine and its different HRs display a complex system with distinct functions of receptor subtypes and their differential expression, which changes according to the stage of cell differentiation as well as microenvironmental influences. The demonstration of histamine-cytokine crosstalk, the ability to newly synthesize and liberate histamine without storage by immunocompetent cells, the discovery of a novel receptor HR4, preferentially expressed on hematopoietic and immunocompetent cells, and the demonstration of T cells as the target for H₁ antihistamine in an adoptive transfer model are the major recent developments which open a new window for therapeutic approaches based on combined anti-HR1/anti-HR4 blockade or on the development of selective dual HR1/HR4 antagonists. Whether such therapies will provide further benefit to suppression of allergic inflammatory responses as observed after HR1 blockade remains to be elucidated.

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