

Histamine Receptors in Immune Regulation and Allergen-Specific Immunotherapy

Marek Jutel, MD, PhD^{a,b,*}, Kurt Blaser, PhD^b,
Cezmi A. Akdis, MD, PhD^b

^a*Department of Internal Medicine and Allergy, Wroclaw Medical University, Traugutta 57,
Wroclaw 50-417, Poland*

^b*Swiss Institute of Allergy and Asthma Research (SIAR), Obere Strasse 22,
CH-7270 Davos, Switzerland*

Histamine (2-[4-imidazole]-ethylamine) is a low-molecular-weight amine synthesized from L-histidine exclusively by histidine decarboxylase (HDC). It is produced by various cells throughout the body, including central nervous system neurons, gastric mucosa parietal cells, mast cells, basophils, and lymphocytes [1,2]. Since its discovery as a 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*, when it was isolated first from liver and lung tissue and then from several other sites. Its smooth muscle stimulating and vasodepressor actions were demonstrated in the first experiments by Dale and Laidlaw [3], who found that the effects of histamine mimicked those occurring during anaphylaxis.

Histamine is involved in the regulation of many physiologic functions, including cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing [2–6]. Within the central nervous system, it affects cognition and memory, the regulation of the cycle of sleeping and waking, and energy and endocrine homeostasis [4]. In human pathology, histamine triggers acute symptoms owing to its rapid activity on vascular endothelium and bronchial and smooth muscle cells, leading to the development of symptoms

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* Corresponding author. Department of Internal Medicine and Allergy, Wroclaw Medical University, Traugutta 57, Wroclaw 50-417, Poland.

E-mail address: mjutel@ak.am.wroc.pl (M. Jutel).

such 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 several chronic phase inflammatory events [1,2]. Consequently, the antihistamines should be viewed as systemic antiallergic agents and immune regulators. This article highlights the relevance of these findings for possible application of histamine signal in tolerance induction during therapeutic modalities such as allergen-specific immunotherapy (SIT).

Histamine receptors

The pleiotropic effects of histamine are triggered by activating on one or several 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 [5].

Histamine receptor 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, lead-

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, dendritic cells, T and B cells	Ca ⁺⁺ , cGMP, phospholipase D, phospholipase A ₂ , NFκB	G _{q/11}
HR2	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, dendritic cells, T and B cells	Adenylate cyclase, cAMP, c-Fos, c-Jun, PKC, p70S6K	Gα _s
HR3	Histaminergic neurons, eosinophils, dendritic cells, monocytes, low expression in peripheral tissues	Enhanced Ca ⁺⁺ , MAP kinase	G _{i/o}
HR4	High expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, dendritic cells, T cells, basophils, mast cells; low expression in nerve cells, hepatocytes, peripheral tissues, spleen, thymus, lung, small intestine, colon and heart	Inhibition of cAMP Enhanced Ca ⁺⁺² , Inhibition of cAMP	G _{i/o}

ing 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 histamine receptor [5]. In reporter gene assays, constitutive HR1-mediated nuclear factor (NF)- κ B activation has been shown to be inhibited by many of the clinically used H1 antihistamines, indicating that these agents are inverse HR1 agonists [5]. Constitutive activity has now been shown for all four histamine receptors [5].

Specific activation or blockade of histamine receptors showed that they differed in expression, signal transduction, or function and improved understanding of the role of histamine in physiology and disease mechanisms. Most positive effects of histamine are mediated by HR1, whereas HR2 is mostly involved in 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 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, and T and B cells [1,2]. Histamine binds to transmembrane domains 3 and 5. Activation of the HR1-coupled $G_{q/11}$ stimulates the inositol phospholipid signaling pathways, resulting in formation of inositol-1,4,5-triphosphate (IP_3) and diacylglycerol and an increase in intracellular calcium [6]. The rise in intracellular calcium accounts for nitric oxide production, liberation of arachidonic acid from phospholipids, and increased cyclic AMP (cAMP). The HR1 also activates phospholipase D and phospholipase A_2 and the transcription factor NF- κ B through $G_{q/11}$ and $G_{\beta\gamma}$ upon agonist binding. Constitutive activation of NF- κ B occurs only through $G_{\beta\gamma}$ [6]. The HR1 is responsible for the development of many symptoms of allergic disease. Targeted disruption of the H1-receptor gene in mice results in impairment of neurologic functions, such as memory, learning, locomotion, and nociception, and aggressive behavior. Immunologic abnormalities have also been described in HR1-deleted mice, with impairment of T- and B-cell responses [7]. 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 adenylate cyclase and phosphoinositide second messenger systems by separate GTP-dependent mechanisms including G_{α_s} and induces activation of c-Fos, c-Jun, PKC, and p70S6 kinase [8]. Studies in different species and several human cells have 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 that consists of four exons on chromosome 20 was demonstrated in 1987 and has recently been cloned [9]. HR3 was initially identified in the central and peripheral nervous system as a presynaptic receptor 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 the mitogen-activated protein kinase (MAPK) pathway.

R- α -methylhistamine and imetit are agonists of HR3, whereas thioperamide and clobenpropit are antagonists. 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 is encoded by a gene containing three exons separated by two large introns located in chromosome 18q11.2. It has 37% to 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 [10]. HR4 shows high expression in 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 [11]. Until now, relatively little has been known about the biologic function of HR4. It seems to be involved in immune regulatory functions including chemotaxis and cytokine secretion [1,2].

Histamine receptors form dimers and even oligomers, which allows cooperation between the histamine receptors and other G protein–coupled receptors; therefore, the effects of histamine upon receptor stimulation can be complex.

Synthesis and metabolism of histamine

The classical cellular sources of histamine are mast cells and basophils, gastric enterochromaffinlike cells, platelets, and histaminergic neurons. Interestingly, cells in the immune system, which do not store histamine, show high HDC activity and are capable of producing high amounts of histamine, which is secreted immediately after synthesis [12]. These cells include platelets, monocytes/macrophages, dendritic cells, neutrophils, and T and B lymphocytes.

Histamine is synthesized by decarboxylation of histidine by L-HDC, which is dependent on the cofactor pyridoxal-5'-phosphate [13]. 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 and T cells), which do not store histamine, show high HDC activity and are capable of producing high amounts of histamine [12]. HDC activity is modulated by cytokines, such as interleukin-1 (IL-1), IL-3, IL-12, IL-18, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage-colony stimulating factor, tumor necrosis factor- α (TNF- α), and calcium ionophore, *in vitro* [14]. HDC activity has been demonstrated *in vivo* in conditions such as lipopolysaccharide (LPS) stimulation, infection, inflammation, and graft rejection [6]. 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 [10]. IgE binding to the Fc ϵ RI on IL-3-dependent mouse bone marrow-derived mast cells induces the expression of HDC through a signaling pathway distinct from that operating during antigen-stimulated Fc ϵ RI activation [15]. More than 97% of the histamine is metabolized in two major pathways before excretion [16]. 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 signal in chronic inflammatory responses

A chronic inflammatory response is one of the hallmarks of allergic diseases. Over the course of pollen season, there may be a tenfold increase in the number of nasal epithelial submucosal mast cells. Histamine released from these cells may not only induce acute allergic symptoms but also be crucial for sustaining this response into a chronic phase, because increasing evidence suggests that it influences several immune/inflammatory and effector functions [2].

Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of proinflammatory cytokines, such as IL-1 α , IL-1 β , and IL-6, as well as chemokines such as RANTES or IL-8, in several cell types and local tissues [17–20]. Histamine induces the CC chemokines, monocyte chemotactic proteins 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. Endothelial cells express functional HR1 and HR2, and increased adhesion molecule expression such as ICAM-1, VCAM-1, and P-selectin has been demonstrated by histamine infusion via HR1 [21–23]. Histamine regulates the expression of its own receptors on endothelial cells and influences the overall inflammatory reaction [24].

Histamine regulates granulocyte accumulation to tissues in distinct ways. Allergen-induced accumulation of eosinophils in the skin, nose, and airways is potentially inhibited by H1 antihistamines [25]. The effect of histamine on eosinophil migration may differ according to the dose. High doses inhibit eosinophil chemotaxis via HR2, whereas low doses enhance eosinophil chemotaxis via HR1 [26]. Recently, it has been shown that the histamine receptor responsible for the selective recruitment of eosinophils is HR4 [27]. Histamine possesses all of the properties of a classical leukocyte chemoattractant (ie, 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 [26–29]. Nevertheless, histamine upon activation of the HR4 induces enhanced migration of eosinophils toward eotaxin and eotaxin-2 [28]. 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 cytokines specific for the differentiation, activation, and survival of eosinophils [27]. Triggering of HR4 also induces chemotaxis of mast cells [30]. Experiments in mice showed that mast cells from wild-type and HR3-deleted mice migrated in response to histamine, whereas mast cells from the HR4-deleted mice did not. 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 owing 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 [31]. 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 [32]. Low concentrations of H1 antihistamines, cetirizine, and azelastine have been demonstrated to downregulate NF- κ B expression in parallel with inhibition of pro-inflammatory cytokines [33]. A recent study with HDC-deficient and mast cell-deficient mice demonstrated that histamine mainly derived from non-mast cells had an essential role in angiogenesis and the generation of inflammatory granulation [34]. Pretreatment of the nasal mucosa and conjunctivae with topical H1 antihistamines has been shown to downregulate inflammation locally after an allergen challenge [35]. Decreased macrophage production of IL-6, as well as decreased expression of CD86 and decreased IL-8 production in dendritic cells, was shown [36,37].

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 lead to a re-evaluation of this approach. Histamine has been found in the airways of asthma patients even during asymptomatic periods [38,39]. An increased number of degranulated mast cells and basophils has been detected in biopsies of asthmatic airways long after an acute asthma attack [40]. The level of histamine in bronchoalveolar lavage fluid (BALF) has been found to correlate with the severity of asthma and airway hyperresponsiveness [41].

Inhaled and intravenous histamine causes bronchoconstriction as one of the first recognized properties, which is inhibited by H1 antihistamines. As a manifestation of airway hyperresponsiveness, asthmatic individuals are more sensitive to the bronchoconstrictor effect of histamine than are normal individuals. In addition, *in vitro* studies have shown increased histamine release in basophils and mast cells obtained from asthmatic subjects when compared with cells obtained from persons without asthma [38]. In lavage fluid of patients treated with

H1 antihistamines, decreased levels of proinflammatory cytokines and mediators (eg, histamine, leukotrienes, prostaglandin), cell adhesion molecules (eg, intercellular adhesion molecules and vascular cell adhesion molecules), cells (eg, eosinophils and neutrophils), and plasma exudation along with a reduced symptom score have been found [42].

The potential efficacy of H1 antihistamines in asthma has been investigated intensively [42]. Inhalation, intravenous, or oral administration of clemastine or chlorpheniramine induces significant bronchodilatation, whereas second-generation H1 antihistamines induce only a limited increase of FEV1 (5% to 10% over baseline) with recommended doses [43,44]. There is variable effect on allergen challenge or exercise-induced bronchospasm. Only terfenadine given in three times the recommended dose inhibited early and late bronchoconstrictor responses [44]. Terfenadine, cetirizine, and loratadine in two to five times the usual dose appeared to improve symptoms in patients with mild seasonal or perennial asthma, but did not block the development of bronchial hyperresponsiveness in seasonal pollen asthma nor show apparent benefit in patients with more severe asthma [43,44]. In patients with concurrent symptoms of allergic rhinitis and asthma, treatment with H1 antihistamine results in a significant decrease in symptoms of rhinitis and asthma, a decrease in the use of beta-2 agonists, and some improvement of airway function [45]. Montelukast sodium, a leukotriene receptor antagonist, showed a similar effect as desloratadine [45].

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 [46]. Treatment with fexofenadine diminished the Th2-like response that typically follows sensitization and challenge with allergen. Decreased secretion of IL-4 and IL-5, prevention of the allergen-specific IgE increase, reduced eosinophilia in lung tissue and BALF, as well as normalization of airway response to metacholine was observed.

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 naïve recipient mice triggered airway hyperresponsiveness and allergic inflammatory features after allergen challenge. In contrast, naïve mice that received T cells from sensitized mice treated before with fexofenadine showed no such responses to allergen challenge [46]. The inability of T cells from HR1 antihistamine-treated allergen-sensitized 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 human lung parenchyma was inhibited by fexofenadine but not by ranitidine, an H2 receptor antagonist [47]. 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. Treatment with cetirizine over period of 18 months delayed the onset of asthma in some young children with atopic dermatitis [48]. Although H1 antihistamines clearly show weaker anti-inflammatory effects than corticosteroids, they may subtly affect the immune response by

modulating the balance among Th1, Th2, and T regulatory cells and suppressing the accumulation of inflammatory cells.

Although previous studies have suggested a basal tone of smooth muscle mediated by histamine binding to HR1, constitutive intrinsic activity of HR1 without any occupation by histamine could be more relevant. Histamine also induces proliferation of cultured airway smooth muscle cells [49].

A difference in histamine response between species has been reported, indicating a role for HR2-mediated bronchodilatation in the cat, rat, rabbit, sheep, and horse [50]. In humans, H2 antihistamines such as cimetidine and ranitidine do not cause bronchoconstriction in normal or asthmatic individuals [51]. Although there is no direct evidence that it has a role in disease pathogenesis, HR2-mediated gastric secretion is impaired in asthma [52]. Histamine may have an important role in modulation of the cytokine network in the lung via HR2, HR3, and HR4, which are expressed in distinct cells and cell subsets. Apparently, owing to the same signal transduction patterns, β 2-adrenergic receptors may function similar to HR2 in humans. The role of histamine and other redundant G protein-coupled receptors in regulation of the immune/inflammatory pathways in the lung will be the focus of future studies.

Histamine signal in the regulation of immune response

Antigen-presenting cells

Dendritic cells are often located near 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 dendritic cells. 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 dendritic cell differentiation, which acts in autocrine and paracrine fashion and modifies dendritic cell markers [53]. Histamine actively participates in the functions and activity of dendritic cell precursors as well as their immature and mature forms (Fig. 1). Immature and mature dendritic cells express all four histamine receptors; however, a comparison of their levels of expression has not yet been performed. 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 [54,55].

In monocytes stimulated with Toll-like receptor-triggering bacterial products, histamine inhibits the production of proinflammatory IL-1-like activity, TNF- α , IL-12, and IL-18, but enhances IL-10 secretion through HR2 stimulation [17,55]. Histamine also downregulates CD14 expression via H2 receptors on

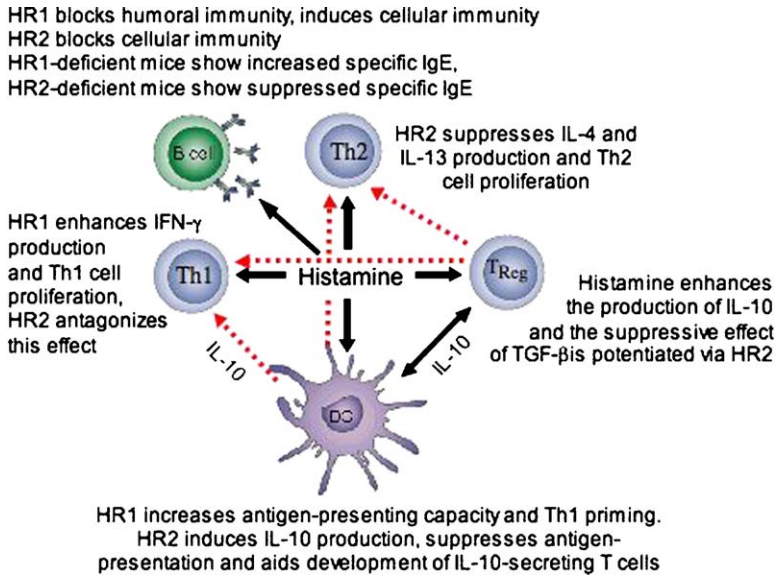


Fig. 1. Histamine regulates monocyte, dendritic cell (DC), T cell, and B cell functions. Monocytes and DCs express all four histamine receptors. Activation of HR1 and HR3 triggers proinflammatory events and increases antigen-presenting cell capacity. HR2 has a suppressive role on monocytes and monocyte-derived 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 in 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 affects 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. Histamine regulates the functions of antigen-presenting cells and T cells. The controlled release of histamine from effector cells of allergy induces IL-10 in dendritic cells (DCs) and suppresses Th1 and Th2 responses through HR2. HR1-deficient mice show increased specific IgE, whereas HR2-deficient mice show suppressed specific IgE production from B cells. IL-10 affects the maturation of DCs to IL-10-producing types, which may further contribute to T regulatory cell generation. DCs express all known histamine receptors. HR1 and HR3 induce proinflammatory activity and increased antigen-presentation capacity; in contrast, HR2 has a suppressive role in DCs. Th1 cells show predominant expression of HR1, whereas Th2 cells show a higher expression of HR2. HR1 induces increased proliferation and IFN- γ production in Th1 cells. HR2 acts as a negative regulator of proliferation, IL-4, and IL-13 production in Th2 cells. HR2 negatively regulates Th1 and Th2 responses, induces IL-10 production, and potentiates the suppressive effect of TGF- β (solid line: activation; dotted line: suppression).

human monocytes [56]. 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 [57].

Histamine induces intracellular Ca^{++} flux, actin polymerization, and chemotaxis in immature dendritic cells owing to stimulation of HR1 and HR3 subtypes. Maturation of dendritic cells results in loss of these responses. In maturing dendritic cells, 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 [58].

T cells and antibody isotypes

Histamine has been shown to intervene in the Th1, Th2, and T regulatory 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 (Fig. 1) [59]. Th1 cells show predominant, but not exclusive, expression of HR1, whereas 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 owing to activation of different biochemical intracellular signals [59]. In mice, deletion of HR1 results in suppression of $\text{IFN-}\gamma$ and dominant secretion of Th2 cytokines (IL-4 and IL-13). HR2-deleted mice show upregulation of Th1 and Th2 cytokines. *Bphs*, a non-major histocompatibility complex-linked gene involved in the susceptibility to many autoimmune diseases, has been identified as the HR1 gene in mice. HR1-deleted mice showed delayed disease onset and decreased disease severity when immunized to develop experimental allergic encephalomyelitis [60]. Histamine stimulation induces IL-10 secretion through HR2 [1,2]. Increased IL-10 production in dendritic cells 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 cells but not on Th2 cells [59].

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 [7], 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 [7]. 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 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 . These findings suggest that HR1 and the related Th1 response may have a dominant role in the suppression of humoral immune response.

The relevance of histamine signal during allergen-specific immunotherapy

The rationale for the use of H1 antihistamines during SIT is diverse and may include the reduction of side effects, which may develop immediately after shots of vaccine, and providing help in the long-term induction of allergen tolerance induced by vaccination. Pretreatment with antihistamines was proposed as early as the 1980s as an effective approach to reduce the side effects of allergen immunotherapy [61]. Several studies have confirmed that administration of high doses of second-generation H1 antihistamines before vaccine shots of insect venom or grass pollen is effective in reducing local allergic reactions and generalized symptoms of urticaria and angioedema [62–64]. Unfortunately, this modality is much less effective in the reduction of more severe systemic symptoms [62–64].

The effect of pretreatment 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 [65]. 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 had a systemic allergic reaction to the re-exposure by either a field sting or a sting challenge, whereas 6 of 21 given placebo did have a reaction. This highly significant difference suggests that H1 antihistamine premedication during the initial dose increase phase may have enhanced the long-term efficacy of immunotherapy and indicates a positive role for histamine in immune regulation during SIT [66]. Similarly, the ETAC (Early Treatment of the Atopic Child) study, a double-blind, placebo-controlled trial, was performed to determine the preventative effect of cetirizine on the development of asthma. The ETAC included 830 children with atopic dermatitis aged 12 to 24 months and showed that treatment with cetirizine reduced the relative risk of developing asthma for children sensitized to grass pollen or house dust mites [67]. These findings indicate the immunoregulatory and anti-inflammatory effects of H1 antihistamines. The underlying mechanisms are not fully elucidated. On one hand, treatment with HR1 antagonists also results in HR2 predominance. Moreover, the expression of HR1 on T lymphocytes is strongly reduced during ultrarush 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 SIT [68]. 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 have an essential role [69,70]. Histamine interferes with the peripheral tolerance induced during SIT in several

pathways. It induces the production of IL-10 by dendritic cells [54]. In addition, histamine induces IL-10 production by Th2 cells [71]. Furthermore, histamine enhances the suppressive activity of TGF- β on T cells [72]. 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. These 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 HR2 might be a more promising approach as compared with the use of H1 antihistamines, thus far, it has not been investigated *in vivo*.

Selective HR2 antagonists have attracted interest because of their potential immune response-modifying activity [73]. 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.

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