Rostrum

Histamine in the immune regulation of allergic inflammation

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Histamine was the first mediator implicated in mechanisms of allergy, asthma, and anaphylactic shock because it has been discovered to mimic several features of these diseases. In addition to its well-characterized effects in the acute inflammatory and allergic responses, it was recently demonstrated that histamine regulates several essential events in the immune response. Histamine affects the maturation of immune system cells and alters their activation, polarization, chemotaxis, and effector functions. Histamine also regulates antigen-specific T_H1 and T_H2 cells, as well as related antibody isotype responses. Histamine binds to 4 different G protein–coupled receptors that transduce signals to cells through distinct pathways. The expression of these receptors on different cells and cell subsets is regulated, and apparently, the diverse effects of histamine on immune regulation are due to differential expression of 4 histamine receptors and their distinct intracellular signals. This article highlights novel discoveries in histamine immunobiology and discusses clinical findings or disease models that indicate immune regulation by histamine. (J Allergy Clin Immunol 2003;112:15-22.)

Key words: *Histamine, histamine receptors, T cells, B cells, dendritic cells, antihistamines, G protein–coupled receptors, allergy, asthma, chemotaxis, antibodies, IgE*

Histamine (2-[4-imodazole]-ethylamine) was discovered as a uterine stimulant in different extracts more than 100 years ago. Its smooth muscle–stimulating and vasodepressor action was demonstrated in the first experiments by Dale and Laidlaw.[1] In 1927, histamine was isolated from liver and lung tissue, followed by several other tissues, demonstrating that it is a natural constituent of the body, and hence the name histamine was coined after the Greek word for tissue, *histos*. Now, almost a century after its discovery, histamine research has provided researchers with intensive knowledge about its metabolism, receptors, signal transduction, and physiologic and pathologic effects. However, the complex interrelationship and cross-talk by histamine and its receptors remain to be elucidated.

Abbreviations used
cAMP: Cyclic adenosine monophosphate
DC: Dendritic cell
HDC: L-Histidine decarboxylase
HR: Histamine receptor
NF: Nuclear factor
OVA: Ovalbumin

SYNTHESIS AND METABOLISM OF HISTAMINE

Histamine is synthesized by decarboxylation of histidine by L-histidine decarboxylase (HDC), which is dependent on the cofactor pyridoxal-5′-phosphate.[2] 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.[3,4] 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.[5,6] HDC activity has been demonstrated in vivo in conditions such as LPS stimulation, infection, inflammation, and graft rejection.[7] 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.[8] 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.[9]

More than 97% of the histamine is metabolized in 2 major pathways before excretion.[10] 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.

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TABLE I. Histamine receptors

Histamine receptors	Expression	Activated intracellular signals	G proteins
HR1	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, neutrophils, eosinophils, monocytes, DCs, T cells, 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 cells, B cells	Adenylate cyclase, cAMP, c-Fos, C-Jun, PKC, p70S6K	$G\alpha_s$
HR3	Histaminergic neurons, eosinophils, DC, 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, heart	Enhanced Ca^{2+}, inhibition of cAMP	$G_{i/o}$

cGMP, Cyclic guanosine monophosphate; *PKC,* protein kinase C; *MAP,* mitogen-activated protein.

HISTAMINE RECEPTORS, AGONISTS, AND ANTAGONISTS

Histamine exerts its effects by activating histamine receptors (HRs), of which 4 subtypes (HR1, HR2, HR3, and HR4) are recognized (Table I). All of these receptors belong to the G protein–coupled receptor family, comprising 7 transmembrane domains, NH2-terminal glycosylation sites, and phosphorylation sites for protein kinases. The superfamily of 7-transmembrane G protein–coupled receptors is the largest and most diverse group of membrane-spanning proteins.[11] Within all identified human genes, approximately 1000 encode G protein–coupled receptors. Many established G protein–coupled receptor systems have been successfully exploited by the pharmaceutical industry to become the target for approximately 40% of the currently available drugs.[11] Specific activation or blockade of HRs has led to a tremendous increase in the knowledge of the roles of histamine in physiology and disease mechanisms.

In the studies to find HR blocking agents, classical models of G protein–coupled receptors require the occupation of receptors by an agonist to initiate activation of signal transduction pathways. Recently, the expression of G protein–coupled receptors in recombinant systems revealed a constitutive spontaneous receptor activity that is independent of receptor occupancy by an agonist.[12] 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 through the HR1. An inverse agonist (antagonist in the old terminology) 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 through HR1.[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 H_1-antihistamines, indicating that these drugs are inverse HR1 agonists.[13] Constitutive activity has now been shown for all 4 HRs.[13] In addition to 4 membrane receptors, histamine binds to some intracellular receptors, such as cytochrome p450 and cytochrome c and high-affinity lipocalins isolated from saliva of ticks.[14]

Histamine receptors were first distinguished into HR1 and HR2 by Ash and Schild in 1966. The $G_{q/11}$-coupled HR1 encoded on chromosome 3 in humans is responsible for many symptoms of allergic disease. Activation of the HR1-coupled $G_{q/11}$ stimulates the inositol phospholipid signaling pathways, resulting in formation of inositol-1,4,5-triphosphate and diacylglycerol and an increase in intracellular calcium content.[15] In addition, HR1 activates phospholipase D and phospholipase A_2. More recently, HR1 has also been shown to activate the transcription factor NF-κB.[16]

The gene encoding HR2 is located on chromosome 5. HR2 is coupled to both adenylate cyclase and phosphoinositide second messenger systems by means of separate guanosine triphosphate–dependent mechanisms, including $G\alpha_s$, and also induces activation of c-Fos, c-Jun protein kinase C, and p70S6 kinase.[17] Studies in different species and several human cells demonstrated that inhibition of characteristic features of the cells by primarily cyclic adenosine monophosphate (cAMP) formation dominates in HR2-dependent effects of histamine.

Human HR3 encoded on chromosome 20 was demonstrated in 1987 and has been cloned recently.[18] HR3 has been identified in the central and peripheral nervous system as presynaptic receptors controlling the release of histamine and other neurotransmitters. 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 pathway. R-α-methylhistamine and imetit are agonists of HR3, and 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.[19] Dysregulation of

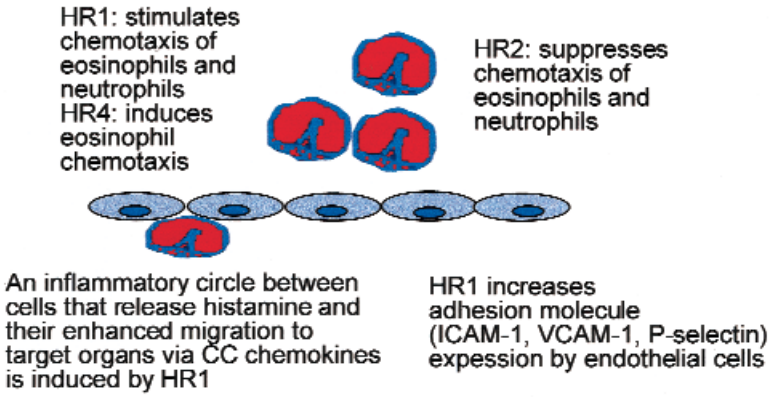

FIG 1. Histamine regulates inflammatory cell adhesion and chemotaxis. Histamine enhances adhesion molecule expression on endothelial cells. HR1 activates and induces the chemotaxis of eosinophils and neutrophils. HR2 inhibits the chemotaxis of eosinophils and neutrophils. HR4 also plays a role in eosinophil chemotaxis.

this feedback loop might lead to excessive inflammatory responses and suggests a novel therapeutic approach by using HR3 agonists.

Human HR4, which is encoded by chromosome 18, has 37% to 43% homology to HR3 (58% in the transmembrane region). HR4 is functionally coupled to the G protein $G_{i/o}$, inhibiting forskolin-induced cAMP formation like HR3.[20] 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.[20] Both basophils and mast cells express HR4 mRNA.[21] Related to high homology between the 2 receptors, presently available HR3 agonists and antagonists are also recognized by HR4.[20]

IMMUNE REGULATION BY HISTAMINE IN ALLERGIC INFLAMMATION

The interaction of histamine with HR1 mediates a variety of effects, such as vasodilatation, bronchial smooth muscle contraction, mucus secretion, and pruritus, which lead to bronchial obstruction, increased vascular permeability, nasal blockade, sneezing, and itchy wheals and flares in urticaria.[22] Although the classical effects of histamine are emphasized in allergy, an increasing amount of evidence suggest that it influences several immune-inflammatory and effector functions.[23]

Histamine in the pro-inflammatory activity, adhesion, and migration of inflammatory cells

Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of pro-inflammatory cytokines, such as IL-1α, IL-1β, and IL-6, as well as chemokines like RANTES or IL-8, both in several cell types and in local tissues (Fig 1).[24-27] Histamine induces the CC chemokines monocyte chemotactic protein 1 and 3, RANTES, and eotaxin in explant cultures of human nasal mucosa through HR1, suggesting a prolonged inflammatory cycle in allergic rhinitis between the cells that release histamine and their enhanced migration to nasal mucosa.[28] Endothelial cells express functional HR1 and HR2, and increased adhesion molecule expression, such as intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and P-selectin was demonstrated by histamine infusion through HR1.[29-31] Histamine regulates the expression of its own receptors on endothelial cells and influences the overall inflammatory reaction.[32]

Histamine regulates granulocyte accumulation to tissues in distinct ways. Allergen-induced accumulation of eosinophils in the skin, nose, and airways is potently inhibited by H_1-antihistamines.[33] The effect of histamine on eosinophil migration differs according to the dose. Whereas high doses inhibit eosinophil chemotaxis through HR2, low doses enhance eosinophil chemotaxis through HR1.[34] Recently, HR4 and its dominant role on eosinophil chemotaxis was also implied.[35] The role of histamine on neutrophil chemotaxis is studied in human subjects by means of histamine infusion, subcutaneous injection, and inhalation.[36] Inhibition of neutrophil chemotaxis is demonstrated because of HR2 triggering, which was mimicked by impromidine (HR2 agonist) but not by betahistine (HR1 agonist). In addition, histamine inhibits neutrophil activation, superoxide formation, and degranulation through HR2.[37]

Downregulation of NF-κB, which acts as a potent transcription factor in initiating inflammation, might represent a possible mechanism for H_1-antihistamines to inhibit inflammatory cell accumulation.[38] Low concentrations of the H_1-antihistamines cetirizine and azelastine have been demonstrated to downregulate NF-κB expression in parallel with inhibition of pro-inflammatory cytokines.[39] A recent study with HDC-deficient and mast cell–deficient mice demonstrated that histamine mainly derived from nonmast cells plays an essential role in angiogenesis and the generation of inflammatory granulation.[40]

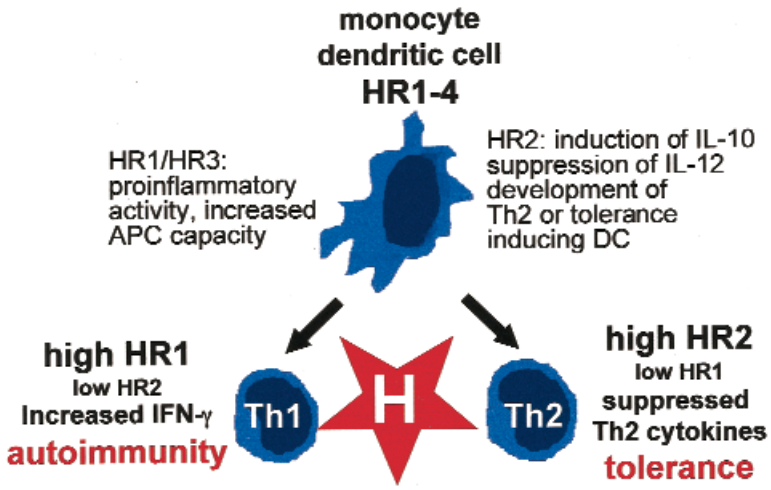

FIG 2. Histamine regulates monocytes, dendritic cells, and T cells. Monocytes and dendritic cells express all known HRs. HR1 and HR3 induce pro-inflammatory activity and increased antigen-presenting cell capacity, whereas HR2 plays a suppressive role on monocytes and monocyte-derived DCs. T_H1 cells show predominant, but not exclusive, expression of HR1, whereas T_H2 cells show upregulation of HR2. Histamine induces increased proliferation and IFN-γ production in T_H1 cells. T_H2 cells express predominantly HR2, which acts as the negative regulator of proliferation and IL-4 and IL-13 production. Histamine enhances T_H1-type responses by triggering HR1, whereas both T_H1- and T_H2-type responses are negatively regulated by HR2. These distinct effects suggest roles of HR1 and HR2 on T cells for autoimmunity and peripheral tolerance, respectively.

Regulation of antigen-presenting cells by histamine

DCs are professional antigen-presenting cells that mature from monocytic and lymphoid precursors and acquire DC1 and DC2 phenotypes, which in turn facilitate the development of T_H1 and T_H2 cells, respectively. Endogenous histamine is actively synthesized during cytokine-induced DC differentiation, which acts in autocrine and paracrine fashion and modifies DC markers.[3] Histamine actively participates in the functions and activity of DC precursors, as well as their immature and mature forms (Fig 2). Immature and mature DCs express all 4 HRs; however, comparison of their levels of expression has not yet been studied.[41-44] In the differentiation process of DC1 from monocytes, HR1 and HR3 act as positive stimulants that increase antigen-presentation capacity, pro-inflammatory cytokine production, and T_H1 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 T_H2 cells.[45-47]

In monocytes stimulated with Toll-like receptor–triggering bacterial products, histamine inhibits the production of pro-inflammatory IL-1–like activity, TNF-α, and IL-12, but enhances IL-10 secretion, through HR2 stimulation.[24,47,48] Histamine induces intracellular Ca^{++} flux, actin polymerization, and chemotaxis in immature DCs as a result of 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 through HR2.[46]

Histamine regulates T cells and antibody isotypes

It has been demonstrated that differential patterns of HR expression on T_H1 and T_H2 cells determine reciprocal T-cell responses after histamine stimulation (Fig 3).[49] T_H1 cells show predominant, but not exclusive, expression of HR1, whereas T_H2 cells show increased expression of HR2. Histamine enhances T_H1-type responses by triggering HR1, whereas both T_H1- and T_H2-type responses are negatively regulated by HR2 as a result of activation of different biochemical intracellular signals.[49] In mice deletion of HR1 results in suppression of IFN-γ and dominant secretion of T_H2 cytokines (IL-4 and IL-13). HR2-deleted mice show upregulation of both T_H1 and T_H2 cytokines. In addition, IL-3 stimulation significantly increases HR1 expression on T_H1, but not on T_H2, cells. Moreover, it has been shown that histamine stimulation induced IL-10 secretion through HR2.[50] Increased IL-10 production in both DCs and T cells might account for an important regulatory mechanism in the control of inflammatory functions through histamine.

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-trinitrophenyl-Ficoll is decreased,[51] 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.[49] HR1-deleted mice produced high OVA-specific IgG1 and IgE in comparison with that produced by wild-type mice. In contrast, HR2-deleted mice showed decreased serum levels of

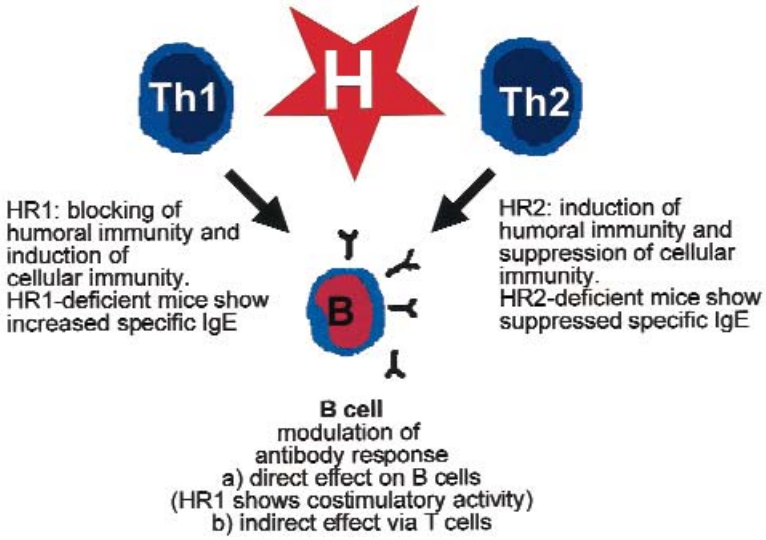

FIG 3. Histamine modulates antibody production. Histamine directly causes B-cell antibody production as a costimulatory receptor on B cells. HR1 predominantly expressed on T_H1 cells might block humoral immune responses by enhancing T_H1-type cytokine IFN-γ. In contrast, HR2 enhances humoral immune responses. 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.

OVA-specific IgE in comparison with that seen in 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 T_H1 response might play a dominant role in the suppression of humoral immune response.

CLINICAL EVIDENCE FOR IMMUNE REGULATION BY HISTAMINE

Histamine and HR2 in peripheral T-cell tolerance

Considerable evidence has emerged to suggest that histamine participates in the immune regulation of the inflammatory response in several diseases. 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.[52] Although multiple suppressor factors, including contact-dependent or contact-independent mechanisms, might be involved, IL-10 and transforming growth factor β predominantly produced by allergen-specific T cells play an essential role.[52,53] Histamine interferes with the peripheral tolerance induced during specific immunotherapy in several pathways. Histamine induces the production of IL-10 by dendritic cells.[46] In addition, histamine induces IL-10 production by T_H2 cells.[50] Furthermore, histamine enhances the suppressive activity of transforming growth factor β on T cells.[54] All 3 of these effects are mediated through HR2, which is relatively highly expressed on T_H2 cells and suppresses IL-4 and IL-13 production and T-cell proliferation.[49] Apparently, these recent findings suggest that HR2 might 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.[55] After an average of 3 years, 41 patients were re-exposed to honeybee stings. Surprisingly, none of 20 patients who had been given HR1 antihistaminic premedication but 6 of 21 patients 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 antihistamine premedication during the initial dose-increase phase might have enhanced the long-term efficacy of immunotherapy. Expression of HR1 on T lymphocytes is strongly reduced during ultrarush immunotherapy, which might lead to a dominant expression and function of tolerance-inducing HR2. This indicates a positive role of histamine in immune regulation during specific immunotherapy.[56]

Selective HR2 antagonists have attracted interest because of their potential immune response–modifying activity.[57] 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.

Histamine and HR1 in autoimmunity

The role of histamine in autoimmune reactions was often questioned in the past.[58,59] Because of inadequate model systems and reagents, the roles and mechanisms of histamine in autoimmunity remained unclear. Recently, the gene encoding HR1 was identified as *Bphs*, which represents an autoimmune disease locus.[60] HR1 differs at 3 amino acid residues in autoimmune orchitis– and allergic encephalomyelitis–susceptible and resistant mice. T cells from HR1-deficient mice produce significantly less IFN-γ associated with significantly less severe autoimmune disease. Apparently, the IFN-γ–inducing capacity of HR1 on T cells might play a role in tissue injury mechanisms of several other diseases of allergic, infectious, and autoimmune origin, as well as allograft rejection.

Effects on airway function: Are some of them immunologic?

Inhaled and intravenous histamine cause bronchoconstriction as one of the first recognized properties of histamine, which is inhibited by HR1 antagonists. Antigen-induced IgE-mediated mast cell degranulation in the lung causes an increase in both cAMP and cyclic guanosine monophosphate.[61] The rise in cyclic guanosine monophosphate is blocked by H_1-antihistamines, suggesting that this effect is mediated by HR1. Histamine stimulates phosphoinositide hydrolysis,[62] increases the concentration of inositol-1,4,5-triphosphate, and increases intracellular Ca^{++}.[63] Histamine contracts both the central and peripheral airways in vitro, with a more potent effect on peripheral airways. As a manifestation of airway hyperreactivity, asthmatic individuals are more sensitive to the bronchoconstrictor effect of histamine than normal individuals. Although previous studies suggested a basal tone of smooth muscle mediated by histamine binding to HR1, currently constitutive intrinsic activity of HR1 without any occupation by histamine could be more relevant. Histamine also induces proliferation of cultured airway smooth muscle cells.[64]

A difference in histamine response between species has been reported, indicating a role for HR2-mediated bronchodilatation in cats, rats, rabbits, sheep, and horses.[65] However, in human subjects H_2-antihistamines, such as cimetidine and ranitidine, do not cause bronchoconstriction in normal or asthmatic individuals.[66,67] Although there is no direct evidence that it plays a role in disease pathogenesis, HR2-mediated gastric secretion is impaired in asthma.[68] Rather, a beneficial effect of H_2-antihistamines given for the treatment of gastritis was observed in asthma.[69] In addition, recent studies suggest that histamine might play an important role in the modulation of the cytokine network in the lung through HR2, HR3, and HR4, which are expressed in distinct cells and cell subsets.[44,70] Apparently, because of the same signal transduction patterns, β_2-adrenergic receptors might function similar to HR2 in human subjects.[71] 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 malignancies

Histamine might play a major role in the growth of normal and malignant tissue as a regulator of proliferation and angiogenesis. Specific HRs have been identified on the surface of bone marrow cells, immune competent cells, endothelial cells, fibroblasts, and also malignant cells. This has prompted tumor treatment by specific HR agonists and antagonists.[72] Results from such studies are currently accumulating and suggest that the HR2 antihistamines have potential beneficial effects in the treatment of certain malignant diseases, either alone or in combination with other drugs.[73] The beneficial effect of HR2 antihistamines as adjuvant single drugs to reduce trauma-, blood transfusion–, and sepsis-induced immunosuppression has indicated combined treatment regimens in major surgery, particularly in patients operated on for malignant diseases. Two different mechanisms are probably acting concordantly: direct inhibition of tumor cell proliferation by the HR2 antihistamines and activation of the local immune response characterized by IFN-γ production. These findings might help to elucidate the possibility of a rationally designed antihistamine strategy in tumor therapy.

CONCLUSION

Historical data and recent studies indicate an essential role of histamine in the immune dysregulation of allergy, asthma, autoimmunity, and malignancies. Histamine and so far 4 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. Although contrasting findings have been reported, HR1 activates the immune system cells, potentiating a pro-inflammatory activity for higher migration to inflammation area, as well as increased effector functions. HR2, on the other hand, seems to be a potent suppressor of inflammatory and effector functions. Limited data on the role of HR3 and HR4 in immune regulation provide a temptation to speculate on their HR1-potentiating and HR2-antagonizing activity, as evidenced by associated signal transduction elements.

More importantly, other G protein–coupled receptors engaged with the same signal transduction pathways as HRs might be responsible for a redundancy with agonistic and antagonistic activities of histamine. The generation of HR1-, HR2-, and HDC-deficient mice brought new insights to the understanding of interactions of the immune system cells and histamine. Studies on several disease models with these mice will help to better understand where and how histamine and relevant receptors play a role in the complexity of immune regulation by histamine.

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