

Mechanisms of allergic diseases

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Regulation of the immune response and inflammation by histamine and histamine receptors

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Histamine is a biogenic amine with extensive effects on many cell types, including important immunologic cells, such as antigen-presenting cells, natural killer cells, epithelial cells, and T and B lymphocytes. Histamine and its 4 receptors represent a complex system of immunoregulation with distinct effects dependent on receptor subtypes and their differential expression. These are influenced by the stage of cell differentiation, as well as microenvironmental influences, leading to the selective recruitment of effector cells into tissue sites accompanied by effects on cellular maturation, activation, polarization, and effector functions, which lead to tolerogenic or proinflammatory responses. In this review we discuss the regulation of histamine secretion, receptor expression, and differential activation of cells within both the innate and adaptive immune responses. It is clear that the effects of histamine on immune homeostasis are dependent on the expression and activity of the 4 currently known histamine receptors, and we also recognize that 100 years after the original identification of this biogenic amine, we still do not fully understand the complex regulatory interactions between histamine and the host immune response to everyday microbial and environmental challenges. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

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Terms in boldface and italics are defined in the glossary on page ■■■.

Abbreviations used

cAMP:	Cyclic adenosine monophosphate
DC:	Dendritic cell
EPAC:	Exchange protein directly activated by cyclic adenosine monophosphate 1
Foxp3:	Forkhead box protein 3
GPCR:	G protein-coupled receptor
HDC:	Histidine decarboxylase
HR:	Histamine receptor
ICAM-1:	Intercellular adhesion molecule 1
IP3:	Inositol 1,4,5-trisphosphate
MAPK:	Mitogen-activated protein kinase
NK:	Natural killer
PKA:	Protein kinase A
PLC:	Phospholipase C
PRR:	Pattern recognition receptor
SOCS3:	Suppressor of cytokine signaling 3
TLR:	Toll-like receptor
Treg:	Regulatory T

The immune response is governed by strict effector and regulatory processes that normally result in protection from infection and tolerance of innocuous environmental antigens. However, in patients with inflammatory diseases, the activated immune response results in a chronic proinflammatory state characterized by activated innate pathways with aberrant expansion and polarization of T_H1, T_H2, **T_H9**, **T_H17**, **T_H22**, or regulatory T (Treg) lymphocyte populations. Thus the identification of appropriate controlling factors that augment protective immune responses while limiting tissue damage is urgently required. Many cellular metabolites influence immune reactivity (eg, retinoic acid), and one factor that is receiving more attention as an immunomodulator is histamine (2-[4-imidazolyl]-ethylamine).^{1,2}

This short-acting endogenous amine, which is widely distributed throughout the body, is synthesized by histidine decarboxylase (HDC), which decarboxylates the semiessential amino acid L-histidine. Originally discovered at the beginning of the 20th century, histamine was first chemically synthesized by Windaus and Vogt in 1907. Soon afterward, in 1910, the first biological functions of histamine were reported by Dale and Laidlaw. These authors recognized that histamine had the ability to mimic smooth muscle-stimulating and vasodepressor action previously observed during anaphylaxis.^{3,4} Histamine was isolated from liver and lung tissue in 1927 before purification from other tissues succeeded and gave histamine its name based on the Greek word *histos*, which means tissue.

Histamine is produced by a wide variety of cell types and is involved in many physiological functions, including cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing.⁵⁻⁹ Mast cells, basophils, gastric *enterochromaffin*-like cells, and histaminergic neurons are the best-described cellular sources of histamine, but other cell types, such as platelets, dendritic cells (DCs), and T cells, can also express HDC after stimulation. HDC expression is influenced by cytokines, including IL-1, IL-3, IL-12, IL-18, GM-CSF, macrophage colony-stimulating factor, and TNF- α .^{1,10} Mast cells and basophils store large quantities of histamine, which is released on degranulation in response to immunologic and nonimmunologic stimuli. However, other cell types, such as DCs and lymphocytes, do not store histamine intracellularly but secrete it after synthesis.¹¹⁻¹³ Although histamine is well recognized for its effects in the immediate-type hypersensitivity response (ie, increased vascular permeability, smooth muscle contraction, activation of *nociceptive* nerves, wheal-and-flare reaction, and itch response), the pathological relevance of increased histamine levels at diseased sites is less well understood in other disorders, such as inflammatory bowel disease and irritable bowel syndrome.^{14,15} Indeed, histamine might negatively or positively influence parasitic or bacterial infections.^{16,17} Cells of both the innate and adaptive immune response can be regulated by histamine.^{5,6,18-20} These cells express histamine receptors (HRs) and under certain circumstances can 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 tolerogenic or proinflammatory responses.

In this review we discuss HR expression and differential activation of cells within both the innate and adaptive immune response and the signal transduction mechanisms that influence their activity.

HRS

The regulatory nature of histamine in immunology is dependent on its binding to 4 subtypes of HRs, which are named chronologically in order of their discovery: H1R to H4R.

Although it had been suspected for a long time that more than 1 HR existed based on functional observations, the first definitive differentiation between H1R and H2R was described in 1966,²⁰ H3R was identified in 1999,²¹ and the fourth receptor was designated H4R in 2000.²² These 4 receptors belong to the rhodopsin-like family of G protein-coupled receptors (GPCR), which are differentially expressed in numerous cell types and contain 7 transmembrane domains.^{7,23} Receptor diversity has been confirmed by means of pharmacologic studies and by their low protein homology, which is suggestive of their evolution from different ancestral genes.²⁴ For example, H1R and H2R are approximately 35% homologous, whereas H3R and H4R are more closely related. HR antagonists can be cross-reactive with other GPCRs (eg, anticholinergic effects of H1R antagonists), which is a potential explanation for the side effects, such as obesity and appetite stimulation, of the H1R antagonists. However, this has not been proved *in vivo*. In addition, there is cross-reactivity between antipsychotic and tetracyclic antidepressants with H1R and H4R, although the same study showed that the current H1R antagonists did not bind H4R, at least not with high affinity.²⁵

H1R

H1R is encoded by an intronless gene, which is located on chromosome 3p25 and contains 487 amino acids. The 56-kd H1R is expressed by a broad range of cell types, including neurons, airway and vascular smooth muscle cells, hepatocytes, chondrocytes, endothelial cells, DCs, monocytes, neutrophils, and T and B cells.²⁶⁻²⁹ H1R gene expression can be upregulated by IL-3, IL-4, and histamine.³⁰ H1R activation results in airway and vascular smooth muscle cell contraction, increased vascular endothelial cell permeability, synthesis of prostacyclin and platelet-activating factor, and release of von Willebrand factor and *nitric oxide*.^{29,31,32} Typical immediate hypersensitivity responses of allergic reactions, such as redness, itching, and swelling, are the result of H1R activation. Rhinorrhea, bronchoconstriction, anaphylaxis, conjunctivitis, and urticaria are important peripheral H1R-mediated effects, whereas central associated H1R effects include the regulation of food and water intake, convulsion,

GLOSSARY

AQUAPORIN: Proteins that function as transmembrane water channels.

CD25: Binds to IL-2, also known as IL-2 receptor α chain.

CPG: An unmethylated DNA motif located on bacteria and DNA viruses that is a ligand for TLR9.

ENTEROCHROMAFFIN: Epithelial cells of the intestinal mucosa that stain especially with chromium salts. They often contain serotonin.

IL-2: A cytokine that promotes clonal T-cell proliferation, as well as acting as a growth factor for regulatory T cells. IL-2 is also involved in activation of multiple other immune cells, including natural killer cells.

LANGERHANS CELLS: A subset of dendritic cells found in the epithelia and skin draining lymph nodes. Because of their long cytoplasmic processes, Langerhans cells occupy as much as 25% of the surface area of the epidermis, even though they constitute less than 1% of the cell population.

NITRIC OXIDE: A factor released from endothelial cells that causes vasodilation by relaxing vascular smooth muscle cells.

NOCEPTIVE: Responsive to a painful or injurious stimulus.

PARIENTAL CELL: A cell in the gastric mucosa that secretes hydrochloric acid.

PLASMACYTOID DENDRITIC CELLS (DCs): A type of DC with a distinct histologic morphology that can produce high levels of type I interferon. They are thought to play special roles in antiviral host defense and autoimmunity.

SPLICE VARIANTS: Single-base mutations resulting in a base change at or near an mRNA splice junction, resulting in skipped exons or premature truncation of the protein.

T_H9: A T_H2-related family of lymphocytes that produce high levels of IL-4 and IL-9.

T_H17: A T_H family induced by IL-23 and IL-6 that is involved in defense against extracellular bacteria.

T_H22: A population of lymphocytes found in the skin of a variety of inflammatory dermatologic conditions, such as psoriasis and atopic dermatitis. They are thought to play a role in wound healing.

TOLL-LIKE RECEPTOR 3 (TLR3): A TLR located on endosomal membranes that binds to double-stranded RNA from viruses.

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attention, and sleep regulation.^{27,31,33} H1R signaling can antagonize or amplify H2R-mediated responses depending on the time and context of receptor activation.^{34,35} Murine H1R knockout models have revealed significant immunologic (impairment of T- and B-cell responses), metabolic, and behavioral abnormalities.³⁶⁻³⁸

H2R

The human H2R is a 40-kd 359-amino-acid protein encoded by an intronless gene located on chromosome 5q35.5, and human H2R shows a high sequence homology (83% to 95% identity) to other species (guinea pig, mouse, rat, and dog).^{39,40} Similar to H1R, expression of H2R is found in a variety of tissues and cells, including the brain, gastric *parietal cells*, smooth muscle cells, T and B cells, DCs, and cardiac tissue. H2R exhibits spontaneous and constitutive activity.⁴¹ In contrast to H1R, the absence of histamine can promote downregulation of H2R in a tissue-specific manner.⁴² As mentioned above, H2R can antagonize certain H1R effects; for example, H2R is responsible for relaxation of smooth muscle cells in the blood vessels, uterus, and airways. In addition, H2R can modulate a range of immune system activities, such as mast cell degranulation, antibody synthesis, T_H1 cytokine production, and T-cell proliferation.^{6,43,44} Murine H2R knockout mice display defects in gastric and immune-regulatory functions,⁴⁵ as well as selective cognitive defects associated with impairments in hippocampal long-term potentiation⁴⁶ and abnormalities in nociception.⁴⁷

H3R

The third HR, H3R, is a 70-kd 445-amino-acid protein, and its gene, containing 4 exons, is located on chromosome 20q13.33.⁴⁸ Initially, this receptor was identified for its ability to regulate the release of histamine and other neurotransmitters and therefore was classified as a presynaptic autoreceptor in the peripheral and central nervous system.⁴⁹ Uncommon features of H3R include its high degree of constitutive activity *in vivo*^{50,51} and the large number of *splice variants*.^{52,53} The majority of naturally occurring splice variants have similar pharmacologic properties as the full-length protein; however, splice variants with altered or loss of functionality have also been described. H3R is important in the sleep-wake cycle, cognition, homeostatic regulation of energy levels, and inflammation.⁴⁹ These findings were confirmed with H3R knockout mice, which showed altered behavior and locomotion.⁵⁴ In addition, H3R knockout mice display a metabolic syndrome characterized by hyperphagia, late-onset obesity, and increased insulin and leptin levels.^{55,56} Other studies demonstrated that knockout of H3R resulted in an increased severity of neuroinflammatory diseases, and these mice show enhanced expression of macrophage inflammatory protein 2, IFN-inducible protein 10, and CXCR3 by peripheral T cells.⁵⁷ Human safety and pharmacokinetic studies with H3R antagonists (eg, GSK239512) have been completed, but phase II/III clinical studies have yet to be reported (clinicaltrials.gov).

H4R

H4R is the most recently identified HR, and its gene contains 3 exons and 2 introns on chromosome 18q11.2 encoding the 390-amino-acid human H4R. Mouse, rat, and guinea pig H4R are

68%, 69%, and 65% homologous, respectively, to human H4R, with human and guinea pig H4R displaying higher affinity for histamine than rat and mouse H4R.⁵⁸ H4R exhibits molecular and pharmacologic properties that are similar to those of H3R. However, in contrast to H3R, the expression of H4R within the bone marrow and by leukocytes, including neutrophils, eosinophils, mast cells, DCs, T cells, and basophils, has been described.^{59,60} H4R is emerging as an important receptor for the chemoattraction of immunologically relevant cells, such as eosinophils, mast cells, neutrophils, T cells, and DCs, as well as influencing cytokine production by these cells.⁶¹⁻⁶⁵ H4R has also been shown to play a role in nociception, autoimmune disorders, and colon and breast cancer, as well as in allergy.⁶⁶⁻⁶⁹ Animal models using selective H4R antagonists have supported the importance of this receptor in the modulation of inflammatory responses associated with asthma, arthritis, colitis and pruritis.^{70,71}

HR SIGNALING

H1R to H4R are GPCRs, which are a large receptor family (>800 different receptors have been described), and GPCRs have been found in all eukaryotes, including yeasts.^{72,73} These receptors are characterized by an extracellular N-terminal domain followed by 7 transmembrane α -helical domains connected by 3 intracellular and 3 extracellular domains. G protein refers to a protein that is able to bind guanyl nucleosides and has the ability to act as an exchanging factor by catalyzing replacement of the bound guanosine diphosphate by guanosine triphosphate. GPCRs bind diverse ligands, varying in size from small molecules to large proteins, and include light-sensitive compounds, pheromones, hormones, and neurotransmitters. In general, GPCRs are attractive drug targets because of their roles in many different disease states, and approximately 30% of modern medical drugs target this receptor family.⁷⁴ Table I summarizes the expression and signaling cascades described for the 4 HRs.

If no ligand is available, the receptors and G proteins are usually in an inactive state. However, ligand binding promotes association of the GPCR with heterotrimeric G proteins, consisting of α - β - γ subunits, leading to activation of classical and nonclassical intracellular signaling pathways. The classical pathway requires association with specific $G\alpha$ subunits ($G\alpha_q$, $G\alpha_s$, and $G\alpha_{i/o}$), and each $G\alpha$ subunit activates distinct molecular signaling cascades. H1R binding leads to activation of $G\alpha_q$, H2R is coupled to $G\alpha_s$, and H3R and H4R are both activators of $G\alpha_{i/o}$.⁷⁵ Histamine binding to H1R- $G\alpha_q$ results in the activation of phospholipase C (PLC), which cleaves phosphatidylinositol 4,5-bisphosphate into diacyl glycerol and inositol 1,4,5-trisphosphate (IP3). Increased intracellular IP3 binds to IP3 receptors, including calcium channels, in the endoplasmic reticulum, resulting in increased cytosolic calcium levels and leading to a cascade of intracellular changes and activity. In addition, calcium and diacyl glycerol activate protein kinase C, which can phosphorylate other molecules, thus altering their activity.⁷⁶ A recent study showed that H1R-mediated blockade of cell proliferation requires PLC-dependent pathways.⁷⁷ H2R binding and subsequent $G\alpha_s$ activation results in enhanced adenylate cyclase activity, thereby promoting cyclic adenosine monophosphate (cAMP) formation and activation of protein kinase A (PKA). PKA leads to cAMP response element-binding activation, resulting in altered gene expression, whereas PKA can also

TABLE I. HR expression and signaling

Receptor	GPCR α -subunit	Expression	Intracellular signals
H1R	G α_q	Smooth muscle cells, endothelial cells, nerve cells, epithelial cells, neutrophils, eosinophils, monocytes, macrophages, DCs, T and B cells	PLC, PIP2, DAG, IP3, Ca ²⁺ , PKC
H2R	G α_s	Smooth muscle cells, endothelial cells, nerve cells, epithelial cells, neutrophils, eosinophils, monocytes, macrophages, DCs, T and B cells	Adenylate cyclase, cAMP, PKA, CREB, EPAC
H3R	G $\alpha_{i/o}$	Histaminergic neurons, monocytes, eosinophils	Inhibits adenylate cyclase and cAMP, increases Ca ²⁺ levels
H4R	G $\alpha_{i/o}$	Eosinophils, DCs, Langerhans cells, neutrophils, T cells, basophils, mast cells	Inhibits adenylate cyclase and cAMP, increases Ca ²⁺ levels

CREB, cAMP response element-binding; DAG, diacyl glycerol; PIP2, phosphatidylinositol 4,5-bisphosphate.

phosphorylate other protein targets with diverse effects on the cell. In addition, G α_s is also able to open ion channels, such as Na⁺, Ca²⁺, and Cl[−] channels. Induction of cAMP by H2R might be important for histamine-mediated modulation of immune function, but the classical downstream signaling pathway involving PKA might not be involved. Increasingly, cAMP-responsive genes are being described that are regulated in a PKA-independent manner. These genes include neuronal nitric oxide synthase, prostaglandin G/H synthase, *aquaporin*, IL-1 β , IL-6, and suppressor of cytokine signaling 3 (SOCS3).^{78–82} For example, adenylate cyclase activation promotes SOCS3 induction in epithelial cells, which inhibits leptin and soluble IL-6 receptor α /IL-6 trans-signaling complex activation of the Janus kinase/signal transducer and activator of transcription pathway. In the same study it was demonstrated that exchange protein directly activated by cAMP-1 (EPAC1) and not PKA appeared to be necessary for cAMP-mediated activation of CCAAT/enhancer-binding protein family transcription factors resulting in SOCS3 induction.^{82,83} In addition, other PKA- and EPAC1-independent cAMP sensors seem to be responsible for transient activation of extracellular signal-regulated kinase, which is required for subsequent inhibition of cytokine receptor activation of both the Janus kinase/signal transducer and activator of transcription and extracellular signal-regulated kinase signaling pathways.⁸⁴

In contrast to the activation of G α_s , initiation of G $\alpha_{i/o}$ by H3R or H4R binding blocks adenylate cyclase activity and reduces cAMP levels. Activation of type I carotid cells through H3R significantly reduced intracellular cAMP levels, which negatively regulates EPAC, resulting in inhibition of Ca²⁺ release caused by muscarinic receptor activation.⁸⁵

The relevance of nonclassical signaling by the G protein $\beta\gamma$ subunits are not well described for the different HRs, but the $\beta\gamma$ subunits can directly activate mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinase, and Jun.⁷³ The $\beta\gamma$ subunits of histamine-stimulated GPCRs have been shown to activate phosphoinositide 3-kinase, leading to Akt phosphorylation and phosphodiesterase activation, thereby decreasing intracellular cAMP levels.⁸⁶ The nonclassical pathways might be important for histamine-associated functional effects because histamine-induced Akt1 activation has been shown to mediate the junctional permeability changes in endothelial cells.⁸⁷ In addition, H1R activation leads to enhanced transcription of IL-8 through nuclear factor of activated T cells,⁸⁸ and costimulation with TNF- α , IL-1 α , or LPS enhances IL-8 levels when combined with histamine. This effect was blocked by inhibitors of MAPK, nuclear factor

κ B, and PLC, indicating that H1R's effects are mediated by classical and nonclassical pathways.⁸⁹

IMMUNE REGULATION BY HISTAMINE

Histamine exerts multiple opposing or complementary effects on cells with immune, vascular, muscular, neuronal, epithelial, and endocrine function, but for the purposes of this review, we will focus primarily on the regulatory effects of histamine on immune cells.

Histamine's effects on cells of the innate immune system

DCs are potent antigen-presenting cells that are present throughout the body and are central players in initiating and regulating innate and adaptive immune responses. DC survival, activation, maturation, and polarization are largely influenced by local factors within their microenvironment, such as microbial components, cytokines, and metabolic products. DCs shape the functional polarization and differentiation of the reactive T cells into T_H1, T_H2, T_H9, T_H17, and Treg responses by producing cytokines such as IL-12, IL-18, IL-23, IL-11, IL-10, or TGF- β .⁹⁰ The selection of an appropriate cytokine secretion pattern by DCs is dependent on a number of factors but is particularly influenced by the binding of microbial ligands, termed pathogen-associated molecular patterns, to pattern recognition receptors (PRRs), such as *Toll-like receptors* (TLRs) and C-type lectin receptors.^{91,92} DCs are often found in close proximity to degranulated mast cells, particularly at mucosal sites, and can secrete histamine after activation. Although DCs have been shown to express H1R, H2R, H3R, and H4R, it is not definitively established whether the level of HR expression is altered during maturation or whether different DC subsets (eg, myeloid or *plasmacytoid DCs*) preferentially upregulate or downregulate individual HRs after specific microenvironmental cues. DCs exposed to histamine have been shown to upregulate their antigen-presenting capacity and T_H1 polarization through H1R, whereas activation of H2R on DCs preferentially drives IL-10 secretion and, under certain circumstances, promotes T_H2 polarization.^{93–95} H2R activation on human plasmacytoid DCs leads to a significant downregulation of IFN- α and TNF- α secretion after *CpG* stimulation.⁹⁶ In addition, accumulation of plasmacytoid DCs and CD11b⁺ DCs, but not CD8⁺ DCs, in draining lymph nodes is H2R dependent.⁹⁷ Furthermore, histamine reduces the production of nicotinamide adenine dinucleotide phosphate oxidase-derived oxygen radicals by several types of myeloid cells,

an effect mediated by H2R.⁹⁸ In contrast to other DC subsets, *Langerhans cells* within the epidermis seem to be regulated uniquely by histamine because they do not express H1R or H2R.⁹⁹ However, Langerhans cells do express H4R, and human inflammatory dendritic epidermal cells can express H4R after exposure to IFN- γ , which results in the downregulation of CCL2 and IL-12 secretion in an H4R-dependent mechanism.^{100,101} In contrast, murine studies suggest that inhibition of H4R on DCs leads to decreased cytokine and chemokine production, which limited their ability to induce T_H2 responses. Interestingly, certain bacterial strains present within the human diet express the HDC gene and have been shown to release histamine.¹⁰² However, the *in vivo* homeostatic consequences of histamine release by these bacteria has not yet been determined, although it is likely that histamine-producing bacterium could affect the DC response to the bacterial strain itself and other bacterial strains through a bystander effect.

In addition to DCs, TLR stimulation of monocytes is altered by histamine coinubation because secretion of proinflammatory cytokines, such as TNF- α , IL-12, and IL-18, is suppressed, whereas IL-10 secretion is enhanced. This effect is mediated primarily by H2R.^{103,104} In addition, histamine downregulates CD14, intercellular adhesion molecule 1 (ICAM-1), and CD80 expression through H2R on human monocytes. Monocytes stimulated by advanced glycation end products are known to upregulate adhesion molecule expression, but this effect is inhibited by H2R.¹⁰⁵ Macrophages purified from human lung tissue, monocyte-derived macrophages, and DCs express higher levels of H1R compared with precursor monocytes. In contrast, monocyte differentiation into macrophages is associated with downregulation of H2R, whereas differentiation into DCs has no significant influence on H2R expression.¹⁰⁶

Epithelial cells

Human intestinal epithelial cells have been shown to express H1R, H2R, and H4R.¹⁰⁷ Intestinal epithelial cells might be protected from pathogenic bacterial infection as a result of histamine signaling because epithelial cells exposed to histamine have lower numbers of invasive intracellular pathogens *in vitro*, which was mediated in part by the H1R.¹⁰⁸ However, TLR2/NOD2-stimulated mast cells release histamine, which reduced the epithelial barrier function of cocultured gastrointestinal epithelial cells, suggesting that protection of the gastrointestinal mucosa from pathogen invasion might be dependent, in part, on the local concentration of histamine.^{109,110} Low levels of histamine might be protective, whereas higher levels might be detrimental to epithelial protection from infection. In addition, modulation of conjunctival and nasal epithelial cell adhesion molecule expression (eg, ICAM-1) by H1R antagonists suggests that H1R is important for the upregulation of adhesion molecule expression in epithelial cells after allergen exposure.¹¹¹

In addition to their essential role in maintaining barrier function, epithelial cells are essential in the early response to microbial exposure because of their expression of PRRs. H1R activation on pulmonary epithelial cells enhanced expression of TLR3, and stimulation of these cells with the TLR3 ligand poly (I:C) in the presence of histamine resulted in enhanced IL-8 secretion and nuclear factor κ B phosphorylation, suggesting that H1R enhances epithelial cell responsiveness to certain microbial ligands.¹¹² However, it is unknown whether HR activation alters

the epithelial cell cytokine response to other PRR ligands or adherent microbes.

Natural killer cells and histamine

Natural killer (NK) cells are large granular lymphocytes that use a battery of activating and inhibitory receptors to distinguish normal cells from aberrant cells that should be eliminated. Thus activating receptors on NK cells bind their corresponding ligands on target cells to activate NK cells, whereas inhibitory receptors, such as killer cell immunoglobulin-like receptors, interact with specific MHC class I molecules on target cells, with subsequent NK cell inactivation.¹¹³ NK cells express H4R, which promotes chemotaxis of NK cells to histamine.¹¹⁴ Interestingly, histamine in combination with **IL-2** is currently being assessed as a possible immunotherapy for patients with cancer. It is thought that histamine-H2R-dependent inactivation of the nicotinamide adenine dinucleotide phosphate oxidase system protects NK cells from inactivation and thereby allows effector lymphocytes to respond to IL-2 stimulation. In the presence of oxygen radical-producing myeloid cells, coadministration of histamine and IL-2 was shown to trigger efficient NK cell-mediated killing of several types of leukemic cells, including freshly recovered human acute myeloid leukemia blasts, whereas IL-2 alone was less effective.¹¹⁵ In a more recent study, postconsolidation immunotherapy with histamine and IL-2 was shown to be superior to IL-2 alone in the prevention of relapse in patients with acute myeloid leukemia.¹¹⁶ Invariant NK T cells constitute a distinct population of T lymphocytes that are identified by the nonpolymorphic MHC class I-like molecule CD1d. In histamine (ie, HDC) knockout mice, these cells are numerically and functionally impaired, with diminished secretion of IL-4 and IFN- γ after stimulation with the agonist α -galactosylceramide.¹¹⁷ H4R signaling was essential for the histamine effect on invariant NK T-cell cytokine secretion.

Histamine and HRs on granulocytes

Neutrophils, eosinophils, and basophils comprise the cellular family termed granulocytes. It has been demonstrated that histamine regulates granulocyte accumulation to tissues in a number of ways, including allergen-induced accumulation of eosinophils in the skin, nose, and airways, which is inhibited by H1R antagonists.¹¹⁸ The effect of histamine on eosinophil migration is dependent on the dose of histamine examined because high concentrations of histamine inhibit eosinophil chemotaxis through H2R, whereas lower doses enhance eosinophil chemotaxis through H1R.¹¹⁹ In addition, eosinophil recruitment is also influenced by H4R, which enhances the migration of eosinophils toward eotaxin and eotaxin-2.^{61,70} However, the relative chemoattractive effect of histamine is not as strong as other chemoattractive substances, such as the CCR3-binding chemokines.^{61,63,64} In addition, H1R antagonists can modulate the expression of eosinophil adhesion molecules, such as ICAM-1, suggesting that H1R is important for eosinophil migration at multiple levels.¹²⁰ Furthermore, the potential for histamine to act as an eosinophil chemoattractant agent *in vivo* might be augmented by additional factors, such as growth factors or cytokines, such as IL-5, which is the specific cytokine for the differentiation, activation, and survival of eosinophils.⁶⁵ Mast cells that express H4R can also migrate in response to histamine⁶⁴ because murine experiments demonstrated that mast cells from wild-type and H3R-deleted

mice migrated in response to histamine, whereas mast cells from the H4R-deleted mice did not. Thus it seems that chemotaxis of eosinophils and mast cells through histamine is promoted mainly through H4R. These results suggest that combination therapies with H4R and H1R antagonists could provide additional efficacy in dampening the proinflammatory effects of histamine. However, receptor expression by a given cell type is critical because histamine inhibits neutrophil chemotaxis caused by triggering of H2R, whereas neutrophil activation, superoxide formation, and degranulation are also suppressed through histamine binding to H2R.

Role of histamine in adaptive immune responses

T cells. In addition to the effects of histamine on the innate immune system, which could potentially result in altered T-cell polarization, T cells themselves express HRs and are influenced by histamine stimulation. T_H1 cells express relatively high levels of H1R, whereas H2R is preferentially expressed by T_H2 cells. Cytokines such as IL-3 can enhance H1R expression by T_H1 cells, but this is not observed with T_H2 cells.⁶ Histamine affects T_H1 responses by triggering H1R, whereas both T_H1- and T_H2-type responses can be suppressed by HR2 because of activation of different biochemical intracellular signals.¹⁸ HR2 knockout mice display upregulation of both T_H1 and T_H2 cytokines. After triggering of H2R, histamine dose-dependently enhanced TGF- β -mediated suppression of CD4⁺ T cells, which was cAMP/PKA dependent.¹²¹ It has also been shown that histamine, through H2R, can induce IL-10 secretion from T cells.¹²² Increased IL-10 production by T cells might account for an important regulatory mechanism by which histamine suppresses aberrant inflammatory responses. On the other hand, inhibition of H2R by selective antagonists can have stimulatory effects on the immune system. Vaccination models that included H2R antagonists resulted in a more robust CD4⁺ T-cell antigen-specific secretion of IL-4 and IFN- γ , whereas IFN- γ secretion by CD8⁺ T cells was enhanced, suggesting that vaccination against certain infectious microbes might be improved by H2R inhibition.¹²³ In addition, several open-label trials evaluating the use of H2 antagonists for *Verruca vulgaris* reported high response rates, but these results have not been corroborated by more rigorous clinical trials.¹²⁴ Deletion of HR1 in the mouse results in the suppression of IFN- γ secretion associated with enhanced secretion of the T_H2 cytokines IL-4 and IL-13. By using an experimental allergic encephalomyelitis model, disease onset was delayed and disease severity was reduced in HR1-deleted mice.¹²⁵ At the molecular level, H1R activation at the time of T-cell receptor ligation was required for full activation of p38 MAPK, a known regulator of IFN- γ expression. Importantly, re-expression of H1R in CD4⁺ T cells alone was sufficient to fully restore both the IFN- γ production and the experimental allergic encephalomyelitis susceptibility of H1R-deficient mice. These data suggest that histamine stimulation of H1R-expressing CD4⁺ T cells regulates early T-cell receptor signals that lead to T_H1 differentiation and autoimmune disease.¹²⁶ In addition, H1R mediates the chemotactic effect of histamine on T cells.¹²⁷ Treg cells express H1R, and activation of H1R by histamine decreases Treg cell suppressive functions, which was associated with decreased expression of CD25 and forkhead box protein 3 (Foxp3).¹²⁸ H4R is expressed by CD4 T cells, but it is currently not known whether H4R is differentially expressed by polarized T-cell subsets. H4R or H2R stimulation of CD8 T cells induced secretion of IL-16, which is a T-cell chemoattractant.

Similarly, selective activation of H4R in murine models induced the migration of CD25⁺Foxp3⁺ Treg cells.^{129,130} The HR expression profile of recently described T-cell lineages, such as T_H9, T_H17, and T_H22 cells, is currently unknown. In addition, it has not been conclusively shown which molecular mechanism or mechanisms are responsible for the preferential induction of T-box transcription factor-positive T_H1 cells, GATA-3⁺ T_H2 cells, or Foxp3⁺ Treg cells by histamine. It is likely that both direct and indirect mechanisms are involved; for example, modulation of cytokine secretion by histamine binding H1R or H2R could be partly responsible for the effects on lymphocyte polarization. Fig 1 summarizes the potential histamine effects on DCs and T-cell subsets.

B cells. Histamine exerts diverse effects on B-cell immunoglobulin secretion, and these effects are different depending on the requirement for T-cell help. Antibody levels to T cell-independent antigens (eg, TNP-Ficoll) are reduced in H1R knockout mice.¹³¹ In addition, histamine enhanced anti-IgM-induced proliferation of B cells, which was abolished in H1R knockout mice, suggesting that H1R signaling plays an important role in responses triggered from B-cell receptors. In contrast, IgG1 and IgE antibody responses to T cell-dependent antigens (eg, ovalbumin) are enhanced in H1R knockout mice, whereas H2R knockout mice showed decreased serum levels of ovalbumin-specific IgE in comparison with wild-type and H1R knockout mice.¹³¹ Thus differential activation of H1R or H2R on B and T cells plays an important role in the suppression or activation of the humoral immune response. However, these were not B cell-specific knockout animals, and therefore the influence of histamine on antibody production could be both direct (ie, on the B-cell itself) and indirect because of abnormal responses of other cell types (eg, DCs or T cells).

HISTAMINE AND INFLAMMATORY DISORDERS

Histamine has been studied in a wide range of inflammatory and infectious disorders, which is not surprising given its multiple effects on the immune system. H1R was identified as the autoimmune disease locus controlling *Bordetella pertussis*-induced histamine sensitization (*Bphs*), suggesting that H1R-dependent IFN- γ secretion might play a role in tissue injury associated with T_H1 responses.¹²⁵ Recently, DC H1R expression was shown to be required for IFN- γ production by CD8 cells, resulting in atopic dermatitis in a murine model.¹³² Interestingly, IL-17⁺ CD8 cells were induced by DCs lacking H1R. Human keratinocytes express H1R, and histamine suppressed CCL17 (a T_H2 chemokine) while enhancing CXCL10 (a T_H1 chemokine) secretion, suggesting that H1R might block T_H2 responses while enhancing T_H1 responses within the skin.¹³³

Histamine plays an important role in the immune response to infectious agents. Sedating first-generation H1R antihistamines and H2R blockers impair optimal innate immune responses in severe murine bacterial sepsis, suggesting that histamine signaling is required for appropriate defense against bacterial infection.¹⁷ In contrast, histamine binding to H1R and H2R increases the susceptibility of mice to infection with *Plasmodium* species, and HDC knockout animals are protected from lethal *Plasmodium* strains.¹⁶ A better understanding of the molecular basis for histamine's effects in infectious disease will lead to new therapeutic opportunities for HR agonists or antagonists, depending on the type of infection.

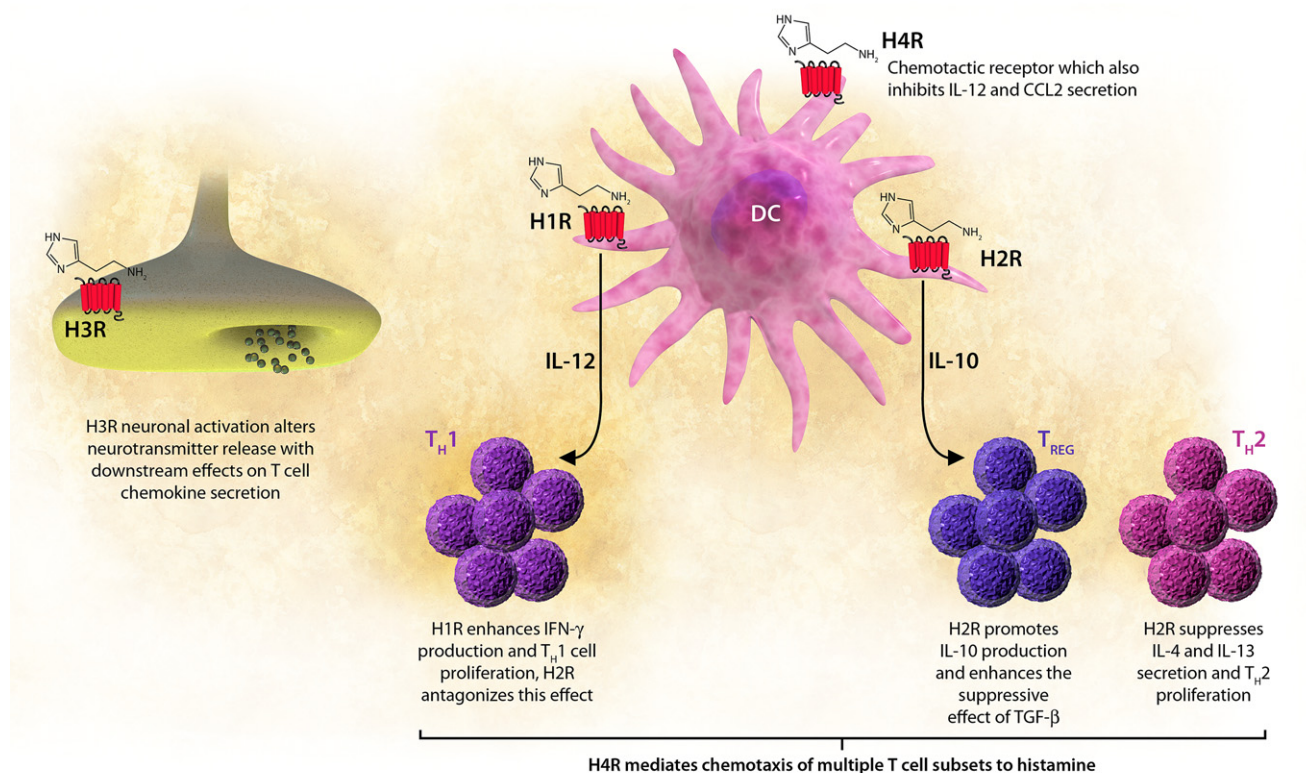


FIG 1. Histamine influences DC migration (H4R) and cytokine secretion, resulting in increased IL-12 (H1R) or IL-10 (H2R) responses. H1R is expressed by T_H1 cells, and histamine further promotes the T_H1 program by enhancing IFN- γ secretion. H2R suppresses both T_H1 and T_H2 functions while promoting the potency of Treg cells. H4R is expressed on certain leukocytes as an important chemotactic receptor. H3R activation on neuronal cells results in altered neurotransmitter release, with subsequent effects on T-cell chemokine release.

The rapid promotion of antigen-specific Treg cells *in vivo* is a key feature protecting the host from allergic and inflammatory disease. This was clearly demonstrated in beekeepers who, during the bee season (associated with multiple bee stings), had increased numbers of allergen-specific IL-10 $^{+}$ T cells with reduced numbers of allergen-specific IL-4 $^{+}$ or IFN- γ $^{+}$ T-cells. The situation was reversed out of season (ie, no bee stings), with higher numbers of IL-4 $^{+}$ and IFN- γ $^{+}$ T cells and reduced numbers of IL-10 $^{+}$ T cells. H2R, but not H1R or H4R, gene expression increased in IL-4 $^{+}$ T cells during the bee season, and stimulation of these cells with histamine resulted in decreased secretion of IL-4 and increased secretion of IL-10, which was H2R dependent.⁴³ CD4 and CD8 T cells isolated from the peripheral blood of asthmatic patients displayed increased expression of both H1R and H2R. *in vitro* cocubation of these cells with histamine decreased the percentage of T cells staining positive for IL-4, IL-13 and IFN- γ , an effect that was not blocked by an H1R antagonist, suggesting that H2R might play a role in this inhibitory effect.¹³⁴ These studies strongly support a growing body of evidence that H2R represents an essential receptor by which histamine promotes peripheral tolerance through the induction of IL-10 and the direct suppression of T-cell proliferation *in vivo*. However, in allergic patients the reasons for the lack of histamine-induced H2R suppression are not clear and might involve genetic, immunologic, and environmental factors.¹³⁵ For example, histamine stimulation of peripheral blood cells from

patients with allergic rhinitis did not result in suppression of IL-4 or IL-13 production.¹³⁴

CONCLUSIONS

The recent developments in histamine research have prompted a re-evaluation of the role that histamine plays in innate and adaptive immune responses. Histamine and its 4 receptors represent a complex system of immunoregulation, with distinct effects dependent on receptor subtype expression. The role for differential expression or activation of HRs on immune-competent cells in patients with chronic inflammatory diseases is surprisingly poorly described to date, and further examination of this potent immunoregulatory network will likely lead to a better understanding of these disorders. In addition, elucidation of the molecular mechanisms underpinning HR cross-talk with immune-relevant pathways (eg, TLR signaling) will identify novel therapeutic targets for inflammatory diseases.

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