

The role of histamine H₁ and H₄ receptors in allergic inflammation: the search for new antihistamines

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Abstract | Histamine has a key role in allergic inflammatory conditions. The inflammatory responses resulting from the liberation of histamine have long been thought to be mediated by the histamine H₁ receptor, and H₁-receptor antagonists — commonly known as antihistamines — have been used to treat allergies for many years. However, the importance of histamine in the pathology of conditions such as asthma and chronic pruritus may have been underestimated. Here, we review accumulating evidence suggesting that histamine indeed has roles in inflammation and immune function modulation in such diseases. In particular, the discovery of a fourth histamine receptor (H₄) and its expression on numerous immune and inflammatory cells has prompted a re-evaluation of the actions of histamine, suggesting a new potential for H₄-receptor antagonists and a possible synergy between H₁ and H₄-receptor antagonists in targeting various inflammatory conditions.

Mast cell

A cell found in connective tissue that contains numerous basophilic granules and releases substances such as leukotrienes and histamine in response to various stimuli, such as bacterial products or specific antigen binding to surface immunoglobulin E.

Histamine was first identified as a mediator of biological functions in the early 1900s and drugs targeting its receptors have been in clinical use for more than 60 years. Histamine exerts a range of effects on many physiological and pathological processes and new roles are still being elucidated. The best characterized roles of histamine are those in inflammation, gastric acid secretion and as a neurotransmitter (FIG. 1). During inflammation, histamine is released from preformed stores in mast cells and basophils. Histamine acts on vascular smooth muscle cells and endothelial cells, leading to vasodilation and an increase in vascular permeability. In the skin, this results in the 'triple response', which is an immediate local reddening due to vasodilation, a wheal due to increased vascular permeability and a flare response due to indirect vasodilation via the stimulation of axonal reflexes¹. In the gastrointestinal system, histamine is essential for gastric acid secretion². Gastrin and vagal stimulation induce enterochromaffin-like cells in the gut to release histamine. This histamine can then act on parietal cells to stimulate H⁺, K⁺ ATPases, leading to the secretion of H⁺ and subsequent acidification that assists in digestive processes. Histamine is also a neurotransmitter in the CNS with a role in sleep–wake cycles, appetite, learning and memory³. It is produced in a subset of neurons in the tuberomammillary nucleus of the hypothalamus and its effects are transmitted widely to other regions of the brain.

These effects have led to the development of drug therapies for allergy, gastric ulcers, motion sickness and insomnia and have been so successful and widespread that the word antihistamine has entered the common lexicon. However, histamine has also been postulated to be involved in other conditions. For example, histamine is increased in bronchoalveolar lavage fluid from patients with allergic asthma and this increase negatively correlates with airway function^{4–9}. An increase in histamine levels has been noted in the skin and plasma of patients with atopic dermatitis^{10,11} and in chronic urticaria^{12,13}. Histamine levels are also increased in multiple sclerosis¹⁴ and in psoriatic skin¹⁵. Both plasma and synovial fluid of patients with rheumatoid arthritis and plasma of patients with psoriatic arthritis have increased histamine levels^{16,17}. For all of these conditions, the traditional antihistamines are generally regarded to be ineffective, leading to the conclusion that histamine is not involved in their pathology. However, it is now known that the diverse biological effects of histamine are mediated through four different histamine receptors, including the most recently described histamine H₄ receptor. The antihistamines that are currently used in the clinic have little, if any, affinity for the H₄ receptor and, as outlined in this Review, this receptor has been shown to function in inflammatory responses *in vitro* and *in vivo*. This emerging role for the H₄ receptor and recent data on

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Wheal and flare

The characteristic immediate reaction to an injected allergen in a skin test, in which an irregular blanched wheal appears, surrounded by an area of redness (flare). First described by Lewis in 1927 and attributed as a response to histamine.

the H_1 receptor in animal models suggest that the role of histamine in conditions such as asthma and chronic pruritus (itch) should be reassessed.

Histamine receptors

All of the receptors for histamine are of the G-protein-coupled receptor (GPCR) family and share conserved motifs common to other monoamine GPCRs. Despite sharing certain key residues that are involved in activation and histamine binding, overall, the receptors have surprisingly low sequence homology, ranging from

16–35% at the protein level. Although other histamine receptors share a high degree of homology across species, this is not true for the H_4 receptor for which the homology ranges from 65–72%, which translates into substantial differences in histamine affinity^{18–20}. As indicated, all these receptors signal through coupling with and activating specific G-proteins (TABLE 1). H_1 receptors couple to G_q proteins leading to phospholipase C activation, inositol phosphate production and calcium mobilization²¹. H_2 receptors activate G_{α_s} and increase cyclic AMP formation²¹. H_3 receptors mediate their function through $G_{\alpha_{i/o}}$ proteins, leading to inhibition of cAMP formation, enhancing calcium mobilization and activating mitogen-activated protein kinases (MAPKs) and ion channels²². In primary cells, activation of the H_4 receptor appears to be mainly coupled to pertussis-toxin-sensitive $G_{\alpha_{i/o}}$ proteins, which signal through increases in intracellular calcium. However, in H_4 receptor transfected cells inhibition of cAMP can also be observed²³. Activation of MAPKs and the transcription factor AP-1 have also been reported^{24,25}. All of the receptors have been shown to have constitutive activity in transfected cells^{21,23}, therefore opening up the possibility that inverse agonists may have different properties to those of neutral antagonists.

H_1 receptors are expressed on multiple cell types including endothelial cells and smooth muscle cells, where they mediate vasodilation and bronchoconstriction. Antagonists of H_1 receptors, such as diphenhydramine and loratadine (FIG. 2), have been used for many years in the treatment of allergic inflammatory responses. In addition, H_1 receptors mediate many of the CNS effects of histamine, such as sleep–wake cycles, with the first generation of H_1 receptor antihistamines having sedative effects due to penetration across the blood–brain barrier. Reduced locomotor activity, exploratory behaviour, cognitive functions, pain sensation and feeding behaviour are observed in H_1 receptor-deficient mice²⁶.

The discovery of functions of histamine that were not antagonized by H_1 receptor antihistamines led to the proposal for the existence of two histamine receptors²⁷, which was proven by the development of selective ligands for the second receptor, H_2 (REF. 28). Similar to H_1 receptors, H_2 receptors are also expressed on many cell types and one of the main functions of the H_2 receptor is the mediation of gastric acid release. This has led to the development of H_2 receptor antagonists such as cimetidine and ranitidine (FIG. 2) for the treatment of gastric acid disorders.

Evidence for the existence of a third histamine receptor (H_3) was based on actions of histamine that were not blocked by H_1 or H_2 receptor antagonists²⁹, but the sequence was not discovered until many years later³⁰. In particular, it was found that histamine inhibited its own release and could also inhibit the release of other neurotransmitters. The receptor mediating this response was identified as the H_3 receptor, which acts as a presynaptic autoreceptor and is expressed primarily in the nervous system playing a role in central and peripheral neurotransmission. Although H_3 receptor ligands are not currently in clinical use, several, including thioperamide and clobenpropit, have been used extensively as research

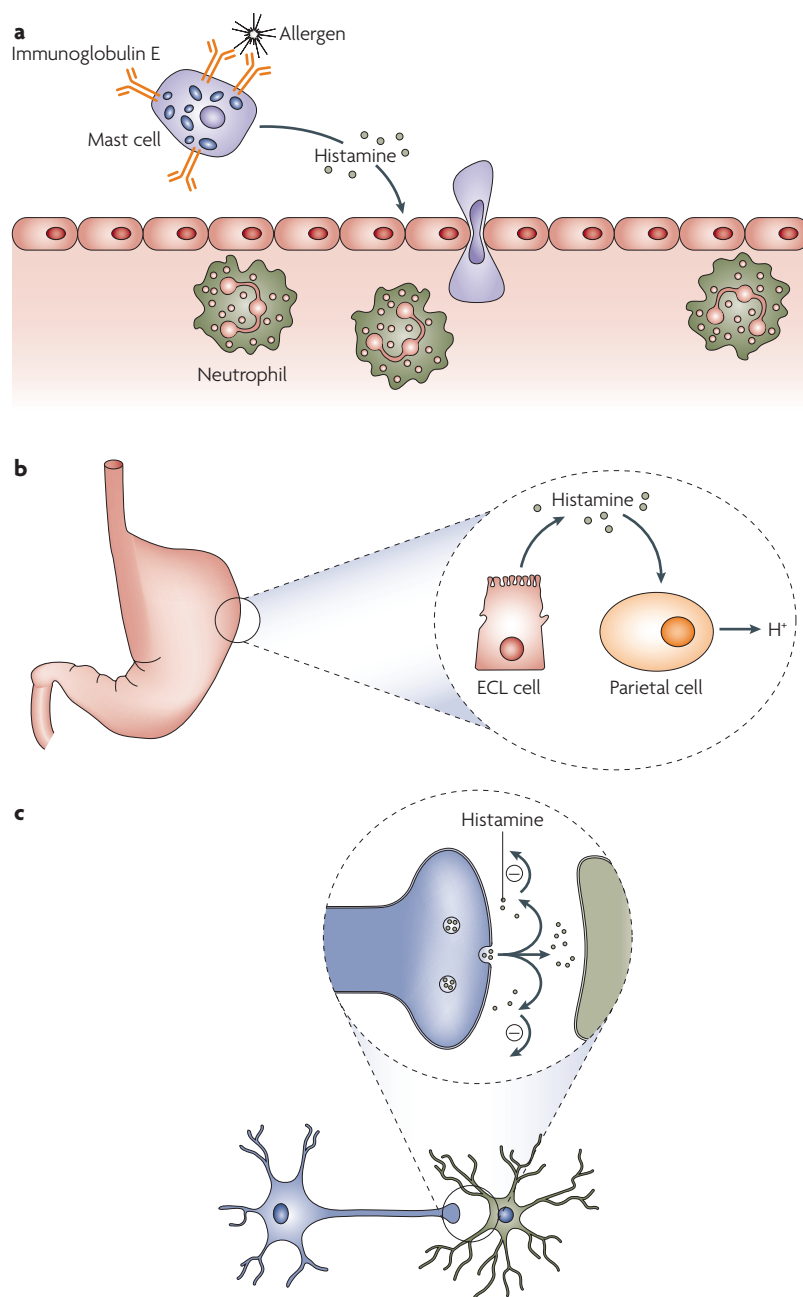


Figure 1 | The major classical physiological roles of histamine. a | Histamine has long been known to be a major mediator of inflammation. **b** | Histamine is also released in the gut by enterochromaffin-like cells (ECL) where it then acts on parietal cells to increase acid secretion. **c** | In addition, histamine is stored by neurons and can be released to act as a neurotransmitter both in the central and peripheral nervous system.

Table 1 | Comparison of different histamine receptors*

Characteristic	H ₁	H ₂	H ₃	H ₄
Best characterized function	Acute allergic reactions	Gastric acid secretion	Neurotransmitter modulation	Immunomodulator
G-protein coupling	G α_q	G α_s	G $\alpha_{i/o}$	G $\alpha_{i/o}$
Major signalling pathway	Increases in Ca ²⁺	Increases in cAMP	Inhibition of cAMP	Increases in Ca ²⁺
Histamine pK _i	4.2	4.3	7.8	8.1
Diphenhydramine pK _i	7.9	>10,000 [‡]	<5	<5
Loratadine pK _i	6.8	ND	ND	<5
Cetirizine pK _i	8.0	ND	ND	<5
Fexofenadine pK _i	8.3	ND	ND	<5
Ranitidine pK _i	<4	7.1	<5	<5
Cimetidine pK _i	<5	6.2	<5 [§]	<5
Thioperamide pK _i	<5	<4	7.3	7.2
JNJ 777120 pK _i	<5	>4.5	5.3	8.4

*All pK_i values (negative log of the apparent dissociation constant) are from REF. 39 except where noted. [‡]From REF. 195. [§]From REF. 34. cAMP, cyclic AMP; ND, not determined.

Antihistamines

Drugs that block the action of histamine and most commonly used to designate histamine H₁ receptor antagonists. In general, first-generation antihistamines are classified as having CNS activity; second-generation antihistamines have little or no activity in the CNS.

Chronic urticaria

An inflammatory skin condition associated with chronic pruritus. Often the result of an autoimmune reaction to self-immunoglobulin E that causes degranulation of mast cells.

Monoamine GPCR

A monoamine G-protein-coupled receptor (GPCR) is a receptor whose ligand contains one amino acid; for example, serotonin, dopamine, noradrenaline or histamine.

Eosinophil

A white blood cell with a physiological role in the destruction of parasites. Eosinophils are strongly implicated in allergic inflammation with an ability to release an array of cytotoxic mediators.

tools. There are reports of clinical trials with H₃ receptor antagonists, but all appear to be in very early stages³¹. However, these antagonists are considered to have utility in treating cognition disorders, obesity, insomnia, and myocardial ischaemic arrhythmias²². Recently, it has been shown that H₃ receptors may be involved in blood–brain barrier function and therefore play a role in neuroinflammation³².

In contrast to the other histamine receptors, the H₄ receptor was discovered via a genomic approach based on searches using the H₃ receptor sequence^{33,34}. However, there were previous results suggesting a non-H₁, H₂ or H₃ receptor on eosinophils^{35–37}, although it was not recognized at the time as a fourth receptor. Compared with the H₁ and H₂ receptors, the H₄ receptor has a more selective expression pattern being found mainly in cells of haematopoietic origin, in particular dendritic cells, mast cells, eosinophils, monocytes, basophils and T cells. Most ligands that target the H₁ and H₂ receptors have little affinity for the H₄ receptor (TABLE 1). In particular, H₁ receptor antagonists that are most commonly used for the treatment of allergy, such as diphenhydramine, cetirizine, desloratadine and fexofenadine, have shown no inhibition of the H₄ receptor at concentrations of up to 10 μ M^{38,39}. One study⁴⁰ reported that several H₁ receptor ligands had affinity for the H₄ receptor; however, these results have not been confirmed in other studies and should be treated with caution⁴¹. By contrast, some H₃ receptor ligands and H₂ receptor agonists are also potent ligands for the H₄ receptor³⁹. Furthermore, recent work has characterized a small number of selective H₄ receptor ligands such as JNJ 777120 that have been useful for determining some of the physiological functions of the receptor³⁹. There is one report⁴² of CCL16 binding to the H₄ receptor, but this has not been confirmed in

other laboratories (R.L.T., unpublished observations). Although there is still much work to be done to uncover the function of the H₄ receptor, it has been implicated in mast cell, eosinophil and dendritic cell chemotaxis, as well as cytokine production from T cells and dendritic cells. In addition, *in vivo* work has implicated the receptor in mediating inflammatory and pruritic responses^{43–48}. These recent discoveries have prompted a reassessment for the role of histamine in immune and inflammatory responses and, in particular, the relative roles of the H₁ and H₄ receptors in mediating the function of histamine.

Histamine and the inflammatory response

In general, it has been found that many cells involved in inflammatory responses express H₁, H₂ and H₄ receptors. Therefore, histamine can have varying and sometimes counteracting effects on a particular cell depending on the concentration used and which histamine receptors are activated. Furthermore, receptor levels may change during different stages of cell development or under pathophysiological conditions and could vary among species. For example, H₁ receptor expression increases on *in vitro* differentiation of monocytes into macrophages⁴⁹, and inflammatory stimuli can upregulate the expression of H₄ receptors in monocytes⁵⁰. Clearly, an understanding of receptor regulation is important in relation to chronic conditions in humans. The following section will discuss the effects of histamine on different cells involved in the inflammatory response (BOX 1).

Mast cells. Mast cells and basophils are generally thought to be the major sources of histamine and can themselves be modulated by histamine as they express H₁, H₂ and H₄ receptors, although how this varies between different mast-cell types is not yet clear^{51–53}. In particular, it has been shown that histamine acting through H₄ receptors can induce chemotaxis of murine mast cells *in vitro*⁵¹ and lead to changes in tissue localization *in vivo*⁴³, effects that may be related to the reported redistribution of mast cells to the epithelial lining of the nasal mucosa in rhinitic responses to allergens^{54,55}. Furthermore, activation of H₄ receptors in human mast-cell precursors can synergize with other chemoattractants such as CXCL12 (REF. 53). Histamine does not appear to have any direct effect on mast-cell degranulation^{51,56}. There are many other reports of the effects of H₁ receptor antagonists on mast cells, but these results may be due to off-target effects (BOX 2). H₂ receptors in mast cells can have various effects including inhibition of histamine release and modulation of cytokine production^{57–59}. There are also reports of H₃ receptor function on mast cells, but many of these activities may be attributed to the H₄ receptor, as the ligands used are not particularly selective and studies have reported that H₃ receptor expression is not detected in some types of mast cells^{51,52}.

Eosinophils. As for mast cells, histamine, via H₄ receptors, at low concentrations can induce chemotaxis of human eosinophils and can enhance the effects of other chemotactic agents^{35,60,61}. At higher concentrations (>1 $\times$ 10^{–6} M),

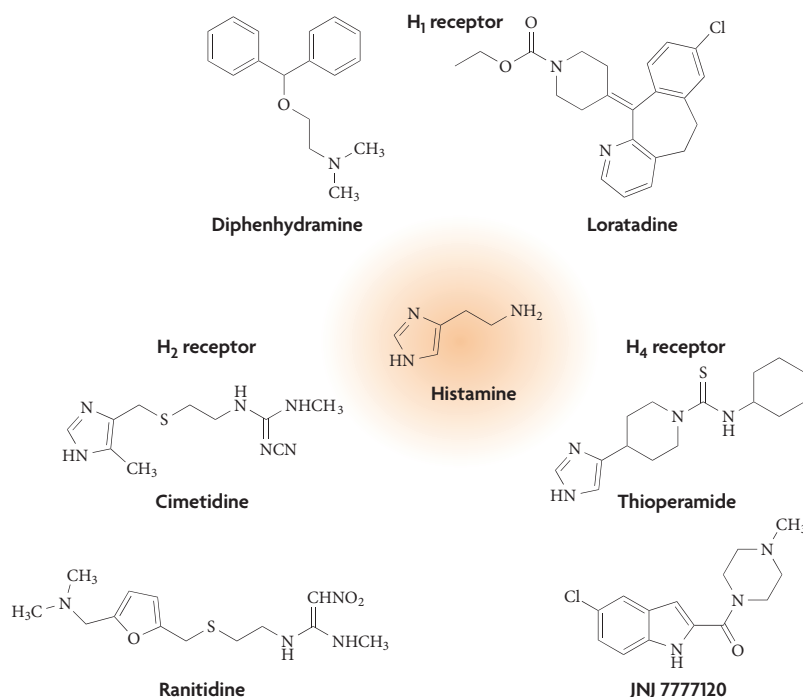


Figure 2 | Representative histamine receptor ligands.

Dendritic cell

An antigen-presenting leukocyte that is found in the skin, mucosa and lymphoid tissues and initiates a primary immune response by activating T lymphocytes and secreting cytokines.

Monocyte

A circulating, phagocytic white blood cell with the ability to release numerous inflammatory cytokines, such as tumour necrosis factor- α (TNF α) and interleukin 6. Monocytes can differentiate into tissue macrophages.

T-cell

A lymphocyte that matures in the thymus and has the ability to recognize specific peptide antigens through the receptors on its cell surface. Subdivided into CD4⁺ (T-helper) and CD8⁺ (T-cytotoxic) T cells.

Chemotaxis

The characteristic movement of a cell along a chemical concentration gradient formed by a chemokine or other chemotactic substance.

T_H2 cell

A CD4⁺ T-helper cell that is strongly implicated in the pathogenesis of allergic disease.

H₂ receptors are activated and histamine-induced chemotaxis is weakened^{62,63}. Histamine can also stimulate adhesion molecule upregulation and actin polymer reorganization by H₄ receptors^{60,61}. Histamine can induce superoxide production⁶⁴ and complement receptor upregulation⁶⁵ in human eosinophils and these effects are mediated by H₁ receptors. An H₁ receptor antagonist, loratadine, attenuates platelet activating factor (PAF)-induced chemotaxis and superoxide production at concentrations that are consistent with its H₁ receptor affinity⁶⁶. However, there are also reports of other H₁ receptor antagonists such as fexofenadine, olopatadine and ketotifen having effects on eosinophils, but the concentrations needed suggest that these may not be H₁ receptor-mediated^{67,68}.

Dendritic cells. Another cell type on which histamine exerts various effects are dendritic cells, which express H₁, H₂ and H₄ receptors. As for mast cells and eosinophils, histamine can induce chemotaxis of human dendritic cells^{25,69–71}, which is primarily mediated by H₄ receptors with some contribution attributed to H₁ receptors. Cytokine secretion, including inhibition of interleukin 12p70 (IL12p70) and enhancement of IL10 and IL6 production, can be modulated by histamine^{25,45,69–75}. Data suggest that histamine acting on dendritic cells can drive T-helper 2 (T_H2) T-cell polarization in human and mouse cells, which is mediated by H₁ and H₄ receptors^{45,69,72,74,76}. This may be accomplished by inhibiting T_H1 polarizing cytokines such as IL12 and by stimulating cytokines such as IL10 and IL6 that can drive T_H2 responses (FIG. 3). Furthermore, effects of chemokines such as thymus and activation-regulated chemokine (TARC; also known as

CCL17), CCL22, IL10 and macrophage inflammatory protein 1 α (MIP1 α ; also known as CCL3) could also influence T-cell polarization^{45,73,74,77}.

T lymphocytes. Not only does histamine act on dendritic cells to modulate T-cell activity, it can also have direct effects on T lymphocytes, as H₁, H₂ and H₄ receptors are all expressed on CD4⁺ and CD8⁺ T cells. Although T_H1 cells were said to express mainly H₁ receptors and T_H2 cells H₂ receptors⁷⁸, there are now conflicting data from *in vitro* and *in vivo* studies. Similar to other cell types, histamine can induce chemotaxis of human T cells *in vitro* and there is evidence for both H₁ and H₄ receptor involvement^{79,80}. The effect of histamine on T-cell proliferation seems to vary. In some cases histamine has been shown to increase proliferation through H₁ receptors^{78,81–83}, but inhibit proliferation through H₂ receptors^{78,84–86}. In addition, histamine can affect cytokine production by T cells. The production of IL2, IL4, IL13 and interferon- γ (IFN γ) can be inhibited by histamine acting mainly through H₂ receptors^{84,86–95}. By contrast, it appears that IL10 and IL5 can be induced by histamine^{94,96}. Using *in vitro* polarized T cells, histamine inhibits IL4 and IL13 production by T_H2 cells, but stimulates IFN γ production in T_H1 cells, although the differences are small⁷⁸. *In vivo* the story is more complicated with T cells from H₁ receptor-deficient mice showing lower levels of IFN γ and increases in IL13^{78,81,97}. However, one study shows that these cells also produce lower levels of IL2 and higher levels of IL4 (REF. 81), whereas another shows no change in these cytokines⁷⁸. Therefore, it is difficult to determine whether there is true skewing to a T_H2 phenotype in H₁ receptor-deficient animals. T cells from H₂ receptor-deficient animals have increased levels of IFN γ and IL4 suggesting that this receptor plays a general inhibitory role^{78,97}. Sonobe *et al.*⁹⁸ studied the activation of CD4⁺ and CD8⁺ T cells from both H₁ and H₂ receptor-deficient mice and found that CD4⁺ cells from either H₁ receptor or H₂ receptor-deficient mice expressed increased levels of IL4, but lower levels of IL10 and IL2. In CD8⁺ cells, H₁ or H₂ receptor deficiency leads to increases in IFN γ , but lower IL10 and IL2. Furthermore, activation of H₄ or H₂ receptors on human CD8⁺ T cells can lead to IL16 release⁹⁹.

Monocytes and macrophages. Human monocytes have been shown to express H₁, H₂ and H₄ receptors. Histamine inhibits lipopolysaccharide (LPS)-induced production of IL12, IL18 and IL1 and downregulates CD14 expression in human monocytes by H₂ receptors, but enhances LPS-induced IL10 levels^{100–105}. In addition, histamine blocks constitutive monocyte chemoattractant protein 1 (MCP1; also known as CCL2) production by H₄ receptors in human monocytes⁵⁰, and H₁ receptor activation appears to increase β -glucuronidase and IL6 release from human lung macrophages^{106,107}.

Endothelial and epithelial cells. Histamine is an important modulator of barrier function in endothelial and epithelial cells. *In vitro* it can interact with endothelial cells^{108,109} and epithelial cells^{110,111} leading to increases in paracellular permeability. The effects on endothelial cells

Box 1 | Histamine is not just produced by mast cells

Extracellular histamine levels can vary considerably and can reach high levels during generalized allergic reactions. In peripheral tissues, mast cells and basophils are the most well-characterized sources of histamine. Enterochromaffin-like cells and neurons are also known to store histamine for rapid release. In all of these cells, histamine is stored in granules as a preformed mediator that can be rapidly released upon cellular activation. However, the enzyme that synthesizes histamine, histidine decarboxylase (EC 4.1.1.22), is ubiquitously expressed and histamine secretion after *de novo* synthesis has been shown in many cells such as macrophages, dendritic cells, neutrophils and T cells. At times this can complicate the interpretation of *in vitro* studies as the production of endogenous histamine may mask the effects of the addition of more histamine to the culture. This is particularly important for the H_4 receptor, which has a very high affinity for histamine. An example of this is the lipopolysaccharide-induced interleukin 6 (IL6) production from mouse dendritic cells⁴⁵. Addition of histamine has no further effect on this production, although an H_4 receptor antagonist can reduce the IL6 levels. However, it was shown that under these conditions dendritic cells synthesize histamine and, if this is blocked, addition of exogenous histamine does increase IL6 production in a H_4 receptor-dependent manner⁴⁵.

in vivo lead directly to changes in vascular permeability allowing for leukocyte infiltration and oedema formation. Histamine acting through H_1 receptors can also upregulate adhesion molecules on endothelial cells^{112–115} leading to adhesion, rolling and diapedesis of leukocytes such as neutrophils^{113,115–119}. In addition to their role in barrier formation, endothelial and epithelial cells also secrete pro-inflammatory signals that can be mediated by histamine. Activation of H_1 receptors on human endothelial cells stimulates the release of inflammatory stimuli such as IL6, IL8 and prostaglandins, and can synergize with other mediators such as lipopolysaccharide and tumour necrosis factor- α (TNF α)^{112,120–123}. On human epithelial cells it has been shown that H_1 receptors mediate activation and increases in the release of mediators such as IL6, IL8 and granulocyte-macrophage colony-stimulating factor (GM-CSF)^{124–129}.

In summary, the *in vitro* studies support a role for histamine in driving immune and inflammatory responses in numerous cell types. It can control barrier functions and adhesion-molecule expression allowing access to sites of inflammation. It can provide direct chemotactic signals or synergize with other chemotactic agents to direct leukocytes to sites of inflammation. On release, it can amplify inflammatory responses by mediating the release of cytokines, chemokine and lipid mediators from both parenchymal and haematopoietic cells. In addition to innate responses, histamine can also act through dendritic cells and T cells to help orchestrate adaptive responses. Therefore, it is easy to see how histamine can be a major player *in vivo* in immune and inflammatory responses, and can be pathogenic in many diseases. In the remainder of this Review we will focus on two conditions, asthma and pruritus, for which recent work has revealed new roles for histamine and its receptors.

Asthma

The prevalence of asthma is increasing dramatically in the developed world¹³⁰ and is characterized by acute and reversible bronchoconstriction driven by airway inflammation that is mainly eosinophilic in nature¹³¹.

Activation of mast cells and macrophages in the airway mucosa sets off a cycle of events leading to the activation of dendritic cells, the recruitment and activation of T_H2 T cells, and the infiltration of eosinophils and neutrophils^{132,133}. Ongoing inflammation also leads to remodelling of the airways, which further affects lung physiology and function^{134,135}. The drugs that are currently used to treat asthma either target the acute bronchoconstriction, such as inhaled β_2 -agonists, or the underlying inflammation, as with leukotriene modifiers and inhaled corticosteroids^{136,137}.

Antihistamines and asthma. H_1 receptor antihistamines are not currently a front-line treatment for asthma, but the provocative similarity between the physiological effects of histamine and the pathological symptoms of asthma has resulted in an enduring investigation into the possible utility of antihistamines in asthma. Promising results were initially obtained with first-generation antihistamines demonstrating acute bronchodilatory effects in asthmatic patients¹³⁸ and against histamine and allergen-induced bronchoconstriction that appeared independent of their antimuscarinic activity¹³⁹. Despite this, doses that were absent of sedation were ineffective in modulating exercise or naturally occurring asthma¹⁴⁰. Consequently, it was not until the development of more potent and non-sedative second-generation antihistamines in the 1980s that the role of antihistamines in asthma was reappraised.

Although a meta-analysis of properly designed studies ultimately reached an overall conclusion that second-generation antihistamines were ineffective in the treatment of asthma¹⁴¹, some interesting trends were apparent that require further discussion. Notably, doses of antihistamines much greater than those observed to be effective in rhinitis appeared to offer some benefit^{142–146}, and there may be synergy with other concomitant therapies^{147,148}. Overall, the limited clinical efficacy of H_1 receptor antagonists in asthma does not seem to warrant their use over existing steroid-sparing therapies, such as montelukast, although in some instances co-therapy may be useful. Studies in mice are beginning to tease out the possible immunomodulatory role of H_1 receptor antagonists (see below), and may additionally explain the observed prophylactic effects of antihistamines in reducing asthma development in atopic children¹⁴⁹.

The plethora of pro-inflammatory and physiological properties attributed to histamine, such as the fact that histamine levels are rapidly increased in the airways and in plasma¹⁵⁰ correlating with disease severity^{4–9}, makes the general lack of clinical efficacy of H_1 receptor antagonists in the clinical setting perplexing and may indicate a role for other histamine receptors. Activation of the H_2 receptor certainly mimics some pathophysiological aspects of asthma, such as mucus secretion¹⁵¹ and vasodilation¹⁵², but H_2 receptor antagonists have had no efficacy in allergic asthma^{140,153}. The role for H_4 receptors in many cells associated with asthma suggests that it may be involved, but as of yet, no clinical trials with H_4 receptor antagonists have been reported. As the pharmacological actions of histamine on the airways

Endothelial and epithelial cells

Endothelial cells line the closed spaces of the body such as the inside of blood vessels, lymphatic vessels, the heart and body cavities. By contrast, epithelial cells make up the outside layer of cells that covers all open surfaces of the body including the skin and mucous membranes.

Diapedesis

The movement or passage of blood cells, especially white blood cells, through intact capillary walls into surrounding body tissue.

Airway mucosa

A membrane lining the respiratory tract and forming an interface with air. Also contains glands that secrete mucus.

Box 2 | Histamine receptors have varying affinities for histamine

The H_1 and H_2 receptors have a low affinity in the micromolar range, whereas the H_3 and H_4 receptors are high-affinity histamine receptors with affinities of 5–10 nM. However, receptor affinity is not the whole story for agonists, as the concentration of agonist needed to activate a receptor depends on both the affinity for the agonist and the existence of receptor reserves. In general, an increase in the number of receptors expressed will result in increases in agonist potency. Therefore, even though the affinity of the H_1 receptor may be in the micromolar range, it may take much lower amounts to activate the receptor. The converse appears to be true for the H_4 receptor, in which it takes concentrations greater than the ligand affinity to trigger receptor activation. To add further complication, the levels of receptor reserve can vary from species to species, cell type to cell type and even in response to various stimuli.

Selective ligands have been identified for all four of these receptors and are useful tools for dissecting the physiological function of the individual receptors. However, knowledge about the selectivity is not always completely known or has changed with the identification of the H_3 and H_4 receptors. For example, dimaprit and 4-methylhistamine have been used for many years as H_2 receptor agonists, but now it is known that they are also H_4 receptor agonists³⁸. In addition, many H_3 receptor ligands, such as *R*- α -methylhistamine and thioperamide, are also H_4 receptor ligands. Furthermore, when dealing with cells from different species or *in vivo* animal models the selectivity needs to be considered in the species of interest as well as the classification of antagonist, partial agonist and agonist. Finally, there are issues surrounding the concentrations used in dictating outcomes. For example there are many reports of H_1 receptor antagonists inhibiting mast-cell function; however, most of these effects are seen at concentrations many times higher than those needed to block the H_1 receptor and are thought to be mediated by other (receptor-independent) targets¹⁹². One such example, olopatadine, inhibits immunoglobulin E (IgE)-mediated histamine release from human conjunctival mast cells with an IC_{50} of ~600 μ M¹⁹³. However, it blocks histamine-induced phosphoinositide turnover in human conjunctival epithelial cells with an IC_{50} of 10 nM and has an affinity for the H_1 receptor of 30 nM¹⁹³. Such off-target effects have recently been reported for several H_4 receptor agonists¹⁹⁴.

and cells involved in the asthmatic response mimic many of the pathophysiological features of asthma, these observations continue to point to a pathologically relevant role for histamine in the disease.

Histamine receptors in animal models of asthma

Recently, animal models of asthma have yielded further insights into the role of histamine in asthma as well as highlighting the relative contributions of H_1 and H_4 receptors. H_1 receptor antagonists have limited efficacy in the clinic and there are results in some animal models that shed light onto these clinical findings. Two studies in mice have shown that desloratadine can block lung inflammation and bronchial hyperresponsiveness in response to different allergens when given before sensitization^{154,155}. The H_1 receptor antagonist reduces T_H2 responses in the lung and in the periphery as measured by reduced IL5, IL4 and IL13, although there does not appear to be an effect on antibody production. The role of H_1 receptors in asthma models has also been supported in H_1 receptor-deficient mice^{79,156}, which have a similar phenotype to mice treated with desloratadine. One difference, however, is that T_H2 cytokines such as IL4, IL5 and IL13 are reduced in the lung, but they are increased upon restimulation of splenocytes⁷⁹, which suggests that while systemic responses may be skewed towards a T_H2 response, the T_H2 response in the lung is blunted. Bryce *et al.*⁷⁹ show that H_1 receptor deficiency on T cells leads to a reduction in T-cell number in the lung upon allergen

exposure and may account for these lung-specific effects. The difference between the systemic T_H2 effects in knockout mice and in compound-treated mice still remains unexplained, although it could be related to differences in the mouse strain used, or the results in the knockout mice may reflect some developmental defect that cannot be mimicked by short-term compound treatment. However, in relation to treatment of established asthma in humans, the mouse models suggest that treatment with H_1 receptor antagonists would only be effective when the receptor is blocked before sensitization. Indeed, if H_1 receptor antagonists are given to animals at normal therapeutic doses around the time of antigen challenge, they are not effective^{45,155}. However, it has been shown that a high dose of fexofenadine given during the challenge phase and after sensitization can reduce bronchial hyperresponsiveness, lung inflammation and T_H2 cytokines^{157,158}. The effect of fexofenadine appears to be on the T_H2 cells as transfer of T cells from sensitized, untreated mice into naive mice leads to enhanced airway responses and inflammation, whereas those from fexofenadine-treated mice do not^{157,158}. Whether this is due to H_1 receptor antagonism or other non-receptor-mediated anti-inflammatory effects of fexofenadine is unclear, but the results support those found for other H_1 receptor antagonists in human clinical trials (discussed earlier). In total, the data suggest that at normal doses H_1 receptor antagonists may not be effective in established asthma, but if given early in the disease history they may prevent its progression. Furthermore, at high doses there may be therapeutic benefit. Both of these predictions appear to have been borne out in human clinical trials.

The discovery of the H_4 receptor has given investigators new tools to further address the function of histamine and its receptors in asthma. Indeed, H_4 receptor expression and function on mast cells, eosinophils, basophils, dendritic cells and T cells all suggest that this receptor may play a role in the asthmatic response. As the clinically used H_1 receptor ligands have little, if any, affinity for the H_4 receptor^{38,39}, clinical information obtained using these compounds would not be predictive of the role for H_4 receptors in asthma. Indeed, the circumstantial evidence for a role of histamine in asthma, along with the general lack of clinical efficacy of H_1 receptor ligands in the disease may suggest involvement of the H_4 receptor. Although there are no reports of human studies with H_4 receptor antagonists, the receptor does appear to play a role in a mouse model of asthma. As for H_1 receptors, H_4 receptor-deficient mice or those given H_4 receptor antagonists during sensitization have reduced lung inflammation and a reduction in T_H2 and inflammatory cytokines⁴⁵. Furthermore, there is a reduction in antigen-specific antibody responses, which suggests a role for H_4 receptors in the initial priming of the immune system. However, in contrast to some of the H_1 receptor antagonists, H_4 receptor antagonists given during the allergen challenge phase of the model are equally effective to those given during sensitization⁴⁵. The effects seen at both the sensitization and challenge phase of the model appear to be due to a crucial role for

Bronchial hyperresponsiveness

A symptom of asthma: an increase in sensitivity to airway-narrowing stimuli. This is often assessed experimentally, in humans and animals, by the measurement of airway function after inhalation of methacholine or histamine.

Sensitization

The immunization phase in experimental immune models in which animals are rendered reactive to specific antigens by administration of the antigen, normally in conjunction with an adjuvant. Specific T-cell and B-cell antibody responses ensue.

T_H2 cytokines

Proteins such as interleukin 4 (IL4), IL5 and IL13 that are produced by T_H2 cells and have a central role in key allergic responses, such as immunoglobulin E production, eosinophilia, mucus production and bronchial hyperresponsiveness.

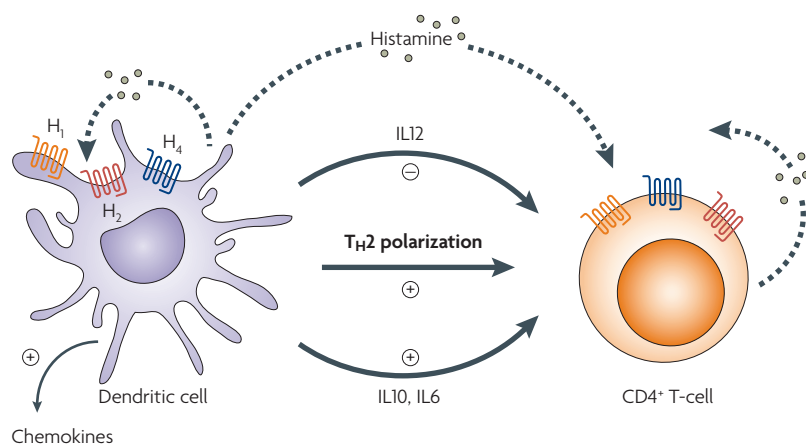


Figure 3 | The effects of histamine on dendritic cell and T-cell interactions. Histamine acting on dendritic cells can drive T helper 2 (T_H2) T-cell polarization. This may be accomplished by inhibiting T_H1 polarizing cytokines such as interleukin 12 (IL12) and by stimulating cytokines such as IL10 and IL6 that can drive T_H2 responses. Furthermore, effects on chemokines such as thymus and activation-regulated chemokine (TARC; also known as CCL17), CCL22 and macrophage inflammatory protein 1 α (MIP1 α) could also influence this. In addition both dendritic cells and T cells can produce histamine when stimulated and this can act in an autocrine or paracrine manner.

H_4 receptors on dendritic cells in the proper education or priming of T_H2 -type T cells. Restimulation of splenocytes or lymphocytes showed a reduction in T_H2 and inflammatory cytokines upon blocking H_4 receptor activation, but no effect on proliferation⁴⁵. Also of significance is that the *in vivo* effects of H_4 receptor antagonists were independent of mast cells, showing that these cells were not the source of histamine in this model. *In vitro* data⁴⁵ suggest that histamine production by dendritic cells may be important in activating H_4 receptors; however recent data have also suggested that neutrophils may be a major source of histamine in the lung¹⁵⁹. The dual H_4/H_2 receptor agonist, 4-methylhistamine, has been shown to reduce airway hyperreactivity and inflammation when given by an inhaled route in a similar mouse model of asthma, which is thought to be due to the recruitment of regulatory T cells⁸⁰.

Therefore, although evidence exists for a role of histamine in driving asthmatic responses (FIG. 4), there is little evidence for clinical efficacy of H_1 receptor antagonists in the management of the disease. However, their use at high doses or early in the disease history to prevent progression is supported by recent animal data and may be warranted. Furthermore, H_4 receptors may account for other functions of histamine that are not blocked by H_1 receptors. In the future, H_4 receptor antagonists may prove beneficial for the relief of asthma symptoms and could perhaps work in synergy with H_1 receptor antagonists.

Pruritus

Pruritus or itch is an unpleasant and potentially debilitating symptom that is associated with numerous dermatological disorders. The mechanisms underlying itch are complex and poorly understood, and it has been classified into various categories on the basis of mechanism, clinical diagnosis and treatment. For the purpose of this Review, itch

associated with atopic dermatitis and idiopathic chronic urticaria are particularly relevant considering the reported increase in histamine in these diseases^{160,161}. However, autoimmune, neurological, metabolic and psychological disorders, without an obvious allergic or histaminergic component, may also exhibit pruritic dermatoses.

The neurological pathways causing itch have only recently been described with the identification of dedicated itch-sensing C-fibres in the periphery¹⁶² and histamine-specific spinal neurons projecting into the thalamus of the brain¹⁶³, which appear to define an itch-specific pathway (FIG. 5). Dorsal root ganglion neurons have been shown to express H_1 receptors¹⁶⁴ and exhibit H_1 receptor-dependent firing in response to histamine^{164,165}. Similar expression of H_4 receptors has not yet been demonstrated on these itch-sensing neurons, but its existence on other peripheral neurons has been reported^{166,167}. As will be discussed later, pruritic responses in mice that are induced by intradermally administered selective H_4 receptor agonists may indicate their existence⁴⁶.

Numerous pruritogenic mediators released in the periphery can directly activate the itch-sensitive C-fibres by specific receptors on the nerve terminal or, alternatively, they can act indirectly by releasing pruritic mediators from other cells. Endogenous mediators of pruritus in the skin include amines, proteases, neurokinins, cytokines, cannabinoids and opioids, as recently reviewed¹⁶⁸. The relative importance of the individual mediators no doubt varies with the specific disease, but a major source of many of these mediators in allergic conditions are mast cells, which are intimately associated with peripheral nerve fibres in the skin^{169,170} and accumulate in many pruritic, inflammatory skin diseases^{171,172}.

Histamine and pruritus. Histamine has long been known to be a mediator of itch in normal human skin and it induces increased pruritic responses in diseased skin of patients with atopic dermatitis compared with normal skin¹⁷³. Similar responses to histamine, as identified by increases in scratching behaviour, have been reported in mice, guinea pigs and primates, suggesting an evolutionary-conserved pathway. This pathway probably persists owing to the physiological need for scratching to rid the body of cutaneous parasites, which activate T_H2 and immunoglobulin E (IgE)/ mast-cell driven responses. However, in certain disease settings, inappropriate crosslinking of IgE by environmental allergens or by autoantibodies to IgE receptors, as in chronic idiopathic urticaria, can lead to initiation of these same pathways and cause pathological changes.

Antihistamines and pruritus. An increase in histamine levels has been noted in the skin and plasma of patients with atopic dermatitis^{10,11} or with chronic urticaria^{12,13}. Correspondingly, a direct pruritogenic role for histamine in IgE-mediated conditions such as acute and chronic urticaria, resulting from mast-cell degranulation, is well proven by the therapeutic antipruritic effects that traditional H_1 receptor antihistamines have in these pathologies¹⁷⁴. However, the role of histamine in the pruritus associated with atopic dermatitis is less clear or

Challenge

The effector phase in experimental immune models in which animals previously sensitized to a specific antigen are exposed to the antigen to cause 'disease'. Antigen is normally delivered to the site where the disease response is to be measured, for example, the lung to cause an asthma-like response.

C-fibres

Unmyelinated, slow-conducting nerve fibres identified as sensors and transmitters of pruritic signals.

Pruritogenic mediator

A stimulus or chemical mediator, such as histamine, known to cause itch.

Immunoglobulin E

(IgE). A class of immunoglobulin involved in allergic responses. IgE bound to mast cells can recognize allergens and cause their degranulation and activation.

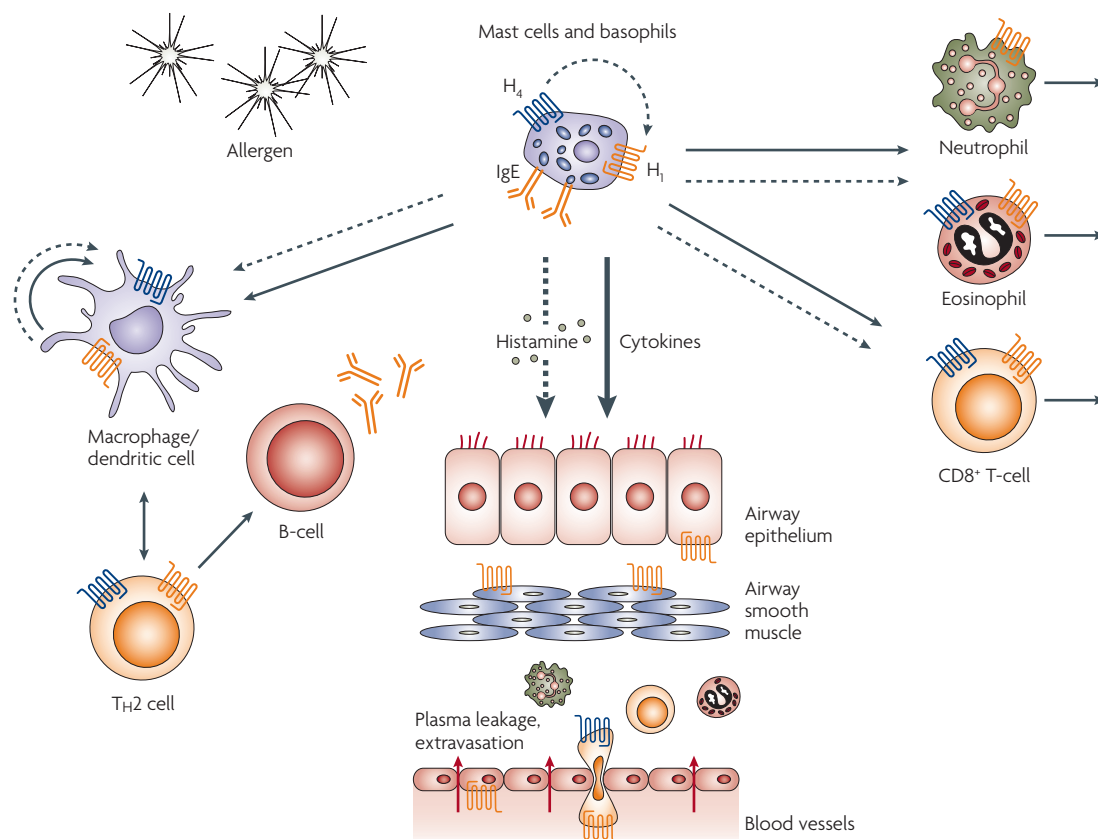


Figure 4 | Potential role of histamine, and histamine H_1 and H_4 receptors in asthma. Allergen entering the airways may crosslink immunoglobulin E (IgE) on mast cells (or basophils) to release histamine, lipid mediators and cytokines. Antigen is also processed by airway dendritic cells and macrophages for presentation to T-helper cells. During this process local release of histamine and cytokines may also occur. Resultant histamine from these processes can act on a variety of cells and at different levels. Histamine can facilitate the recruitment of inflammatory cells by direct chemotaxis of additional dendritic cells, eosinophils and mast cells to the airways via action at H_4 receptors (blue), while also aiding the chemotactic and inflammatory process through effects at H_1 receptors (orange) on the airway epithelium and vascular endothelium. Release of cytokines, such as interleukin 8 (IL8), from the airway epithelium and increased vascular permeability in response to H_1 receptor activation enrich the inflammatory milieu. Constriction and proliferation of airway smooth muscle by H_1 receptors also contributes to the asthma phenotype. Histamine has diverse effects on the activation of leukocytes by H_1 and H_4 receptors. Complex autocrine and paracrine processes in response to dendritic cell histamine and cytokine release control the priming and education of T cells, via cytokines that are released from dendritic cells in response to H_1 and H_4 receptor activation, during antigen presentation. Histamine may additionally affect the cytokine release from $CD8^+$ cells by H_4 receptors and from mast cells, eosinophils and neutrophils through multiple histamine receptor activity. Histamine effects are represented by dashed black arrows, cytokine effects by solid black arrows, and plasma extravasation by red arrows.

accepted¹⁷⁵. This is largely due to the lack of clinical efficacy of H_1 receptor antagonists, but other findings have also been argued to support this conclusion. For example, tachyphylaxis to the vascular and pruritic effects of repeated histamine injection are observed, which might argue against a role for histamine in chronic pruritus of atopic dermatitis¹⁷⁵. Additionally, histamine injection into the normal skin of patients with atopic dermatitis induced a pruritic response that was significantly inhibited by the H_1 receptor antagonists terfenadine and clemastine, whereas disease-associated itch in those patients was unaffected¹⁷⁶. Furthermore, pruritus in response to a mast-cell degranulator, compound 48/80, was reduced by the H_1 receptor antagonist cetirizine in normal subjects but not in patients with atopic dermatitis, which suggests the involvement of mast-cell mediators other than histamine

in the pruritus of atopic dermatitis. However, none of these conclusions is as clear-cut as stated, and often fail to take into consideration the possibility of alternative histamine receptors mediating pruritic responses, or the possible differential expression of such receptors at sites of disease. For example, the validity of the vascular tachyphylaxis argument can be questioned because in mice it has been reported that H_4 receptors are not involved in vascular responses⁴³. Obviously, many of these conclusions were made before the discovery of the H_4 receptor and, therefore, should be reconsidered.

As mentioned previously, histamine is an important mediator of itch in the periphery, and might also function as a transmitter of pruritic signals in the CNS. Histamine is an important central neurotransmitter with physiological and pathophysiological roles in the

Tachyphylaxis

The loss of response to an agonist or antagonist following repeated or prolonged exposure, most often due to downregulation or alteration of the specific receptor.

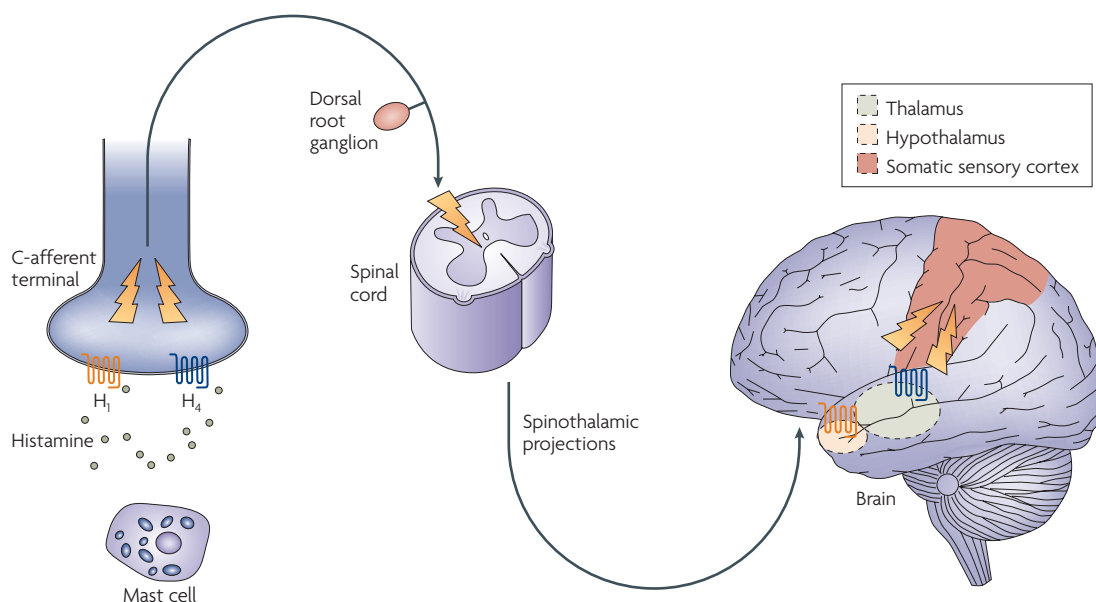


Figure 5 | Proposed role of histamine H_1 and H_4 receptors in peripheral and central transmission of itch responses. Mast cells are the main source of histamine, which may act on H_1 receptors or putative H_4 receptors on C-afferent fibre terminals to transmit itch sensation via spinothalamic projections to the brain. H_4 receptor-positive neurons in the thalamus may activate itch processing in the somatic sensory cortex. H_1 receptors present in the wakefulness centre of the hypothalamus are modulated by centrally acting H_1 receptor antagonists, which also decrease cortical activity.

brain and spinal cord¹⁷⁷. However, central processing of pruritic signals is complex and not well understood, and a role for histamine as a central transmitter of pruritic signals is suggested. Expression of all four known histamine receptors has been demonstrated in the brain, and work in mice has also indicated that centrally administered histamine can initiate scratching behaviour at the spinal level¹⁷⁸. Although this appeared to be attenuated by centrally administered H_1 receptor antagonists, chlorpheniramine and pyrilamine, central H_1 receptor antagonism is sedating and, therefore, genuine antipruritic effects cannot be differentiated accurately using this approach. The role of other histamine receptors, including H_4 receptors, as central transmitters of pruritic responses can therefore not yet be dismissed without further studies. Provocatively, preliminary studies in mice suggest that selective H_4 receptor antagonists may act to inhibit pruritic responses induced by non-histaminergic peripheral stimuli, presumably at a central level⁴⁶.

The therapy of pruritoceptive conditions such as acute urticaria, chronic idiopathic urticaria and atopic dermatitis is traditionally based on the use of well-tolerated H_1 receptor antihistamines. Efficacy of histamine H_1 receptor antagonists against pruritus in acute urticarias, associated with hives and insect stings, and in chronic idiopathic urticaria is well proven. Their continued use and clinical assessment in atopic dermatitis, however, appears largely grounded in this acute activity and the proposed allergic nature of the condition, which is intrinsically associated with IgE, mast cells and histamine. Several studies have demonstrated the antipruritic effect

of first generation, CNS penetrating, antihistamines in atopic dermatitis¹⁷⁹. One of these studies attributed this activity purely to the sedative effects of this class of compounds¹⁸⁰. In this study, a CNS-penetrating antihistamine, trimeprazine, reduced scratching significantly, whereas the non-sedating compounds astemizole and terfenadine had no effect. The conclusion from this study was that peripheral H_1 receptors were unimportant in mediating atopic dermatitis-associated pruritus and, although this study was open with no placebo control, their conclusions appear to have been generally accepted, at least in the United States. Anecdotal reports of the clinical efficacy of sedating antihistamines, particularly in alleviating night-time itch still appear, but the prevailing clinical data are more confusing. Some studies question whether even the sedating H_1 receptor antagonists have any efficacy in atopic dermatitis, with neither of the sedating H_1 receptor antagonists, chlorpheniramine nor clemastine, demonstrating antipruritic activity in two studies^{176,181}. Although other investigators have reported some effects with H_1 receptor antagonists, including non-sedating compounds^{182,183} the consensus of numerous other studies¹⁸⁴, and the conclusion of a retrospective review of all published clinical data¹⁸⁵, is that H_1 receptor antihistamines are mostly ineffective in the treatment of atopic dermatitis-associated pruritus with only modest benefits derived from the sedative properties of the first-generation compounds. H_2 receptor antagonists are also ineffective¹⁸⁶. As discussed previously, this absence of clinical efficacy in part explains the possibly premature conclusions that histamine is not involved in the pruritus of atopic dermatitis.

H₁ and H₄ receptors in animal models of pruritus

Animal models of pruritus are starting to tease out the relative contribution of histamine receptors to pruritic conditions. In acute models, a fundamental role for histamine in inducing scratching responses in mice has been confirmed by directly injecting histamine into skin, although sensitivity varies from strain to strain. Use of H₁ receptor antagonists to inhibit such responses has produced variable effects depending on the antagonist used. Similar trends were observed to those in humans, with increased efficacy with the centrally acting, sedating antihistamines such as diphenhydramine and mepyramine^{46,187}. Similar findings have been demonstrated in pruritus models induced by mast-cell degranulation in the skin, either by compound 48/80 administration or by antigen crosslinking of mast-cell bound IgE^{46,188}, in which H₁ receptor blockade was only partially effective. In addition, H₁ receptor-deficient mice demonstrate only partial protection to IgE-mediated pruritus¹⁸⁹. By contrast, H₁ receptor antagonists have shown antipruritic effects in other disease models^{190,191}, perhaps underscoring the confusion as to the relevant models that may be extrapolated to human pruritic conditions. A consensus of the results appears to demonstrate a varying and incomplete contribution of H₁ receptors to itch in mice.

Two recent studies have raised the possibility that the H₄ receptor may be an additional histamine receptor contributing to histamine-mediated pruritic responses in mice^{46,187}. Specific H₄ receptor agonists were shown to induce itch, whereas these responses, and those of histamine, were blocked by pretreatment with H₄ receptor antagonists⁴⁶. Similarly, histamine or H₄ receptor agonist-induced itch was markedly attenuated in H₄ receptor-deficient animals⁴⁶. H₄ receptor antagonists were effective in reducing 48/80-induced itch or that from IgE-mediated mast-cell activation. The responses were similarly muted in H₄ receptor-deficient mice. There also appeared to be an additional benefit to inhibiting both H₁ and H₄ receptors, as the combination could completely eliminate histamine-induced scratching.

The H₄ receptor-mediated responses were not mast-cell dependent, which suggests that the peripheral role of H₄ receptor in itch might be via expression on other dermal cells or afferent nerves. As discussed previously, a central role for H₄ receptors was also hypothesized, as mast-cell-independent 48/80 responses, putatively through direct activation of C-afferent fibres, were also attenuated. This might have important implications

in terms of H₄ receptors as a pivotal processor of itch responses originating from multiple pathways, but this requires further exploration. The role in more chronic disease model-driven pruritic responses should also be examined, for which the anti-inflammatory properties of H₄ receptor antagonists may offer additional benefit. More chronic studies may also address the concern that the acute models described may not completely translate to chronic human pruritus, especially if there are changes in receptor expression or signalling in the chronic situation.

Taken together, the human and mouse data demonstrate an incontrovertible role for histamine in pruritus across species. However, the exact role of individual histamine receptors in specific diseases is still unclear. Furthermore, as stated, most of the animal studies have been in acute models and how this would translate into chronic pruritus in humans is not clear. Clinical testing of novel histamine receptor antagonists, such as those blocking H₄ receptors, are therefore necessary to fully elucidate the pathogenic role of histamine in pruritic conditions.

Conclusions

Histamine has a key role in many physiological processes including inflammation, and drugs that target H₁ receptors have been successful for the treatment of allergy, but not without limitations. Recently, the scope of histamine's involvement has grown beyond that of innate allergic responses and it has been implicated in adaptive immune responses of both the T_H1 and T_H2 type. Furthermore, the discovery of a fourth histamine receptor, H₄, and its emerging role in inflammation has spurred new interest for the functions of histamine in inflammation, allergy and autoimmune diseases. Early results in animal models suggest that H₄ receptor antagonists may have utility in treating various conditions in humans, in particular in diseases in which histamine is known to be present, and in which H₁ receptor antagonists are not clinically effective. Furthermore, there appears to be some complementation and overlap with H₁ receptor function, thus opening up the possibility for synergy between the two receptors, and suggesting that combined H₁ and H₄ receptor antagonism might bring added benefit over monotherapy. The recent data on the novel functions of H₁ and H₄ receptors have opened an exciting new chapter in the already impressive history of histamine research and should lead to new understanding and, hopefully, breakthrough therapies for the treatment of allergic diseases.

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Competing interests statement

The authors declare competing financial interests: see web version for details.

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