

CHAPTER 6

The Role of Histamine in Asthma

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Abstract

Histamine is a ubiquitous inflammatory mediator intimately associated with the pathology of allergy. Traditional antihistamines, targeting the histamine H₁ receptor, have failed to demonstrate a significant role for histamine in asthma. Novel immunomodulatory roles for histamine and the discovery of a novel histamine receptor, the histamine H₄ receptor, have resulted in a reassessment of its importance in asthma.

Introduction

Asthma is a complex and increasingly prevalent airway syndrome, most often associated with an allergic phenotype. It is characterized by inflammatory infiltrates and episodes of reversible airway obstruction. In its more serious forms chronic airway remodeling may result in persistent airway dysfunction and hyperreactivity.

The association of asthma with allergy has long been apparent, with the atopic phenotype of immunoglobulin-E, mast cell, eosinophil and T-helper-type 2 (Th2) cytokine involvement, commonly displayed. Correspondingly, IgE-mediated mast cell degranulation is thought to be involved in the pathogenesis of allergic asthma through the resultant release of potent physiological and immunological modulators such as eicosanoids, proteases and histamine.

Histamine exerts its effects in the airways, potentially through all four histamine receptors. A pathological role for histamine in asthma has long been proposed, largely due to its increased presence in asthmatic patients and its ability to manifest many symptoms of asthma when administered to the human lung. In spite of this association, frequent and robust analysis of drugs designed to block the action of histamine at the histamine H₁ receptor, namely 'antihistamines', have failed to demonstrate meaningful clinical benefit on symptoms or progression of allergic asthma disease.

More recently a role for histamine in immune modulation has been proposed via its activity at various histamine receptors, notably the histamine H₁ (H₁R), H₂ (H₂R) and H₄ (H₄R). Whilst relatively high concentrations of histamine, as detected in asthmatic airways might be needed to activate low affinity H₁R and H₂R, it is ironic, given the previously stated correlates between high histamine levels and asthma, that minute levels of histamine, acting at high affinity receptors such as H₄R may be more pathologically relevant to the immune malfunction observed in asthma development and persistence. These traditional and emerging hypotheses for the role of histamine in asthma are discussed below.

Histamine in the Asthmatic Airway

Histamine has been considered to be intimately associated with the pathophysiology of asthma since its identification as a potent constrictor of airway smooth muscle by Henry Dale in 1910¹ and the subsequent realisation of its increased presence in diseased tissue by Curry in 1946². In

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addition, the main source of histamine in the airway, IgE stimulated mast cells, have been shown to be increased in the airways of allergic asthmatics.^{3,4} Their infiltration into airway smooth muscle in asthmatics has also been associated with airway dysfunction.⁵ Basophils, were also demonstrated to be a relevant source of histamine in anti-IgE stimulated blood⁶ and have been noted in increased numbers in the BAL fluid of allergen challenged asthmatics and in bronchial biopsies of allergic and non-allergic asthmatics,⁷ particularly during the late phase response, as has also been noted with mast cells.⁴

Correspondingly, upon antigen challenge of the airways, histamine levels are rapidly increased in the airways and in plasma.⁸ This increase has been correlated with disease severity,^{3,9-13} whilst effective management of asthma lowers plasma histamine.¹⁴ Since the pharmacological actions of histamine on the airways and cells involved in the asthmatic response mimic many of the pathophysiological features of asthma, these observations are additionally provocative in terms of a pathologically relevant role for histamine in the disease.

Physiologic Role for Histamine in Lung and Asthma

One of the first identified actions of histamine was its constrictor actions on airway smooth muscle.¹ This response was subsequently shown to exacerbate disease when Weiss reported that administration of histamine to asthmatic patients resulted in breathlessness and decreased vital capacity.¹⁵ This association was strengthened with the observation that the bronchoconstrictor response to histamine was enhanced in asthmatic versus normal individuals and that these responses could be blocked by a prototypical H₁R antihistamine drug.² Subsequently, development of more selective H₁R antagonists allowed for studies to more clearly define the role of histamine and H₁R in bronchoconstriction. In one important study, inhalation of histamine leading to bronchoconstriction and a decrease in FEV₁ (forced expiratory volume in 1 second), was significantly inhibited by oral administration of all H₁R antagonists tested, whose efficacy in the lung correlated well with that observed against histamine induced skin responses in the same patients. In addition, none of the antihistamines were able to inhibit methacholine induced bronchoconstriction.¹⁶ Consequently, this one study demonstrated the selectivity and specificity of the H₁R mediated bronchoconstrictor response to histamine, whilst supporting the theory that the histamine induced vasodilatory responses in skin and bronchoconstrictor responses in lung are mediated by the same receptor.

While histamine is incontrovertibly a constrictor of large and small airway smooth muscle, the direct contractile effect of histamine on airway smooth muscle cells is largely inferred from *in vitro* studies on human tissue. There is some debate as to whether, *in vivo*, H₁R present on sensory nerves may contribute to an indirect contractile response via stimulation of a vagally mediated parasympathetic reflex. Whilst this may be relevant in some species, the lack of effect of anticholinergics on histamine-induced bronchoconstriction in humans would seem to argue against this. In addition, a role for histamine in maintaining bronchial smooth muscle tone, in the absence of nerve innervation has also been demonstrated.¹⁷ Constitutive production of histamine and cysteinyl leukotrienes appeared to impart a resting tone on bronchial smooth muscle that could be significantly reversed by addition of H₁R antagonists and CysLT1 receptor antagonists, respectively. Provocatively, H₁R antagonists dosed to asthma patients can produce immediate bronchodilatory responses, with one study demonstrating that cetirizine was almost as potent a bronchodilatory agent as a β -adrenergic agonist.¹⁸ However, as discussed in detail below, these effects are inconsistent and appear to fade with continuous treatment.

The previously mentioned edematous and vasodilator responses observed in the skin to histamine could additionally have pathological implications in asthmatic airways via the causation of mucosal edema and the facilitation of plasma proteins and leukocyte movement into the affected tissue. These vasodilator effects are mediated by H₁R on vascular endothelium which act to increase paracellular permeability,^{19,20} whilst the movement of cells is additionally facilitated by the H₁R dependent upregulation of adhesion molecules such as ICAM-1, E-selectin and P-selectin

on endothelial and epithelial cells,²¹⁻²³ particularly under inflammatory conditions. Histamine acting on H₁R on endothelium and airway epithelium may have direct pro-inflammatory effects via the release of cytokines such as IL-6 and IL-8^{24,25} and has also been shown to augment the release of IL-16, a potent chemokine for T helper cells, from airway epithelial cells.²⁶ Interestingly, histamine has been shown to similarly induce IL-16 release from CD8⁺ T cells in a H₄R and H₂R dependent fashion.²⁷

All of these actions of histamine on airway structural cells may combine to promote an inflammatory phenotype, however a caveat of all these data is that they have largely been obtained in vitro and their in vivo significance is unknown. Likewise, a role for histamine in airway smooth muscle cell proliferation in vitro has also been reported²⁸ and other studies have suggested histamine receptors to be involved in the hypersecretory response seen in asthmatic airways. Whilst H₁R may be linked to airway secretion via an effect secondary to its role in plasma exudation, the H₂R has been shown to be the sole histamine receptor involved in mucus secretion,²⁹ which is consistent with the expression of H₂R in secretory cells from nasal mucosa.³⁰

In summary, the pharmacological effects of histamine on the lung recapitulate many of the pathophysiological symptoms of asthma and that the potential role of histamine as an important mediator in asthma is further suggested by its increased presence in the asthmatic airway. In the rest of this chapter we will examine whether this 'guilt by association' is borne out by the evidence from clinical studies with antihistamines and whether newer insight into the role of histamine in immune modulation, potentially through receptors not targeted by current antihistamines, may have implications for the future treatment of asthma.

Immunological Modulation by Histamine

Many cells of the immune system associated with asthma have been shown to express a range of histamine receptors, notably H₁R, H₂R and the newly described H₄R. In most cases these receptors are co-expressed so that the net effect of their activation may vary, depending on the exact expression profile and the concentration of histamine in the surrounding milieu, and is further complicated since the receptors may have opposing function. It is therefore difficult to interpret the significance of the in vitro literature in which many of these conditions may be manipulated to observe a specific effect and hence preclinical examination of their role in the whole animal is likely the most relevant predictor of their role in human disease. Nevertheless, the in vitro literature reviewed here demonstrates the broad spectrum of cells and effector functions that may be modulated by histamine. In vivo evidence will be described later. The proposed immune and physiologic roles of histamine in asthma are depicted in Figure 1.

Mast Cells and Basophils

Mast cells are not only the main source of histamine in the lung, but are a source of cytokines and tissue growth factors that may be important in the inflammatory and remodeling processes observed in asthma.³¹ They themselves may be modulated by histamine through expression of H₁R, H₂R and H₄R on their surface. While histamine does not appear to affect degranulation of mast cells, it has been shown to be a potent chemoattractant for mast cells³² and has been shown to enhance chemotaxis of mast cell precursors in response to CXCL12,³³ all via activity at the H₄R. In addition, inhaled histamine was able to increase the number of sub and intra-epithelial mast cells in mouse airways in an H₄R dependent fashion.³⁴ Interestingly, localization of mast cells to the bronchial epithelium has been observed in asthmatics after allergen challenge.³⁵ There are several reports of H₁R antagonists reducing leukotriene and histamine release from human lung mast cells and basophils, but these effects are believed to be independent of their antagonism of histamine, as previously reviewed.³⁶ Histamine acting at the H₂R does appear to have inhibitory effects on mast cells, decreasing histamine and cytokine release^{37,38} and may have similar actions on basophils.³⁷ H₄R has also been detected on basophils but its role in their function has yet to be studied.

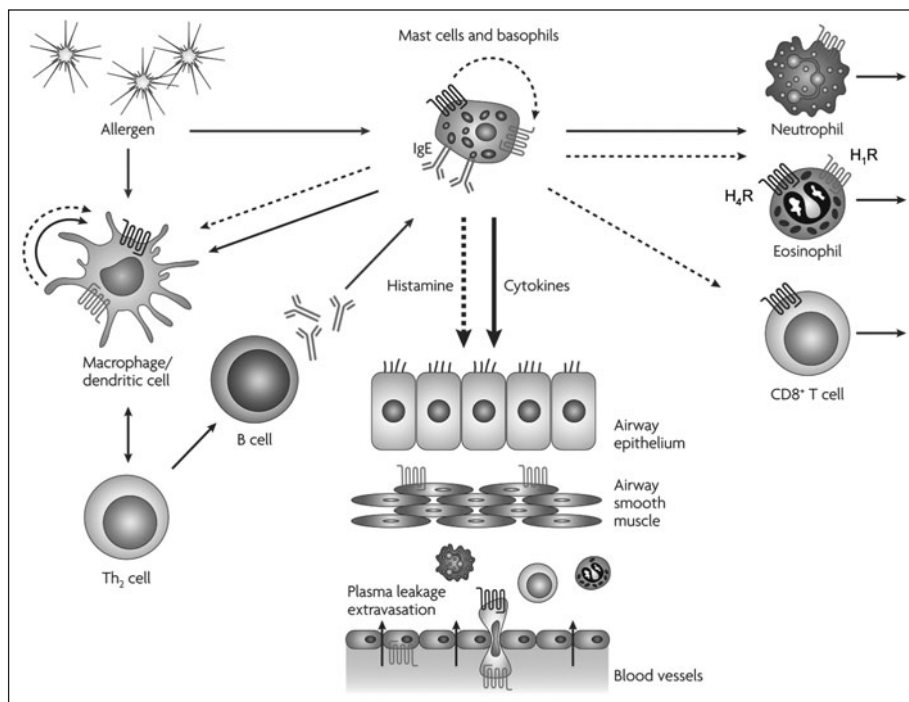


Figure 1. Potential role of histamine in asthma. Allergen entering the airways may cross-link IgE on mast cells (or basophils) to release histamine, lipid mediators and cytokines. Antigen is also processed by airway dendritic cells and macrophages for presentation to T helper cells. During this process local release of histamine and cytokines may also occur. Resultant histamine from these processes can act at a variety of cells and levels. Histamine can facilitate the recruitment of inflammatory cells via direct chemotaxis of additional dendritic cells, eosinophils and mast cells to the airways via action at H_4R , whilst also aiding the chemotactic and inflammatory process through effects at H_1R on the airway epithelium and vascular endothelium. Release of cytokines, such as IL-8, from the airway epithelium and increased vascular permeability in response to H_1R activation enrich the inflammatory milieu. Constriction and proliferation of airway smooth muscle via H_1R also contributes to the asthma phenotype. Histamine has diverse effects on the activation of leukocytes via H_1R and H_4R . 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_1R and H_4R ligation, during antigen presentation. Histamine may additionally affect the cytokine release from $CD8^+$ cells via H_4R and from mast cells, eosinophils and neutrophils through multiple histamine receptor activity. Key: solid arrows: cytokine effect; dashed arrow: histamine effect; light 7TM: H_1R ; dark 7TM: H_4R . A color version of this image is available at www.landesbioscience.com/curie. Reproduced from Thurmond et al. The role of Histamine H_1 and H_4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discovery* 2008; 7:41-53.

Eosinophils

Eosinophils are traditionally one of the major cell types implicated in the pathology of asthma, due to their observed increase in asthmatic lungs and the plethora of cytotoxic and pro-inflammatory mediators, linked with disease progression, that they are able to release. Although a direct causative role in disease has been difficult to prove, recent pharmacologic intervention has suggested their importance in at least a subset of asthma patients.^{39,40} Therefore, it is provocative to note that, as for

mast cells, histamine has been shown to be a potent chemoattractant and enhancer of chemokine mediated chemotaxis, once more through the recently described H₄R.^{41,42} H₄R dependent upregulation of adhesion molecules was also reported.⁴² H₁R antagonists have been investigated for their role in eosinophil function, but effects via nonhistaminergic pathways at irrelevant concentrations confuse the interpretation of these studies. As with mast cells and basophils, these activities appear independent of H₁R activity and are not discussed here, as they do not contribute to an understanding of the role of histamine in asthma.

Neutrophils

The presence of neutrophils in the airways has been demonstrated during asthma exacerbations, after treatment withdrawal⁴³ and in a sub-set of chronic asthma patients with severe disease.^{44,45} In patients that die suddenly from asthma, they are also increased,⁴⁶ with the same study demonstrating elevated histamine levels. Interestingly, neutrophils have also recently been identified as a source of histamine in the lung,⁴⁷ so this correlation may be effect rather than cause. The role of histamine in neutrophil function is also unclear, with any function appearing limited to the H₂R, which may in fact have a negative regulatory role on their function.⁴⁸ Histamine may have an indirect effect on neutrophil chemotaxis via its H₁R-dependent ability to stimulate release of proneutrophilic cytokines and chemokines from airway tissue.^{24,25} Similarly, an indirect role for H₄R has been reported in mast cell dependent models of neutrophilia.^{42,49,50}

Monocytes and Macrophages

Expression of the H₁R, H₂R and H₄R have been demonstrated in human monocytes yet their expression on different macrophage lineages and at different levels of activation may vary and has not been well studied. Alveolar macrophages are the most abundant inflammatory cell in the human lung, yet their association with asthma is not clear, likely due to the difficulty in studying this highly heterogeneous population. However, alveolar macrophage suppression of T-cell proliferation is reduced in asthma and after allergen challenge⁵¹ and some alterations in specific subpopulations have recently been described in asthma.⁵² In vitro studies have demonstrated that histamine may have modulatory effects on LPS stimulated monocytes via the H₂R, including a reduction in the production of IL-12 and an increase in IL-10 release,^{53,54} which could conceivably promote Th2 cell development. The constitutive production of MCP-1 (CCL2) has also been reported to be inhibited via an action at the H₄R.⁵⁵ In alveolar macrophages, specifically, H₁R mediates histamine induced β -glucuronidase and IL-6 release, which may indicate a role for histamine in macrophage-mediated remodeling processes.⁵⁶

Dendritic Cells

Dendritic cells are professional antigen presenting cells that may develop from cells of either lymphoid or monocytic lineage. They are intimately associated with the pathogenesis of asthma through their initiation and maintenance of T-cell responses, particularly Th2 type. Polarization of naïve Th0 cells to Th2 and other T helper sub-sets may be differentially controlled at the level of the interaction between dendritic cells and antigen-specific T cells. Such interaction can be directed by a variety of cytokines, chemokines, toll-ligands and biogenic amines, such as histamine. These are released at sites where antigen is encountered or presented and may sequentially modulate both the dendritic cell and subsequent T helper phenotypes.⁵⁷ All four histamine receptors have been identified on immature and mature dendritic cells. Histamine, released from dendritic cells or more traditional sources, may act in an autocrine or paracrine fashion to modify their phenotype, as measured by alterations in surface markers⁵⁸ or in cytokine release.⁵⁹ Cytokine secretion, including inhibition of IL-12 and enhancement of IL-10 and IL-6, may be modulated by histamine with H₁R, H₂R and H₄R all involved⁶⁰⁻⁶² in these Th2 promoting processes. The autocrine activation of dendritic cells by histamine deserves additional discussion, since it is indicative that low levels of locally released histamine are able to define and control immune responses that may be important in asthma, via actions at high affinity histamine receptors, such as H₄R and at concentrations where low affinity H₁R and H₂R may not be engaged. This may suggest that the high levels of histamine frequently

cited as correlating with asthma severity are unrelated to the underlying immunology of asthma and therefore, at best, may only have a relationship to the physiological *sequelae* previously described.

T Cells

As described above, T cells are pivotal cells in the initiation and perpetuation of adaptive immune response associated with allergic asthma. In addition to being modulated by the effects of histamine on dendritic cells, they may be directly affected by histamine. H_1R , H_2R and H_4R are all expressed on CD4+ and CD8+ cells and have been shown to demonstrate reciprocal responses to histamine, based on the preferential expression of H_1R on Th1 cells and H_2R on Th2 cells, for example.⁶³ Most recently, H_4R has also been described to be functionally active on human Th2 cells⁶⁴, with upregulation of H_4R in response to IL-4 reported. H_4R agonism of these cells resulted in activation of the pro-Th2 transcription factor, AP-1 and the induction of the Th2 cytokine, IL-31. H_1R on Th1 cells appears to enhance Th1 type responses, with deletion in mice leading to a consequent skewing to Th2 type responses after T-cell dependent antigen immunization and resultant enhanced production of IgE and IgG₁.⁶⁵ H_2R appears to negatively regulate both Th1 and Th2 responses, with the surprising net effect of H_2R deletion in mice resulting in decreased IgE in response to immunization, at least in the Th2 predominating system tested.⁶³ This was in spite of the predicted increase in IL-4 and IL-13 production from H_2R deficient mice, suggesting that the concomitant overproduction of IFN γ had a dominant effect on the humoral response.

In vitro, T-cell proliferation has also been reported to be affected by histamine, with once more a pro-inflammatory enhancement of proliferation associated with H_1R activation^{63,66} and an inhibitory effect on proliferation via H_2R activation, reported.^{63,67} On CD8+ T cells deletion of either H_1R or H_2R has been shown to increase their capacity for IFN- γ release whilst reducing IL-2 and IL-10 secretion.⁶⁸ Activation of H_2R and H_4R on CD8+ cells also leads to IL-16 release, a potent T-cell chemoattractant associated with asthma.²⁷ Direct effects of histamine on the chemotaxis of T cells are also apparent, via activity at either H_1R or H_4R .^{69,70} The effect of histamine on T-cell and dendritic cell interactions, through action at H_4R is depicted in Figure 2.

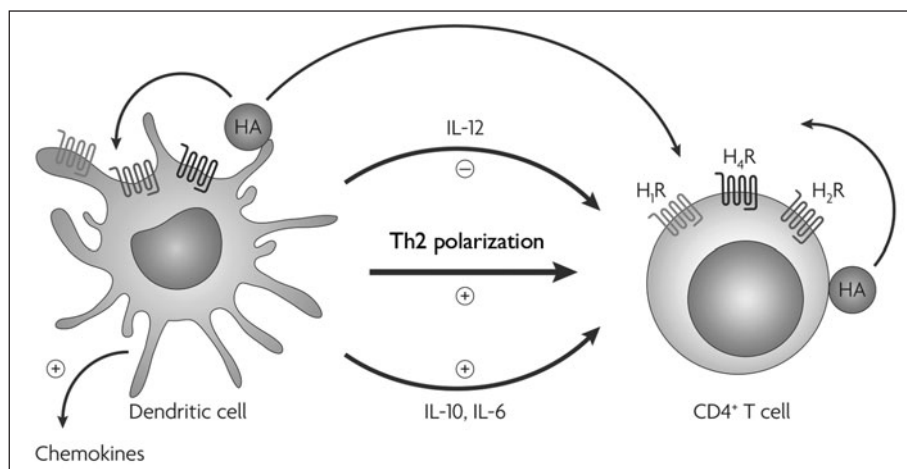


Figure 2. Role of histamine H_4R on dendritic cell and T-cell function. Histamine acting at H_4R on dendritic cells can drive T helper 2 (Th2) cell polarization. This may be accomplished by inhibiting Th1 polarizing cytokines such as IL-12 and by stimulating cytokines such as IL-10 and IL-6. Release of chemokines such as TARC, MDC and MIP-1 α may further influence this and the further recruitment of Th2 cells to sites of antigen capture. Histamine may also act as a direct chemoattractant at H_4R on Th2 cells. Reproduced from Thurmond et al. The role of Histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discovery* 2008; 7:41-53.

iNKT Cells

Although still somewhat controversial, invariant NKT cell are considered to be a potentially important initiator of allergic and inflammatory responses, via their ability to rapidly produce primary cytokines such as IL-4 and IFN- γ .⁷¹ Allergens such as pollen may also act at the invariant TCR to cause their activation, further linking them to allergic conditions.⁷² Modulation of iNKT cells by histamine has recently been reported, whereby histamine deficient mice demonstrated reduced IL-4 and IFN- γ production in response to in vivo iNKT activation. This could be reconstituted with histamine and blocked by a selective H₄R antagonist.⁷³

In concluding this section, the diverse roles of histamine in asthma associated immune cells, dissected from in vitro experiments, would appear to argue for a potential immunomodulatory role for histamine in asthma. The next sections, however, will highlight the caveats of in vitro histamine research, discussed earlier and review the contribution of histamine to in vivo models of asthma and human disease, based on genetic, pharmacological and clinical evidence.

Histamine in Animal Models of Asthma

A role for histamine in the pathogenesis of asthma has also been studied using animal models of asthma. Notably, the role of H₁R has been extensively studied with genetic knockout and pharmacological approaches, while that of H₄R has just begun. Interpretation of these studies is complicated by the exact nature of the model and the dosing regimen applied to each investigation. In general, models have a 'sensitization' phase to allergen, which is comparable to the development of allergy in patients and a 'challenge' phase which is considered analogous to the pro-inflammatory response to an allergen in an already allergic individual, such as an atopic asthmatic. Hence pharmacological intervention around the challenge phase is considered most translational to the therapeutic treatment of pre-existing asthma in patients.

Correspondingly, when H₁R antagonists have been examined therapeutically in mice, and at clinically relevant doses, they appear to have no effect on allergic airway inflammation.^{62,74} These respective studies used loratadine and desloratadine and the results are therefore consistent, being parent and metabolite, respectively. Others have tested high doses of alternate H₁R blockers, such as fexofenadine and have demonstrated an effect with a similar dosing schedule in such models.⁷⁵ Of interest, higher than standard doses of H₁R have also been shown to have more efficacy in urticaria and are the current recommended treatment.⁷⁶ However, these effects may not results completely from blockade of H₁R and as with non-H₁R mediated effects of antihistamines in vitro these findings do not contribute to this discussion of the role of histamine in asthma. Interestingly, high dose loratadine was ineffective in the study previously referenced,⁶² further supporting the hypothesis that the reported effects of fexofenadine may be attributed to non-H₁R activity of the drug.

In contrast, H₁R blockade around the sensitization phase of these models appears to indicate a role for H₁R in the developmental stage of allergic responses. In one study, clinically relevant doses of desloratadine were administered prior to antigen sensitization, resulting in a reduced inflammatory response to allergen challenge.⁷⁴ Specifically, eosinophilic and lymphocytic airway inflammation was reduced with a resultant decrease in airway hyperreactivity in treated animals. Th2 cytokines and immunoglobulins were also decreased, confirming the inhibitory effect of desloratadine on immune sensitization. The effect of H₁R blockade on allergic sensitization may also explain the reported protective effect of H₁R genetic deficiency in mouse asthma models.^{69,77} H₁R deficient mice had a diminished airway inflammation and Th2 cytokine response to allergen challenge as well as a decrease in airway hyperreactivity.⁶⁹ Since in these animals the H₁R is absent at all stages of the model the exact point of effect is difficult to pinpoint, but in these studies, transferring cells from sensitized H₁R deficient mice into wild-types which were then challenged with allergen recapitulated the effect. This reinforces the pharmacological evidence that it is an effect at sensitization that ameliorates the subsequent response to allergen challenge. There is also evidence of synergy between the H₁R and H₄R during the sensitization phase.⁷⁸ Some clinical studies suggest that these findings may be relevant to humans, since treatment of atopic children with antihistamines appeared to reduce the risk of developing asthma in later life.⁷⁹

Other histamine receptors have been studied in similar models. H₂R genetic deficiency resulted in a decrease in ova-specific IgE production which was attributed to an apparent increase in IFN- γ production in these mice.⁶⁵ Pharmacological administration of H₂R antagonist prior to challenge did not affect IgE levels, but did diminish eosinophilia and airway hyperresponsiveness,⁸⁰ whilst low dose H₁R antagonist was once more ineffective. However, the effect of H₂R antagonist in this model do not mirror the non-effect of H₂R antagonists observed in clinical asthma,^{81,82} perhaps highlighting the difficulty in interpreting animal data.

Despite this, compelling *in vivo* evidence does exist for a role of the newly described H₄R in asthma. In a mouse ovalbumin challenge model, H₄R deficient animals were protected from eosinophilic and lymphocytic airway inflammation with concomitant reduction in Th2 cytokines in airway and draining lymph nodes. Ova-specific IgE was also decreased.⁶² In addition, pharmacological intervention at either the sensitization or challenge stage lead to a diminishment of the subsequent allergic response, suggesting H₄R is involved in both the developmental and effector phases of allergic inflammation. Dissection of the cellular basis for these effects indicated that inhibition of H₄R on dendritic cells results in a decrease in their capacity to activate Th2 cells.

Taken together, these investigations demonstrate the ability of histamine receptors to contribute to various stages of allergic inflammation in mouse models. The therapeutic translation of these findings is discussed below.

Antihistamines and Clinical Asthma

This weight of preclinical evidence and 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, over the past 50 years.

Promising results were initially obtained with first generation antihistamines demonstrating their acute bronchodilator effects in asthmatic patients⁸³ and against histamine and allergen induced bronchoconstriction, that appeared independent of muscarinic activity.⁸⁴ Despite this, doses that were absent of dose-limiting sedation were ineffective in modulating exercise or naturally occurring asthma,⁸¹ whilst inhaled antihistamines, aimed at reducing these side-effects, were either irritants or variable in their observed activity.⁸⁵⁻⁸⁸ Consequently, it was not until the development of more potent and nonsedative second generation antihistamines in the 1980s that the role of antihistamines in asthma was reappraised. A selection of these studies is summarized in Table 1.

Whilst a meta-analysis of properly designed studies reached an overall conclusion that second generation antihistamines were ineffective in the treatment of asthma,⁸⁹ some interesting trends are apparent that require further discussion. Notably, doses of antihistamines much greater than those observed to be effective in rhinitis appear to offer some benefit and concomitant therapy with other agents might also be beneficial. Several studies with recommended doses of terfenadine, for example, while demonstrating an ability to produce bronchodilation,¹⁶ or reduce early phase responses to allergen challenge,⁹⁰ showed no effect on late phase responses.⁹¹ However, increasing doses of terfenadine were able to enhance the effect on early phase responses and afford protection against late phase responses.⁹² A similar reliance on increased doses of terfenadine for efficacy in clinical asthma has also been observed. In comparable double-blind placebo controlled studies in mild asthmatics, terfenadine was more active than placebo when dosed at 120 mg twice daily,⁹³ or at 180 mg thrice daily.⁹⁴ The higher dose appeared more effective at increasing peak expiratory flow and reducing use of inhaled beta-agonists, as well as reducing cough and wheeze. A suggestion that disease severity may also determine the efficacy of antihistamines was suggested in another trial where 120 mg twice a day terfenadine was deemed inactive in a population of severe asthmatics.⁹⁵ A more recent low dose trial of fexofenadine, the active metabolite of terfenadine, in moderate disease, demonstrated a mild but transient effect on wheezing and peak expiratory flow.⁹⁶ This transient effect may be related to a loss of the bronchodilator effect that has been observed with repeat dosing of antihistamines, including terfenadine.⁹⁷

Similar trends to efficacy have been seen with other antihistamines such as cetirizine and loratadine. Cetirizine has demonstrated improvement in lung function and symptoms over placebo,⁹⁸ while

Table 1. Clinical assessment of second and third generation antihistamines in asthma

Antihistamine (Ref)	Dose	Asthma Phenotype	Comparator/ Additional Drug (+)	Duration of Study	Symptoms	Function	β-Agonist Use
Cetirizine ⁹⁸	10 mg bid	Seasonal	Placebo	2 wk	Decreased	Improved	Decreased
Cetirizine ¹⁰³	10/15 mg bid	Seasonal	Terfenadine 60 mg bid	4 wk	Decreased (15 mg only)	No change	No change
Fexofenadine ⁹⁶	180 mg qd	Moderate, seasonal		6 wk	Decreased wheezing	Improved PEF	No change
Loratadine ¹⁰¹	20 mg qd	Moderate to severe, perennial		4 wk	No change	Transient improvement	No change
Loratadine ⁹⁹	5 mg bid	Mild, seasonal	+ pseudoephedrine 120 mg bid	6 wk	Decreased	Improved PEF	No change
Loratadine ¹⁰⁰	20 mg qd	Perennial	+ Montelukast 10 mg qd	2 wk	Decreased	Improved	Decreased
Terfenadine ⁹³	120 mg qd	Mild, perennial		2 wk	Decreased	Improved PEF	Decreased
Terfenadine ⁹²	180 mg tid	Mild, seasonal		4 wk	Decreased	Improved PEF	Decreased (NS)
Terfenadine ¹⁰⁴	120 mg bid	Severe, perennial		4 wk	Decreased night time awakening	No change	No change

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another study showed a dose dependent improvement in symptoms, in comparison to terfenadine, but no effect on lung function.⁹⁷ Once more, relatively high doses with some sedative effects were used. The beneficial effects with loratadine have most interestingly been shown in combination with other drugs. The combination of loratadine with pseudoephedrine has been reported to improve both rhinitis and asthma symptoms, with an improvement in peak expiratory flow measurements, versus placebo.⁹⁹ No comparison to individual agents alone was made, however. The addition of loratadine to montelukast therapy was examined by Reicin and colleagues.¹⁰⁰ The dual treatment provided a significant improvement in asthma symptoms and lung function, as determined by peak expiratory flow and FEV₁, when compared to montelukast alone. Mild but transient improvement in lung function has also been observed with high dose loratadine alone,¹⁰¹ perhaps reiterating the apparent development of toleration to the bronchodilator effects of antihistamines.

In summary, the limited efficacy of H₁R antagonists in asthma does not appear to warrant their use over existing steroid sparing therapies, such as montelukast, although cotherapy may be warranted in some instances. The use of totally nonsedating blockers such as fexofenadine at higher doses may prove fruitful in the future. Whether this apparent improved efficacy at high doses is a result of additional anti-inflammatory effects is not clear, but the studies in mice discussed earlier are beginning to tease out the possible immunomodulatory role of H₁R antagonists¹⁰² and may additionally explain the observed prophylactic effect of antihistamines in reducing asthma development in atopic children.⁷⁹

Conclusion

Whilst there is a plethora of preclinical data supporting a role for histamine in the pathophysiology of asthma, the general lack of efficacy of H₁R antagonists in the clinical setting is perplexing and may speak to the importance of histamine's effects on other cell types, mediated by other receptors. Activation of the H₂R certainly mimics some pathophysiological aspects of asthma, but H₂R antagonists have no efficacy in allergic asthma. Therefore, the role of histamine in the modulation of immune cell chemotaxis, function and education, with the recent observations of an important role for H₄R in these events, may provide an additional and novel avenue for successful pharmacological modulation of histamine mediated responses. In addition, to this novel receptor pharmacology some positive studies investigating higher doses of second generation H₁R antagonists in allergic asthma, may help reconcile the current discrepancy between the observed experimental importance of histamine and its apparent clinical irrelevance.

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