

New Developments in the Use of Histamine and Histamine Receptors

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Abstract Histamine and the histamine receptors are important regulators of a plethora of biological processes, including immediate hypersensitivity reactions and acid secretion in the stomach. In these roles, antihistamines have found widespread therapeutic applications, while the last receptor to be discovered, the H₄ histamine receptor, has become a major target of novel therapeutics. Recent studies involving human genetic variance and the development of mice lacking specific receptors or the ability to generate histamine have shown roles for the histamine pathway that extend well beyond the established roles. These include identification of previously unappreciated mechanisms through which histamine regulates inflammation in allergy, as well as roles in autoimmunity, infection, and pain. As a result, antihistamines may have wider applications in the future than previously predicted.

Keywords Histamine · Histamine receptor · Allergy · Mast cell · Basophil · Autoimmunity · Pain · H₁R · H₂R · H₃R · H₄R

Introduction

With more than a century of experimental and clinical investigation to support the concept, histamine is an important mediator of allergic disease. Furthermore, first- and second-generation therapeutics directed at the H₁ histamine receptor (H₁R) have long been the front-line

drugs in the treatment of allergic rhinitis [1]. The established view of IgE-mediated mast cell activation leading to histamine release and histamine receptor-dependent immediate hypersensitivity reactions, including vasodilation and smooth muscle contraction [2], still stands as a crucial response to allergens. However, recent developments in a variety of research fields have begun to unearth a much more complex and diverse story to histamine, the histamine receptors, and the histamine metabolism pathways than could ever have been predicted by the early pioneers of histamine physiology.

Previous reviews have summarized the biology of histamine in great detail [3]; thus, only a brief overview is provided here. Histamine is a diamine derivative of histidine that is produced under the control of a single enzyme, histidine decarboxylase (HDC). In bacteria, histamine has been proposed to be mainly a product of basic metabolism, but in higher animals, it has evolved into the role of a signaling molecule, functioning as a neurotransmitter and a diffusible systemic messenger. Once formed, two enzymes, histamine *N*-methyl transferase (HNMT) and diamine oxidase, independently control histamine degradation. Histamine exerts its functions via four known G protein-coupled receptors, H₁R to H₄R, which possess divergent downstream signaling effects. H₁R and H₂R have wide distribution and are present on many cells. H₃R is expressed in the nervous system, where it serves as a presynaptic feedback receptor on histaminergic neurons. H₄R is a recently identified receptor possessing a more limited expression that includes several specific subsets of immune cells, making it of particular interest as a target for novel immunomodulatory therapies. Highly selective blockers and agonists suitable for *in vitro* and *in vivo* use have been developed for these histamine receptors. These include clinically established H₁R and H₂R blockers, as

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well as novel investigational drugs directed toward H4R. The application of these pharmacologic compounds, as well as the generation of novel research tools such as histamine receptor-deficient mice, has allowed us to examine the roles of histamine in immunity and disease to a much greater level than ever before. Here, we discuss some of the recent advances to our understanding of histamine biology.

Genetic Variance in the Histamine Pathway and Links to Diseases

In recent years, the development of tools to determine genetic variance has advanced our knowledge of particular molecules or pathways in disease susceptibility, severity, and treatment. It is now clear that the histamine pathway exhibits profound genetic variance that may influence diseases, including allergic rhinitis.

Recent work by Gervasini et al. [4•] demonstrated an increased risk of developing allergic rhinitis in individuals with a polymorphism at position 644 of the HDC gene. In two separate populations, they were able to show a Glu644Asp single nucleotide polymorphism strongly associated with allergic rhinitis. Interestingly, the association did not seem to relate to those patients with or without asthma, suggesting that this polymorphism may influence susceptibility to one allergic disease but not another. Additionally, the polymorphism also did not correlate with changes in forced vital capacity in 1 second, supporting the established concept that antihistamines are unlikely to influence airway reactivity. Intriguingly, a previous study had described a polymorphism in HDC that linked to a very different clinical outcome: abnormally early onset of menopause [5]. The authors of this work linked the neurological roles of histamine to the control of female hormone production, although they did not conclusively demonstrate that the polymorphism they described did this. However, this idea does illustrate how modifications in histamine production may impact neurological control due to its role in neurotransmission, as well as the more commonly appreciated effects on allergic-associated responses.

Other parts of the histamine-associated pathway also have been found to possess genetic variances that are associated with increased risk of allergic disease. A polymorphism in HNMT increased the risk of developing atopic dermatitis in children twofold [6], while another related to chronic urticaria [7]. Significantly, Kim et al. [7] actually described a functional effect of a polymorphism on the mRNA stability, whereupon HNMT levels were reduced and, concomitantly, histamine levels would be elevated. Recently, three polymorphisms in H4R have been

associated with increased risk of atopic dermatitis [8]. One of these polymorphisms was shown functionally to cause enhanced expression of H4R as a result of increased protein stability.

Genetic regulation of histamine-associated diseases beyond allergy is also illustrated by several studies of Parkinson's disease and essential tremor. Here, mutations in HNMT have been widely studied for their linkage, albeit with studies showing both positive [9, 10] and negative correlations [11]. Additionally, a polymorphism in H1R has been positively implicated in Parkinson's disease [12]. In mice, Noubade et al. [13•] have defined the role of polymorphisms in the murine H1R that alter the expression levels of H1R. In this elegant study, whereby the susceptibility and resistant forms of H1R were exchanged between strains, the mechanisms underlying the susceptibility of specific murine strains to *Bordetella pertussis* toxin-induced histamine sensitization and central nervous system (CNS)-associated autoimmune inflammation were finally explained.

With the increasing ability of investigators to explore whole genome sequencing and expanded analysis of specific polymorphisms, it seems likely that further study of genetic variance within the histamine pathway will help in our understanding of allergic and nonallergic disease.

New Concepts of Histamine in Allergic Inflammation

Recent studies have challenged the established dogma that histamine has little to no role in asthma pathogenesis. New evidence for the role of histamine in shaping immune responses has come from murine models of allergic airway inflammation. Following sensitization and intranasal challenge with an antigen, these models have allowed dissection of the specific features of human asthma, including airway hyperresponsiveness, eosinophil and lymphocyte influx, and hyperplasia of goblet cells and mucus production. H1R^{-/-}, H4R^{-/-}, and HDC^{-/-} mice have all been evaluated in airway allergy models and display attenuated responses upon antigen challenge. However, the mechanisms described from these models have demonstrated that histamine exerts a variety of responses via different receptors that influence the sensitization to antigen, as well as the generation of inflammatory responses after sensitization. For example, studies using H4R^{-/-} mice demonstrated that histamine derived from the dendritic cell functioned in an autocrine manner via H4R to enhance antigen presentation and the generation of a T-helper type 2 (Th2)-skewed effector T cell [14]. In contrast, we demonstrated that H1R^{-/-} mice failed to generate airway inflammation due to an inability of the CD4⁺ T cells to migrate toward the lung, despite

their systemic reactivity being highly Th2 skewed [15]. H2R^{-/-} mice remain to be studied in allergic models at this time but have been shown to exhibit aberrant T-cell cytokine responses [16] that might predict some roles for H2R also. This is particularly relevant given the findings observed with HDC^{-/-} mice. In contrast to the H1R or H4R^{-/-} studies, in which airway inflammation was profoundly impaired, these histamine-deficient mice display considerably more modest reductions and have been the subject of inconsistent findings in airway allergy models [17–19]. Specifically, whereas two studies reported a substantial reduction in eosinophil influx in HDC^{-/-} mice following challenge, another observed no change in eosinophil influx but rather an increase in macrophage and lymphocyte numbers alongside increased goblet cell hyperplasia [19]. These studies further disagreed on an effect on airway hyperreactivity, reporting a reduction in enhanced pause, a measure of respiratory function used in noninvasive airway studies, or no effect on invasively measured airway resistance. The differences between the single-receptor knockouts and the histamine-deficient mice remain unexplained, but it is intriguing to speculate on a role of the H2R in these responses given that it has been proposed as a negative receptor. Alternatively, are other ligands capable of binding to the histamine receptors that would be generated in an HDC-independent manner? What is clear is that histamine and histamine receptors are critical regulators of allergic inflammation at both the sensitization and elicitation phases. The use of antihistamine therapeutics to intervene in the inflammatory events of rhinitis, asthma, or other allergic diseases is likely to be an avenue for histamine research in the near future.

Histamine in Autoimmune and Inflammatory Diseases

There is now a compelling body of evidence for histamine and histamine receptors in the pathogenesis of autoimmunity from animal studies and clinical observations. In the intestine, it has been known for many years that histamine is elevated in tissue biopsies and secretions in patients with Crohn's disease and ulcerative colitis [20, 21]. Sander and colleagues [22] have demonstrated unique expression patterns of H1R, H2R, and H4R on a wide variety of cells within the intestine, including epithelial cells. Interestingly, they could not detect expression of H3R in any location. Despite this, little is known about the roles of histamine and histamine receptors in regulating intestinal immunity. However, studies using 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis, a model of acute colonic inflammation, showed reduced responses in H4R antagonist-treated rats [23]. In this study, rats treated with the H4

receptor antagonists JNJ 7777120 or JNJ 10191584 were protected from intestinal injury and mucosal thickening. This was accompanied by reduced tumor necrosis factor (TNF)- α production and neutrophil influx, suggesting that H4R may influence innate immune responses in this model.

Inflammatory arthritis, induced by K/BxN serum transfer in a mast cell-dependent model [24], is reduced in HDC^{-/-} mice, but not in H1R^{-/-} or H2R^{-/-} mice, suggesting a role for H3R or H4R in this disease development [25]. In addition to expression on mast cells [26], H4R expression has been reported on the synovium of human rheumatoid arthritis [27]; thus, histamine could be contributing through augmentation of the mast cell responses as well as having direct effects on the synovial cells themselves. Cells from rheumatoid arthritis patients have been shown to yield elevated histamine levels; however, direct injection of histamine into joints fails to promote inflammation and, paradoxically, rheumatoid arthritis patients actually have lower histamine levels in their circulation or synovial fluid than healthy controls [28]. One explanation for this might relate to increased consumption of histamine via increased receptor expression and a similar mechanism that also has been proposed to reduce the levels of joint leptin in rheumatoid arthritis [29].

Of all the autoimmune models, perhaps the best studied (and most mechanistically defined) is experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis. As discussed, autoimmune susceptibility mapping of the *B. pertussis* toxin-induced histamine sensitization locus was finally mapped to the H1R gene [30], and H1R^{-/-} mice have significant protection against EAE. In studies from the same group, H2R^{-/-} mice also exhibited attenuated responses, but unlike the H1R^{-/-} mice, who exhibit a protective Th2-cell cytokine profile, H2R^{-/-} mice appear protected due to enhanced monocyte chemoattractant protein-1, an inhibitory control mechanism for the generation of pathogenic T cells in this model [31]. However, EAE is actually exacerbated in HDC^{-/-} mice, with enhanced clinical and histologic symptoms of disease [32], as well as in H3R^{-/-} mice [33]. Therefore, in the context of autoimmune inflammation of the CNS, H3R may have a critical role in limiting inflammation. Interestingly, whereas EAE is reduced in mast cell-deficient mice under many protocols, mast cell-derived histamine has been shown not to be required, as mast cell-deficient mice reconstituted with mast cells from HDC^{-/-} animals exhibited a similar restoration of disease observed with transfer of wild-type mast cells [34••]. Therefore, while mast cell-derived histamine may contribute to disease, other sources of histamine appear to be involved but remain to be identified.

Histamine in Infection

Histamine production and release has been reported as a phenomenon occurring alongside infection, but the significance of this observation has long been unclear. Recent studies using infection models in histamine receptor and HDC^{-/-} mice have begun to elucidate this response. As might be predicted, because many bacteria are capable of significant histamine production themselves, the function of histamine in infection seems highly context dependent—advantageous for the host in some situations and exploited by the pathogen in others.

A positive role for histamine in infectious processes is evident in the intestine after experimental infection of mice with *Yersinia enterocolitica* [35]. Whereas blockade of H1R had little effect on the course of disease, inhibition of H2R greatly accelerated death, while H2R agonists served to delay the responses. This was independent of H2R's effect on gastric pH, as proton pump inhibitors did not elicit similar effects. Instead, bacterial colonization of the mesenteric lymph node and Peyer's patch was substantially enhanced by H2R blockade, indicating a failure to control bacterial access to the lymphatic system or an altered immune response within the local lymphatic that failed to limit infection. However, the precise mechanism through which H2R regulates this bacterial control is unknown.

Histamine appears to play more of a regulatory role in lung infection with *Mycobacterium tuberculosis*, restraining the acute inflammation but ultimately limiting the mouse's ability to clear the infection [36]. Infected HDC^{-/-} mice showed stronger cytokine responses during the acute phase of infection and more effectively cleared bacteria during the earliest stages of chronic phase, although this difference disappeared as the chronic phase continued. Intriguingly, HDC^{-/-} mice displayed increased nitric oxide production in the lung, suggesting a regulatory interaction between histamine and the innate killing machinery that may be influencing bacterial clearance in this model.

In contrast, a pathological role is observed by the hijacking of host histamine by *Plasmodium berghei*, a murine analogue of the human *Plasmodium* sp responsible for malaria [37••]. This study defined a critical role for histamine in the dissemination of malaria. HDC^{-/-} mice were completely resistant to fatal infection by non-CNS tropic strains of malaria and achieved substantially enhanced survival when infected with a more pathogenic, CNS-tropic strain. Additionally, both H1R^{-/-} and H2R^{-/-} mice showed delayed mortality. This protection may relate to the opening of the blood–brain barrier: infected wild-type mice develop substantial CNS vascular leak, whereas HDC^{-/-} mice are completely protected from this effect. Conversely, recent work has demonstrated an enhanced

response to this malaria model in H3R^{-/-} mice, which also develop accelerated vascular leak [38]. As such, there may be a balance in place between H1R- or H2R-mediated opening of the blood–brain barrier than is countered by an H3R-mediated process. In the case of malaria, this would seem to control entry of the infection into the CNS compartment.

Histamine and Pain Sensation

Mast cells and histamine have been well-characterized for their contribution to itch, in part via H1R-dependent activation of type C neurons [39]. However, recent studies have demonstrated that histamine and histamine receptors directly contribute to pain sensations and that antihistamines are effective in preventing mast cell-associated pain. Mast cells are critical for the pathogenesis observed in pseudorabies virus-induced bladder inflammation, a murine model of interstitial cystitis [40]. In this model, mast cells accumulate within the bladder, and TNF- α is critical for the progression of the severe inflammatory response that develops because TNFR1^{-/-} mice fail to develop urothelial inflammatory lesions [41]. However, in addition to this inflammatory response, bladder-associated pain is seen in this model [42]. We demonstrated that whereas mast cells were critical for the development of urothelial inflammation and pain, TNFR1^{-/-} mice continued to exhibit pain reactivity despite the absence of inflammatory lesions [43••]. Conversely, H1R^{-/-} or H2R^{-/-} mice showed significantly attenuated pain sensitivity. Reconstitution of mast cell-deficient mice with wild-type mast cells restored pain, while HDC^{-/-} mast cells had only modest recovery of the pain response but did exhibit restoration of the inflammatory response. Significantly, blockade of H1R or H2R in wild-type mice reduced the pain responses, suggesting antihistamines may be clinically applicable for reducing pain sensation in some diseases. In our studies, the H3R/H4R blocker thioperamide failed to alter bladder pain sensation. However, other studies have implicated H3R in pain responses. In several models of nociception, including acute mechanical triggering (eg, hot plate contact) or chemical-induced responses (eg, formalin induced), H3R blockers (antagonists and inverse agonists) have been proposed to modulate pain sensitivity [44]. Interestingly, in many of these studies, the H3R blocker was most beneficial if delivered directly to the brain. Therefore, there appear to be several modes through which histamine may link to pain sensations. Perhaps the peripheral activation of mast cells promotes pain via H1R/H2R-dependent sensing, while other stimuli may trigger H3R-dependent responses that require central neuron responses.

Alternative Sources of Histamine

An evolving concept within histamine biology in recent years is that of “inducible” histamine. Increasing evidence is emerging in support of histamine production from cells beyond the established sources of mast cells and basophils. This is easily seen in the models of allergic airway disease. Although HDC- and histamine receptor-deficient mice exhibit impaired responses in the ovalbumin plus alum adjuvant model, mast cells are dispensable [45]. As such, mast cell-independent sources of histamine seem to be responsible for facilitating the development of allergic responses in these animals, although the precise source or level of histamine required remains unknown.

Basophils have substantial histamine content and recently have been the subject of considerable interest due to their described role in the initiation of Th2-associated immune response [46]. Additionally, recent work has established their importance as effector cells in adaptive immune responses [47]. Although much has been elucidated from studies of human basophil histamine release and the mechanisms behind this, the precise roles of basophil-derived histamine beyond the immediate hypersensitivity-associated responses remain unknown, especially when compared with our understanding of mast cell-derived histamine. The recent development of basophil-deficient mice may help provide answers to these questions [47].

In addition to mast cells and basophils, several other cell types have been found to produce histamine. On a per-cell basis, the reported magnitude of release in these cell types is only a fraction of that of a mast cell, but accumulation of many cells or intimate contact between histamine producer and histamine responder (as is the case in acid secretion in the stomach) may result in substantial local histamine concentrations, perhaps equivalent or greater to those attainable through stimulation of mast cells or basophils. This concept was proposed by Xu et al. [48], who demonstrated histamine production from neutrophils in response to *Mycoplasma pneumoniae* infection. In their model, neutrophil influx vastly outweighs mast cell numbers and leads to neutrophil-derived histamine being an important component of disease pathogenesis. Dendritic cells, which come into direct, sustained contact with T cells during antigen presentation in the lymph node, also have been shown to produce histamine and respond in an autocrine fashion [14, 49]. In this capacity, histamine acting via H4R promotes enhanced Th2 skewing [14].

Looking forward, detecting histamine-producing cells has been a serious limitation to fully identifying the range and extent of alternative sources. Development of novel murine strains or novel imaging techniques may offer an improved ability to determine cellular histamine release in tissues [50], giving us a clearer understanding of the

diversity of cells capable of producing histamine and its role in disease.

Conclusions

The recent developments in research associated with the histamine pathway are demonstrating that histamine exerts influences that go well beyond its established role as an effector molecule in immediate hypersensitivity. Histamine and the histamine receptors are important in regulating many aspects of diseases. This seems to be the case not only in allergic rhinitis and other allergic diseases but also in autoimmune diseases and infection. The nature of the inflammation, the strength of response, the resolution of response, as well as more complex elements (eg, the sensing of pain during inflammation) are all influenced by histamine. These developments in our understanding suggest that continued investigations into the histamine pathway could lead to novel and previously unanticipated uses for the antihistamine therapeutics that are currently available.

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