Published in final edited form as:
Curr Allergy Asthma Rep. 2011 April ; 11(2): 94–100. doi:10.1007/s11882-010-0163-6.

New Developments in the Use of Histamine and Histamine Receptors

Craig Smuda and **Paul J. Bryce**
Department of Medicine/Division of Allergy-Immunology, Northwestern University Feinberg School of Medicine, McGaw M315, 240 E. Huron St., Chicago, IL 60611, USA

Paul J. Bryce: p-bryce@northwestern.edu

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,

Correspondence to: Paul J. Bryce, p-bryce@northwestern.edu.

Disclosure No potential conflicts of interest relevant to this article were reported.

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 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.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Ricketti, AJ.; Cleri, DJ. Allergic Rhinitis. In: Grammer, LC.; Greenberger, PA., editors. Patterson's Allergic Diseases. 7th Edition. Philadelphia: Lippincott Williams & Wilkins; 2009.
2. Gandhi, C.; Wasserman, SI. Biochemical Mediators of Allergic Reactions. In: Grammer, LC.; Greenberger, PA., editors. Patterson's Allergic Diseases. 7th Edition. Philadelphia: Lippincott Williams & Wilkins; 2009.
3. Jutel M, Akdis M, Akdis CA. Histamine, histamine receptors and their role in immune pathology. Clin Exp Allergy. 2009; 39:1786–1800. [PubMed: 20085595]
4. Gervasini G, Agúndez JAG, García-Menaya J, et al. Variability of the L-Histidine decarboxylase gene in allergic rhinitis. Allergy. 2010 [Epub ahead of print]. This work connects genetic variance in histamine synthesis with the risk of allergic rhinitis.
5. Zhang F, Xiong DH, Wang W, et al. HDC gene polymorphisms are associated with age at natural menopause in Caucasian women. Biochem Biophys Res Commun. 2006; 348:1378–1382. [PubMed: 16919600]
6. Kennedy MJ, Loehle JA, Griffin AR, et al. Association of the histamine N-methyltransferase C314T (Thr105Ile) polymorphism with atopic dermatitis in Caucasian children. Pharmacotherapy. 2008; 28:1495–1501. [PubMed: 19025430]
7. Kim S-H, Kang Y-M, Kim S-H, et al. Histamine N-methyltransferase 939A>G polymorphism affects mRNA stability in patients with acetylsalicylic acid-intolerant chronic urticaria. Allergy. 2009; 64:213–221. [PubMed: 19178400]
8. Yu B, Shao Y, Zhang J, et al. Polymorphisms in human histamine receptor H4 gene are associated with atopic dermatitis. Br J Dermatol. 2010; 162:1038–1043. [PubMed: 20199554]
9. Agundez JA, Luengo A, Herraez O, et al. Nonsynonymous polymorphisms of histamine-metabolising enzymes in patients with Parkinson's disease. Neuromolecular Med. 2008; 10:10–16. [PubMed: 17985251]
10. Ledesma MC, Garcia-Martin E, Alonso-Navarro H, et al. The nonsynonymous Thr105Ile polymorphism of the histamine N-methyltransferase is associated to the risk of developing essential tremor. Neuromolecular Med. 2008; 10:356–361. [PubMed: 18543121]
11. Keeling BH, Vilarino-Guell C, Soto-Ortolaza AI, et al. Histamine N-methyltransferase Thr105Ile is not associated with Parkinson's disease or essential tremor. Parkinsonism Relat Disord. 2010; 16:112–114. [PubMed: 19773194]

12. Garcia-Martin E, Ayuso P, Luengo A, et al. Genetic variability of histamine receptors in patients with Parkinson's disease. BMC Med Genet. 2008; 9:15. [PubMed: 18366640]
13. Noubade R, Saligrama N, Spach K, et al. Autoimmune disease-associated histamine receptor H1 alleles exhibit differential protein trafficking and cell surface expression. J Immunol. 2008; 180:7471–7479. [PubMed: 18490747] The functional importance of strain-specific mutations in H1R was demonstrated in this study.
14. Dunford PJ, O'Donnell N, Riley JP, et al. The histamine H4 receptor mediates allergic airway inflammation by regulating the activation of CD4+ T cells. J Immunol. 2006; 176:7062–7070. [PubMed: 16709868]
15. Bryce PJ, Mathias CB, Harrison KL, et al. The H1 histamine receptor regulates allergic lung responses. J Clin Invest. 2006; 116:1624–1632. [PubMed: 16680192]
16. Jutel M, Watanabe T, Klunker S, et al. Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. Nature. 2001; 413:420–425. [PubMed: 11574888]
17. Koarai A, Ichinose M, Ishigaki-Suzuki S, et al. Disruption of L-histidine decarboxylase reduces airway eosinophilia but not hyperresponsiveness. Am J Respir Crit Care Med. 2003; 167:758–763. [PubMed: 12480609]
18. Kozma GT, Losonczy G, Keszei M, et al. Histamine deficiency in gene-targeted mice strongly reduces antigen-induced airway hyper-responsiveness, eosinophilia and allergen-specific IgE. Int Immunol. 2003; 15:963–973. [PubMed: 12882834]
19. Yamauchi K, Piao HM, Nakadate T, et al. Enhanced goblet cell hyperplasia in HDC knockout mice with allergic airway inflammation. Allergol Int. 2009; 58:125–134. [PubMed: 19153539]
20. Baenkler HW, Lux G, Gunthner R, et al. Biopsy histamine in ulcerative colitis and Crohn's disease. Hepatogastroenterology. 1987; 34:289–290. [PubMed: 3428863]
21. Raithel M, Matek M, Baenkler HW, et al. Mucosal histamine content and histamine secretion in Crohn's disease, ulcerative colitis and allergic enteropathy. Int Arch Allergy Immunol. 1995; 108:127–133. [PubMed: 7549499]
22. Sander LE, Lorentz A, Sellge G, et al. Selective expression of histamine receptors H1R, H2R, and H4R, but not H3R, in the human intestinal tract. Gut. 2006; 55:498–504. [PubMed: 16299042]
23. Varga C, Horvath K, Berko A, et al. Inhibitory effects of histamine H4 receptor antagonists on experimental colitis in the rat. Eur J Pharmacol. 2005; 522:130–138. [PubMed: 16213481]
24. Lee DM, Friend DS, Gurish MF, et al. Mast cells: a cellular link between autoantibodies and inflammatory arthritis. Science. 2002; 297:1689–1692. [PubMed: 12215644]
25. Rajasekaran N, Solomon S, Watanabe T, et al. Histidine decarboxylase but not histamine receptor 1 or 2 deficiency protects from K/BxN serum-induced arthritis. Int Immunol. 2009; 21:1263–1268. [PubMed: 19762454]
26. Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP. Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells. J Pharmacol Exp Ther. 2003; 305:1212–1221. [PubMed: 12626656]
27. Grzybowska-Kowalczyk A, Wojtecka-Lukasik E, Maslinska D, et al. Distribution pattern of histamine H4 receptor in human synovial tissue from patients with rheumatoid arthritis. Inflamm Res. 2007; 56 Suppl 1:S59–S60. [PubMed: 17806182]
28. Adlesic M, Verdrengh M, Bokarewa M, et al. Histamine in rheumatoid arthritis. Scand J Immunol. 2007; 65:530–537. [PubMed: 17523945]
29. Bokarewa M, Bokarew D, Hultgren O, Tarkowski A. Leptin consumption in the inflamed joints of patients with rheumatoid arthritis. Ann Rheum Dis. 2003; 62:952–956. [PubMed: 12972473]
30. Ma RZ, Gao J, Meeker ND, et al. Identification of Bphs, an autoimmune disease locus, as histamine receptor H1. Science. 2002; 297:620–623. [PubMed: 12142541]
31. Teuscher C, Poynter ME, Offner H, et al. Attenuation of Th1 effector cell responses and susceptibility to experimental allergic encephalomyelitis in histamine H2 receptor knockout mice is due to dysregulation of cytokine production by antigen-presenting cells. Am J Pathol. 2004; 164:883–892. [PubMed: 14982842]
32. Musio S, Gallo B, Scabeni S, et al. A key regulatory role for histamine in experimental autoimmune encephalomyelitis: disease exacerbation in histidine decarboxylase-deficient mice. J Immunol. 2006; 176:17–26. [PubMed: 16365391]

33. Teuscher C, Subramanian M, Noubade R, et al. Central histamine H3 receptor signaling negatively regulates susceptibility to autoimmune inflammatory disease of the CNS. Proc Natl Acad Sci U S A. 2007; 104:10146–10151. [PubMed: 17548817]
34. Sayed BA, Christy AL, Walker ME, Brown MA. Meningeal mast cells affect early T cell central nervous system infiltration and blood–brain barrier integrity through TNF: a role for neutrophil recruitment? J Immunol. 2010; 184:6891–6900. [PubMed: 20488789] This study demonstrated the importance of mast cells in EAE development but elegantly showed that mast cell-derived histamine was not required. Because HDC-deficient mice are affected, this work challenges our understanding of the critical sources of histamine in inflammation.
35. Handley SA, Dube PH, Miller VL. Histamine signaling through the H(2) receptor in the Peyer's patch is important for controlling Yersinia enterocolitica infection. Proc Natl Acad Sci U S A. 2006; 103:9268–9273. [PubMed: 16717182]
36. Carlos D, Fremond C, Samarina A, et al. Histamine plays an essential regulatory role in lung inflammation and protective immunity in the acute phase of Mycobacterium tuberculosis infection. Infect Immun. 2009; 77:5359–5368. [PubMed: 19822651]
37. Beghdadi W, Porcherie A, Schneider BS, et al. Inhibition of histamine-mediated signaling confers significant protection against severe malaria in mouse models of disease. J Exp Med. 2008; 205:395–408. [PubMed: 18227221] The findings from this study illustrate how pathogens can use host-derived histamine to their advantage. Here, the disease severity and spread to the CNS during malaria infection require that histamine be produced in the animals.
38. Beghdadi W, Porcherie A, Schneider BS, et al. Histamine H(3) receptor-mediated signaling protects mice from cerebral malaria. PLoS One. 2009; 4:e6004. [PubMed: 19547708]
39. Kim D, Baraniuk JN. Neural aspects of allergic rhinitis. Curr Opin Otolaryngol Head Neck Surg. 2007; 15:268–273. [PubMed: 17620902]
40. Chen MC, Keshavan P, Gregory GD, Klumpp DJ. RANTES mediates TNF-dependent lamina propria mast cell accumulation and barrier dysfunction in neurogenic cystitis. Am J Physiol Renal Physiol. 2007; 292:F1372–F1379. [PubMed: 17244892]
41. Chen MC, Mudge CS, Klumpp DJ. Urothelial lesion formation is mediated by TNFR1 during neurogenic cystitis. Am J Physiol Renal Physiol. 2006; 291:F741–F749. [PubMed: 16622179]
42. Rudick CN, Chen MC, Mongiu AK, Klumpp DJ. Organ cross talk modulates pelvic pain. Am J Physiol Regul Integr Comp Physiol. 2007; 293:R1191–R1198. [PubMed: 17626130]
43. Rudick CN, Bryce PJ, Guichelaar LA, et al. Mast cell-derived histamine mediates cystitis pain. PLoS One. 2008; 3:e2096. [PubMed: 18461160] This work illustrates how mast cells can elicit multiple components of a disease response. In cystitis of the bladder, TNF-α is crucial for the inflammation, but not pain. Instead, pain is induced via mast cell-derived histamine and histamine receptors.
44. Hough L, Rice FL. H3 Receptor Miniseries: H3 Receptors and Pain Modulation: Peripheral, Spinal and Brain Interactions. J Pharmacol Exp Ther. 2010 in press.
45. Yu M, Tsai M, Tam SY, et al. Mast cells can promote the development of multiple features of chronic asthma in mice. J Clin Invest. 2006; 116:1633–1641. [PubMed: 16710480]
46. Sokol CL, Medzhitov R. Role of basophils in the initiation of Th2 responses. Curr Opin Immunol. 2010; 22:73–77. [PubMed: 20144855]
47. Wada T, Ishiwata K, Koseki H, et al. Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks. J Clin Invest. 2010; 120:2867–2875. [PubMed: 20664169]
48. Xu X, Zhang D, Zhang H, et al. Neutrophil histamine contributes to inflammation in mycoplasma pneumonia. J Exp Med. 2006; 203:2907–2917. [PubMed: 17158962]
49. Gutzmer R, Langer K, Lisewski M, et al. Expression and function of histamine receptors 1 and 2 on human monocyte-derived dendritic cells. J Allergy Clin Immunol. 2002; 109:524–531. [PubMed: 11898002]
50. Seto D, Soh N, Nakano K, Imato T. Selective fluorescence detection of histamine based on ligand exchange mechanism and its application to biomonitoring. Anal Biochem. 2010; 404:135–139. [PubMed: 20450876]