

The New Biology of Histamine Receptors

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The physiologic functions of histamine have been recognized for more than 100 years, yet new roles are still being uncovered. Most importantly, a newly discovered receptor of the amine has helped refine our understanding of histamine. This new receptor, the histamine H_4 receptor (H_4R), has a higher affinity for histamine compared with the histamine H_1 receptor and appears to be more selectively expressed, found mainly on hematopoietic cells. H_4R is involved in chemotaxis and inflammatory mediator release by eosinophils, mast cells, monocytes, dendritic cells, and T cells. Studies in animal models using selective antagonists or H_4R -deficient mice have shown a role for the receptor in inflammation *in vivo*. In particular, H_4R antagonists have shown promise in experimental models of asthma and pruritus, two conditions where currently marketed antihistamines targeting the histamine H_1 receptor are not optimally effective in humans. Thus, a new class of H_4R -specific antihistamines may be distinctively effective in treating allergic diseases associated with chronic pruritus and asthma.

Introduction

Histamine has long been recognized as an important mediator of allergic and inflammatory responses. Histamine is released mainly from mast cells and basophils in response to stimuli such as allergens. During allergic responses, histamine produced by mast cell degranulation causes changes in vascular permeability, drives the infiltration of inflammatory cells, and modulates mediator production by these cells.

Histamine is now known to act through four different G-protein-coupled receptors (Table 1). The histamine H_1 receptor (H_1R) is thought to be responsible for most of

the acute inflammatory responses. Antagonists (or inverse agonists) for this receptor (eg, diphenhydramine and cetirizine) have been successful drugs to treat allergy. The best-characterized function of the histamine H_2 receptor (H_2R) is modulation of gastric acid release, and antagonists for this receptor are used to treat gastroesophageal reflux disease and peptic ulcers, as exemplified by famotidine and ranitidine. The histamine H_3 receptor (H_3R) is highly expressed in the nervous system and modulates neurotransmitter levels. No H_3R -selective antihistamines are currently marketed; however, many are under development to treat sleep and cognition disorders. Although recent advances have occurred in the understanding of H_1R , H_2R , and H_3R biology, including the role of histamine in nonallergic diseases (for example, see Adlesic et al. [1] and Leurs et al. [2]), this review focuses on recent progress regarding the histamine H_4 receptor (H_4R), which has the potential to dramatically change our view of the role of histamine in asthma and allergic responses.

The Histamine H_4 Receptor

H_4R is the most recently identified receptor for histamine. It appeared to have a selective expression pattern restricted to hematopoietic cells, prompting investigation into its role in modulating the effects of histamine in immune and inflammatory responses. Receptor expression coupled with pharmacologic proof of function has been shown for eosinophils, mast cells, dendritic cells, CD8⁺ T cells, and monocytes. However, it appears that the receptor expression levels and activity change in response to inflammatory stimuli and to the state of the cell, thus making definitive determination of where the receptor is expressed difficult. For example, Gantner et al. [3] have shown a clear function for the H_4R in CD8⁺ T cells by quantifying mRNA expression and applying selective pharmacologic agents, but found that the level of expression varied from donor to donor. In contrast, Ling et al. [4] could not detect any expression in CD8⁺ T cells. Similar discrepancies have been reported for monocytes. Dijkstra et al. [5•] have shown H_4R expression in monocytes using antibody staining, and that this expression could be modulated by different inflammatory stimuli. Such modulation may account for some reported discrepancies in expression. In addition to expression on hematopoietic

Table 1. Comparisons of four histamine receptors

	pKi for histamine*	G protein coupling	Expression	Pharmacologic agents†	Disease indications†
H ₁ R	4.2 ± 0.1	Gα _q , Ca ²⁺ influx	Ubiquitous	Diphenhydramine, cetirizine	Allergy, acute pruritus
H ₂ R	4.3 ± 0.1	Gα _s , increases in cAMP	Ubiquitous	Famotidine, ranitidine	Gastroesophageal reflux disease, peptic ulcers
H ₃ R	7.8 ± 0.1	Gα _{i/o} , inhibition of cAMP	Central nervous system	Clobenpropit, thioperamide	Sleep and cognition disorders
H ₄ R	8.1 ± 0.1	Gα _{i/o} , Ca ²⁺ influx	Hematopoietic cells, neurons	Thioperamide, JNJ 7777120	Asthma, pruritus

*Data for histamine pKi from Venable and Thurmond [11].

†Pharmacologic agents listed for H₁R and H₂R are only a few of the currently marketed antihistamines, and those listed for H₃R and H₄R are a few of the tool compounds used in various studies. Similarly, the disease indications for H₁R and H₂R are approved indications, whereas those for H₃R and H₄R are potential indications.

cAMP—cyclic adenosine monophosphate.

cells, there have been reports that H₄R is present on other cell types including intestinal epithelium [6], brain [7], and nerves of human nasal mucosa [8]. Recently, functional data were reported for H₄R on human enteric neurons [9•].

Like other histamine receptors, H₄R is a G-protein-coupled receptor. The H₄R protein sequence is most homologous to H₃R and contains many of the same key amino acid residues involved in histamine binding with the other histamine receptors; however, the overall homology to H₁R and H₂R is quite low. H₄R has a very high affinity for histamine with a K_d value of around 5 nM [10], in contrast to H₁R, which has a more than 1000-fold lower affinity. This divergence in protein sequence and affinity for histamine may have important implications for the physiologic and cellular functions of the different receptors. For example, H₁R activation requires high concentrations of histamine, like those typically found immediately upon mast cell degranulation, whereas H₄R could respond to lower levels of histamine released by other histamine-producing cells. Another aspect that emerged from pharmacologic studies of H₄R is that all the clinically used antihistamines targeting H₁R and H₂R have no affinity for H₄R [11,12]; therefore, the clinical experiences using these compounds are not applicable to H₄R. For example, histamine is produced in large quantities during an asthmatic attack, but neither H₁R nor H₂R antagonists are effective in treating asthma. This has been cited as evidence that histamine has no role in asthma pathology. However, the discovery of H₄R and the demonstration of its role in inflammation may reopen some avenues of clinical investigation and suggest new ones.

In Vitro Effects of the Histamine H₄ Receptor

The availability of H₄R-deficient mice and selective ligands for the receptor has made it possible to study its role both in vitro and in vivo. The first biologic effect reported was on mast cells. Activation of H₄R on mast cells with histamine induced calcium mobilization and

chemotaxis [13]. These effects were abrogated by treatment with H₄R antagonists [13,14], but not antagonists to the other histamine receptors. Neither response was seen in mast cells from H₄R-deficient mice. In this study, however, H₄R did not appear to play a role in immunoglobulin (Ig) E-mediated degranulation, or prostaglandin or leukotriene release [13]. The H₄R-mediated chemotaxis of mast cells is apparent in vivo. Histamine inhalation by mice led to an increase in mast cells in the trachea and to a change in their localization [14]. An H₄R antagonist inhibited these effects. Increases in mast cell density and changes in localization occur in many human inflammatory diseases; in particular, these effects have been shown in nasal tissue upon allergen exposure [15,16]. Histamine also enhances mast cell precursor chemotaxis to CXCL12, but not to stem cell factor (SCF) or leukotriene (LT) B₄; H₄R antagonists—but not antagonists for H₁R or H₂R—blocked this effect [17]. However, this may not be a direct chemotactic effect, because histamine only appeared to prime cells to migrate to CXCL12.

Subsequently, H₄R-mediated chemotaxis in eosinophils, dendritic cells, and T cells has been reported. It is particularly clear in eosinophils where histamine or H₄R agonists induced chemotaxis, cell shape change, and actin polymerization and synergized with other chemotactic agents [4,12,18,19]. H₄R antagonists blocked these histamine-induced effects in eosinophils, and histamine-induced adhesion molecule upregulation in eosinophils [4,18]. Similarly, dendritic cell migration and actin polymerization can also be modulated by H₄R. Both effects can be induced by histamine or H₄R agonists, and the chemotactic effect was inhibited by an H₄R antagonist [20•]. Recent work indicated that T cell migration may be H₁R and H₄R mediated, although the data are far from conclusive. High concentrations of histamine induced T-cell chemotaxis that was mediated by H₁R and H₄R, because the effect was blocked by H₁R or H₄R antagonists [21,22•], and H₁R or H₄R agonists mimicked the histamine response [22•]. However, the selectivity of the agonist at the concentrations used is an open question.

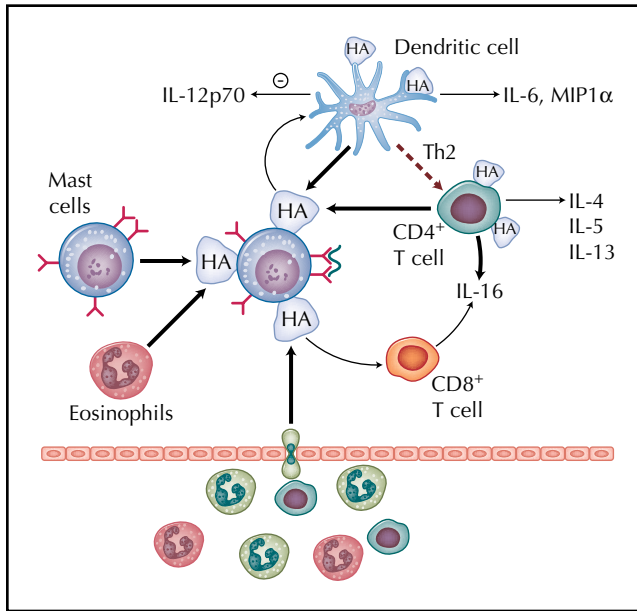


Figure 1. Inflammatory stimuli can induce the release of histamine from mast cells via degranulation or through de novo synthesis in other cells such as dendritic cells and T cells. Histamine is chemoattractant (**bold arrows**) for mast cells, eosinophils, CD4⁺ T cells, and dendritic cells and can lead to their local reorganization in tissues or to recruitment from circulation. Furthermore, histamine can also mediate cytokine production (*thin arrows*) of CD8⁺ T cells and dendritic cells. The effects on dendritic cells help drive T helper (Th) 2 polarization of CD4⁺ T cells by inhibiting IL-12p70 production and inducing IL-6.

In addition to chemotaxis, H₄R is also involved in cytokine production in several cell types. Histamine induced interleukin (IL)-16 production in CD8⁺ T cells [3]; this induction was blocked by H₂R or H₄R antagonists but not by H₁R antagonists. Induction of IL-16 production in CD8⁺ T cells by H₂R and H₄R agonists further confirmed a role for these receptors in this response. IL-16 is an important chemoattractant for T cells; therefore, histamine may have an indirect effect on T-cell recruitment by modulating levels of IL-16. H₄R also modulated mediator release from dendritic cells. Histamine inhibited poly-IC-induced IL-12p70 release from dendritic cells [20•]. This effect was mimicked by an H₄R agonist and blocked by H₄R antagonists. Furthermore, Toll-like receptor (TLR)-stimulated production of IL-6, keratinocyte-derived chemokine (KC), macrophage inflammatory protein (MIP)-1α, interferon-inducible protein (IP)-10, and tumor necrosis factor (TNF)-α were blocked by an H₄R antagonist and attenuated in dendritic cells from H₄R-deficient mice; however, IL-10 and IL-12p70 were unchanged [23••]. In an in vitro study, H₄R antagonist-treated dendritic cells or cells from H₄R-deficient mice were defective in directing the T helper (Th) 2 polarization of T cells [23••]. These results suggest that H₄R on dendritic cells creates a Th2-promoting environment by inhibiting IL-12p70 production and stimulating other proinflammatory cytokines and chemokines, like IL-6 and TNF-α, supporting earlier findings

that histamine can influence the activation of T cells by dendritic cells. Furthermore, it was recently shown that histamine downregulated the constitutive production of monocyte chemoattractant protein (MCP) 1 (CCL2) in human monocytes; this effect was reversed by an H₄R antagonist and was mimicked by an H₄R agonist [5•].

In vitro studies of histamine effects via H₄R lead to the following model for its possible role in inflammatory responses (Fig. 1). Upon exposure to inflammatory stimuli, histamine can be released from several different cells. Allergen-dependent degranulation of mast cells releases a large quantity of histamine from internal stores, but other cells (eg, dendritic cells, T cells, and neutrophils) can also produce it. Once released, histamine can act alone as a chemoattractant factor or in conjunction with other chemoattractants. This can lead to redistribution of tissue resident cells to the sites of inflammation and to recruitment of circulating cells. Furthermore, histamine can activate cells (eg, dendritic cells) that can modulate T-cell activation and polarization. Therefore, the effects of H₄R on mast cells, eosinophils, dendritic cells, and T cells position it at the intersection of innate and adaptive immune responses.

The Histamine H₄ Receptor in Models of Inflammation

In vitro data clearly point to a role for H₄R in inflammatory and immune responses, and this has been borne out in animal models. In a rat model of carrageenan-induced acute inflammation, H₄R antagonists inhibited edema formation at early time points [24]. This is not likely to be a direct effect on vascular permeability because the same antagonists had no effect on histamine-induced edema formation [14]. Interestingly, H₄R antagonists also tended to reverse the thermal hyperalgesia induced by carrageenan injection with a similar time course as the edema [24]. It is unclear whether this is an indirect effect of reducing the inflammation, or if it points to a direct role for H₄R in pain perception. The latter explanation for this nociceptive neural phenomenon is perhaps consistent with effects seen in pruritus models, detailed later.

H₄R antagonists have been shown to reduce neutrophil influx in both zymosan-induced pleurisy and peritonitis models [14,25]. In these models, mice injected with zymosan into the pleural or peritoneal cavity developed neutrophilia within hours after challenge. Zymosan is thought to bind to TLR2 on mast cells and trigger a cascade of signal transduction via MyD88, leading to mast cell activation and neutrophil recruitment. Pretreatment with H₄R antagonists significantly reduced the number of infiltrated neutrophils, whereas H₁R or H₂R antagonists had no effect. Mast cells were identified as the possible target cell, because both the pleurisy and peritonitis models are mast cell-dependent and the recruitment of neutrophils is dramatically reduced in

mast cell-deficient mice (W/W^v) [25,26]. Furthermore, no inhibition of the residual neutrophil influx by an H₄R antagonist was seen in the mast cell-deficient mice [25]. Finally, H₄R antagonists had no effect in mast cell-independent models of pleurisy or peritonitis [14,25]. Therefore, clearly mast cells are required for H₄R-specific effects in this model. One explanation could be that they are the major source of histamine. Alternatively, because H₄R is expressed on mast cells, it is also possible that H₄R mediates other mast cell functions driving neutrophil infiltration. In the zymosan-induced pleurisy model, lack of mast cells or treatment with the dual H₃R/H₄R antagonist, thioperamide, reduced the zymosan-stimulated LTB₄ levels; therefore, it was proposed that H₄R activation on mast cells was crucial for mast cell LTB₄ production. LTB₄ is an important chemoattractant for neutrophils, and its reduction would result in decreased neutrophil influx. It was recently shown that an inhibitor for LTA₄ hydrolase, which is the enzyme that converts LTA₄ to LTB₄, reduced neutrophilia in the zymosan-induced peritonitis model [27]. However, suppression of LTB₄ production by an H₄R antagonist has not been detected in the zymosan-induced peritonitis model (Rao and Thurmond, unpublished results). In addition, an in vitro study showed that H₄R had no effect on IgE-mediated LTB₄ production by mast cells [13]. On the other hand, TLR-stimulated LTB₄ production was not measured in the study, and the known heterogeneity of mast cells in vivo make it difficult to rule out an effect.

H₄R is also involved in inflammation associated with colitis. In a rat model of trinitrobenzene sulphonic acid (TNBS)-induced colitis, H₄R antagonists significantly protected the animals from colon damage, as judged by decreases in lesion area, colon weight, and reversal of body weight loss [28•]. Similar to the peritonitis and pleurisy models, treatment with H₄R antagonists decreased the number of infiltrating neutrophils and thus the myeloperoxidase levels in tissue. Moreover, H₄R antagonist treatment reduced TNF- α levels in tissue. The mechanisms may be similar to the one described in the pleurisy and peritonitis models because this colitis model has been shown to depend on TLR activation.

The Histamine H₄ Receptor in Models of Asthma

Histamine and asthma are linked by a long history. Patients with asthma have higher levels of histamine associated with increased airway inflammation and obstruction [29]. Furthermore, histamine has long been known to have bronchoconstricting properties. Because histamine is a putative mediator of asthma, but H₁R or H₂R antagonists are not effective treatment, ongoing studies are directed to H₄R-related histamine mechanisms in asthma.

Dunford et al. [23••] have used a murine asthma model to help understand the function of H₄R in this disease. Although murine models rarely reproduce completely all the features of human disease, after sensitization and respiratory tract challenges with antigen, mice develop a clinical syndrome that closely resembles allergic asthma, characterized by eosinophilic lung inflammation, airway hyperresponsiveness, increased IgE, mucus hypersecretion, and eventually airway remodeling. The allergic inflammation in the lung is characterized by increased concentrations of Th2 cytokines (IL-4, IL-5, and IL-13). Mice treated with H₄R antagonists during challenge with allergen showed markedly and significantly reduced eosinophil and lymphocyte infiltration into the airways [23••]. Furthermore, decreases in Th2-type (IL-5, IL-4, IL-13) and inflammatory cytokines (IL-6, IL-17) were associated with in vitro restimulation of lymphocytes with antigen [23••]. In contrast, treatment with an H₁R antagonist had no effect when dosed during the challenge phase of this model, consistent with the clinical experience using H₁R antagonists in humans. Similar results were found when H₄R-deficient mice were used, confirming the selectivity of the compound data for H₄R [23••].

Treatment of mice with an H₄R antagonist only during the sensitization phase of the model also reduced lung inflammation and T-cell cytokine production compared to wild-type animals. In addition, antigen-specific IgE and IgG1 levels were reduced in H₄R-deficient mice or those treated with an H₄R antagonist during sensitization, suggesting that H₄R mediated T-cell functions in this model. Dendritic cells and T cells are central to pathogenesis in this mouse asthma model, and the in vivo data clearly suggest that H₄R has an impact on T-cell activation, as evidenced by the inhibitory effects of H₄R antagonists or H₄R-deficient animals on antibody and cytokine production. This was further supported by in vitro data showing that dendritic cells treated with an H₄R antagonist or from H₄R-deficient mice were deficient in their ability to properly polarize Th2 CD4⁺ T cells. T cells polarized when H₄R was absent or blocked on dendritic cells produced lower levels of IL-4, IL-6, and IL-17, even though they proliferated normally. This defect in Th2 T-cell polarization appeared to be due to lack of the proper cytokine environment produced by the dendritic cells, because the levels of major histocompatibility complex (MHC) II and costimulatory molecules were not changed [23••].

Another important aspect of this asthma model is that mast cells were not needed as either the source of histamine or the target cells of H₄R antagonists in vitro or in vivo. The model had previously been described as mast cell independent [30], and the H₄R antagonist was equally efficacious in mast cell-deficient animals [23••]. In this case, dendritic cells may be the source of histamine, because activated dendritic cells were shown to produce histamine in vitro upon stimulation and this was required

for optimal IL-6 production [23••]. Therefore, H₄R activation can occur in the absence of mast cells.

Recently, it was suggested that H₄R may be involved in the recruitment of regulatory T cells [22•]. When delivered intratracheally, 4-methylhistamine, a dual H₂R/H₄R agonist, reduced airway inflammation and hyperreactivity in a murine model of asthma [12]. It was suggested that this was due to recruitment of regulatory T cells (CD25⁺, FoxP3⁺ CD4⁺) to the lung because these cells could also be directly recruited by intratracheal administration of 4-methylhistamine in the absence of inflammation. This is not completely consistent with the previous results using H₄R antagonists or H₄R-deficient mice, but differences in the route of delivery (systemic vs intratracheal) and challenge protocol may account for this. In addition, high concentrations of 4-methylhistamine were used in this study and the authors failed to show the selectivity of the response by blocking it with an H₄R-specific antagonist, especially because 4-methylhistamine selectivity has not been studied extensively in mice. Nevertheless, these results open exciting new possibilities for a role of H₄R in T-regulatory cells.

These recent findings in animal models may help clarify our understanding of histamine in asthma, given the lack of efficacy seen in the clinic with H₁R antagonists. In murine asthma models, H₄R appears to have an impact on Th2 cells and possibly T-regulatory cells. In particular, the Th2 cytokines IL-4, IL-5, and IL-13 are all reduced. IL-5 is a growth factor and activation factor for eosinophils, whereas IL-4 is the main driver of isotype switching in B cells to produce high-affinity IgE. Both cytokines are important factors in Th2 T-cell development. IL-13 is a major mediator of remodeling, airway hyperreactivity, and goblet cell hyperplasia. The combined attenuation of these Th2 cytokines by H₄R antagonists or in H₄R-deficient animals could explain the observations in the murine model of asthma. Effects seen *in vitro* on mast cells and eosinophils may also be key to disease pathology in asthma; thus, it is hoped that antagonists of the receptor will be effective in treating allergic asthma in humans and may help explain the puzzling lack of efficacy of H₁R antagonists in this disease.

The Histamine H₄ Receptor in Models of Pruritus

There are many known mediators of itch, including neuropeptides, amines, cytokines, neurotrophins, proteases, cannabinoids, and opioids; however, histamine has been the most extensively studied (see Paus et al. [31] for a recent review). Antihistamines that target H₁R appear to be fairly effective in controlling acute pruritus, such as that in urticaria. However, efficacy for pruritus associated with chronic diseases like atopic dermatitis and psoriasis is less clear, and a retrospective review of all published clinical data concluded that H₁R antihistamines are inef-

fective for such conditions [32]. As with asthma, it is possible that new antihistamines specific for H₄R might offer the promise of new antipruritic agents for these intractable clinical conditions.

Evidence for this has recently been shown in animal models of itch. Histamine-induced itch in mice can be inhibited by H₄R antagonists and is attenuated in H₄R-deficient mice [33,34••]. Some H₁R antagonists also partially block this effect—but only centrally acting antagonists like diphenhydramine, and not peripherally restricted ones like fexofenadine. Thus, in mice, both H₁R and H₄R may be involved in histamine-induced scratching. Indeed, although treatment with antagonists to either receptor provides only partial inhibition, a combined treatment completely inhibits itch. Furthermore, in H₄R-deficient mice, adding a centrally acting H₁R antagonist completely inhibited the residual histamine-induced scratching [34••]. A role for H₁R and H₄R in mediating itch in mice was further proved when agonists of the receptors induced itch [33,34••].

Clearly, histamine is not the only pruritogenic substance, and during an allergic reaction mast cells and other cells can produce substances known to cause itch. Theoretically, itch associated with mast cell degranulation may be more similar to the itch seen in chronic conditions, as in atopic dermatitis. The role of H₄R in pruritus caused by allergic mechanisms was examined in a murine model using intradermal injection of antigen-specific IgE followed by systemic administration of antigen 24 hours later. In this model an H₄R antagonist significantly attenuated the itch observed at the IgE injection site, and almost no scratching was observed in H₄R-deficient mice [34••]. A centrally acting H₁R antagonist, diphenhydramine, had a slight but significant effect, whereas fexofenadine, a peripherally restricted H₁R antagonist, did not reduce scratching. This finding suggests that H₄R antagonists may be able to inhibit pruritus induced by multiple pruritogens, beyond histamine.

Of particular interest is that expression of H₄R on mast cells or other hematopoietic cells was not required for the pruritic activity of H₄R. Histamine or H₄R agonist-induced scratching was similar in mast cell-deficient and wild-type mice, and inhibition by the H₄R antagonist was also unchanged [34••]. In fact, H₄R expression on any cell of hematopoietic lineage was not required because reconstitution of H₄R-deficient mice with bone marrow from wild-type mice could not restore the pruritic response to an H₄R agonist [34••]. Finally, compound 48/80 can induce itch in a mast cell-independent fashion, and this too can be attenuated by treatment with an H₄R antagonist or in H₄R-deficient mice [34••]. These results led Dunford et al. [34••] to suggest that H₄R-mediated pruritus could result from actions on peripheral neurons. In a recent *in vitro* study with human submucous plexus, histamine excited human enteric neurons; this effect involved not only H₁R and H₂R, but also H₃R and H₄R [9•]. This *in vitro* study with human tissue provides the first evidence for H₄R function in neurons, and

supports a potential neuronal role for H₄R in mediating pruritus in humans.

Itch mechanisms in humans are complicated, and the clinical relevance of animal models of acute itch to human chronic pruritus should not be overstated. However, the observation that H₁R antagonists in animal itch models were minimally effective and required central activity are consistent with current clinical experience using H₁R-targeted antihistamines in human allergic diseases, such as atopic dermatitis. Therefore, it is hoped that the superior efficacy of H₄R antagonists in these models will translate into efficacy in the clinic, and antihistamines targeting H₄R may offer a more effective treatment for human pruritic diseases.

Conclusions

Information obtained from in vitro studies, studies using genetically modified mice, and pharmacologic studies in various animal models have implicated H₄R in inflammation, asthma, and pruritus. In addition to mast cells and eosinophils, the effects of blocking H₄R on dendritic cells, monocytes, and T cells may open the possibility for H₄R antagonists in treating allergic inflammatory diseases, asthma, and autoimmune diseases. The inhibitory effect of H₄R antagonists on neutrophil influx in response to TLR activation in several models suggests that such antagonists may also be useful in treating chronic obstructive pulmonary disease, which is characterized by severe neutrophil invasion. Additionally, the possibility of combined anti-inflammatory and antipruritic effects is especially promising for treating atopic dermatitis and psoriasis. The recent biology of histamine and its latest receptor suggest that a new generation of antihistamines targeting H₄R could have significant clinical implications and offer more effective treatments for a host of human diseases.

Disclosure

Drs. Huang and Thurmond are both employed by Johnson & Johnson.

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- Of major importance

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