

Expert Opinion

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The histamine H₄ receptor in autoimmune disease

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Histamine exerts its actions through four known receptors. The recently cloned histamine receptor, H₄R, has been shown to have a role in chemotaxis and mediator release in various types of immune cells including mast cells, eosinophils, dendritic cells and T cells. H₄R antagonists have been shown to have anti-inflammatory properties and efficacy in a number of disease models, such as those for asthma and colitis *in vivo*. Recently, H₄R antagonists have been developed with high receptor affinity and specificity, which make them good tools for further characterisation of the receptor in animal models and, eventually, in humans. Histamine and the cells that produce it, such as mast cells and basophils, have long been thought to be involved in allergic conditions but there has recently been recognition that they may also play a role in various autoimmune diseases. Given this and the fact that the H₄R has function in mast cells, dendritic cells and T cells, antagonists for the receptor may be useful in treating autoimmune diseases in addition to allergy.

Keywords: dendritic cells, mast cells, multiple sclerosis, rheumatoid arthritis, T cells

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1. Introduction

Autoimmune diseases, diseases of mounting aberrant immunogenic responses against the body's own cells or tissues, are associated with a failure in maintaining self tolerance. Some prominent examples include rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis among others. The actual mechanisms that drive disease initiation and progression are largely unknown. The recently discovered histamine H₄ receptor (H₄R) has been implicated in a variety of allergic conditions [1]. This review discusses the potential involvement of this receptor in the pathophysiology of autoimmune disease.

Since the first report of histamine in 1910 [2], major progress has been made in understanding its functions in multiple physiological and pathological processes. So far, four receptors are known to bind histamine, all of which are G-protein-coupled receptors. The H₁R is expressed in multiple cell types, including endothelial cells and smooth muscle cells, where it mediates vasodilation, bronchoconstriction and so on. Antagonists of the H₁R have been used for many years in the treatment of allergic inflammatory responses [3,4]. The H₂R is also expressed on many cell types and plays a crucial role in gastric acid release, and H₂R antagonists have had success in treating gastric ulcers [5]. The H₃R is expressed primarily in the nervous system and plays a role in central and peripheral neurotransmission. H₃R ligands are not currently in clinical use but have been suggested to have use in treating cognition disorders, obesity, insomnia, myocardial ischaemic arrhythmias and so on [6,7]. The H₄R is the recently characterised histamine receptor and its role in inflammatory, allergic and autoimmune diseases is still being clarified.

The H₄R was independently cloned and characterised by several groups [8-13]. It has a low homology to other histamine receptors, sharing only 35% amino acid

identity with the H₃R (58% homology in its transmembrane regions) and even less with H₁R or H₂R. Phylogenetic analysis indicates that both the H₄R and H₃R are more closely related to muscarinic receptors than to H₁R and H₂R [14]. The human H₄R has 65 – 72% sequence homology with mouse, rat, guinea-pig and porcine H₄R [15,16], indicating it has been poorly conserved during evolution. These differences are reflected in the affinity of histamine and other ligands, which potentially complicates *in vivo* pharmacology work. The monkey H₄R has the highest homology to the human H₄R [17], and may serve as a good model species for pharmacological comparison with humans.

Histamine receptors are G-protein-coupled receptors containing a transmembrane region consisting of a seven α -helical bundle. All of these receptors signal through coupling and activating specific G proteins. The H₁R couples to G α_q protein causing calcium mobilisation; the H₂R couples to G α_s causing cAMP accumulation, and the H₃R couples to G $\alpha_{i/o}$ and inhibits adenylyl cyclase. In primary cells, activation of the H₄R appears to mainly signal through increases in intracellular calcium. Histamine induced a calcium mobilisation in mouse mast cells, which was not present in mast cells from H₄R-deficient mice and could be blocked by a H₄R antagonist [18,19]. This increase can also be blocked by pertussis toxin (thus suggesting G $\alpha_{i/o}$ linkage) and the phospholipase C inhibitor 1-(6-[17 β -3-(methoxyestra-1,3,5[10]-trien-17-yl)amino]hexyl)-1H-pyrrol-2,5-dione (U73122) [18]. In eosinophils, histamine also induces calcium mobilisation via the H₄R [20–22]. A model was suggested that the H₄R binds to G $\alpha_{i/o}$ and the released G $\beta\gamma$ then activates phospholipase C to hydrolyse phosphatidylinositol 4,5-bisphosphate. The product from this process, inositol-1,4,5-trisphosphate, subsequently induces calcium mobilisation and other downstream effects [23]. In H₄R-transfected cells, an increase in calcium mobilisation induced by histamine was also observed in the presence of chimaeric G proteins (G α_{q5} , G $\alpha_{q11/2}$, G α_{q3} , G α_{15} or G α_{16}) [9,11,13,15]. The H₄R can also couple to G $\alpha_{i/o}$ causing decreased cAMP in some transfected cells [10,15]. Other signalling events have been reported for H₄R activation, including MAPKs activation [13] and activator protein 1 transcription factor activation [24]. The receptor has also been shown to have constitutive activity in transfected cells, opening the possibility for the development of inverse agonists that may have different properties than neutral antagonists.

H₄R transcripts have most clearly been shown in spleen, thymus and bone marrow, although very low levels of expression can be seen in lung, colon, small intestine, stomach, and brain. Of particular relevance to autoimmune disease, expression of the receptor has been reported on synovial cells from rheumatoid arthritis patients [25]. The expression in haematopoietic cells has received the most attention. Clear expression coupled with functional activity has been shown on eosinophils, mast cells, basophils, dendritic cells and CD8⁺ T cells [18,24,26,27]. In general, it appears that the H₄R is expressed at low levels and may be regulated by inflammatory stimuli. Indeed, it has been shown that the H₄R promoter

region has several putative regulatory elements that could be activated by TNF- α or IL-6 [28]. These facts have made the determination of expression in other cell types by real time polymerase chain reaction difficult to interpret because positive signals could be due to the impurity of cell preparations and negative signals may lack the proper stimuli. With this in mind, expression of the receptor has also been reported in tonsil B cells, fibroblast, bronchial epithelial and smooth muscle cells, endothelial cells, neutrophils, monocytes and both T_H1 and T_H2 CD4⁺ T cells [8,26,27]. Expression has also been detected in some colon cancer cell lines [29]. Although the sequence homology across species is low, the distinctive expression profile for H₄R seems to be conserved between human, mouse, rat and pig, suggesting its involvement in immune responses.

2. Ligands for the histamine H₄ receptor

Since the discovery of the H₄R in 2000, there has been a significant effort to identify selective modulators of this receptor that may serve as tools for understanding its physiological function. Histamine (1; Figure 1) has been described as binding to the human H₄R with an inhibitory rate constant (K_i) value of 7.7 – 8.4 nM [9–11,13,30]. This is similar to the affinity of histamine for the H₃R (K_i = 5.4 nM) [10], but contrasts to the relatively low affinity of this endogenous amine for the H₁R and H₂R (K_i = 400 – 600 nM) [31,32]. This disparity is also reflected in the affinity of other known histaminergic ligands for the human H₄R as demonstrated in the initial pharmacological characterisation of the H₄R [33,34]. In general, there are fewer histamine H₁R and H₂R ligands with more potent affinity for the H₄R than H₃R ligands, which has been attributed to the higher sequence homology (35 – 48%) of the H₃R and H₄R. Some notable exceptions are the H₁R antagonist clozapine (2; K_i = 510 nM) and the H₂R antagonist burimamide (3; K_i = 63 nM) [10]. Analogues of burimamide 4 – 6 were recently synthesised and evaluated at the H₄R. They were found to have moderate potencies and all demonstrated partial agonist activity in a functional assay, as does burimamide itself [35]. Most interestingly, 4-methylhistamine (7), the known H₂R agonist, was described as a selective histamine H₄R agonist with reported K_i value of 7 and 50 nM and selectivity of 100 to 100,000-fold over the other histamine receptors [35,36]. This will undoubtedly be an important pharmacological tool in the future. There are several imidazole-based H₃R ligands that exhibit moderate to potent activity at the H₄R, including imbutamine (8), the analogous constrained analogue impropip (9) and clobenpropit (10). These compounds are also agonists at the H₄R but are not as selective as 4-methylhistamine (7) [35]. One of the most important tools used in the H₄R area, before the advent of selective H₄R antagonists, is the dual H₃R/H₄R ligand thioperamide (11; K_i = 27 nM) [10], which is an inverse agonist at both receptors.

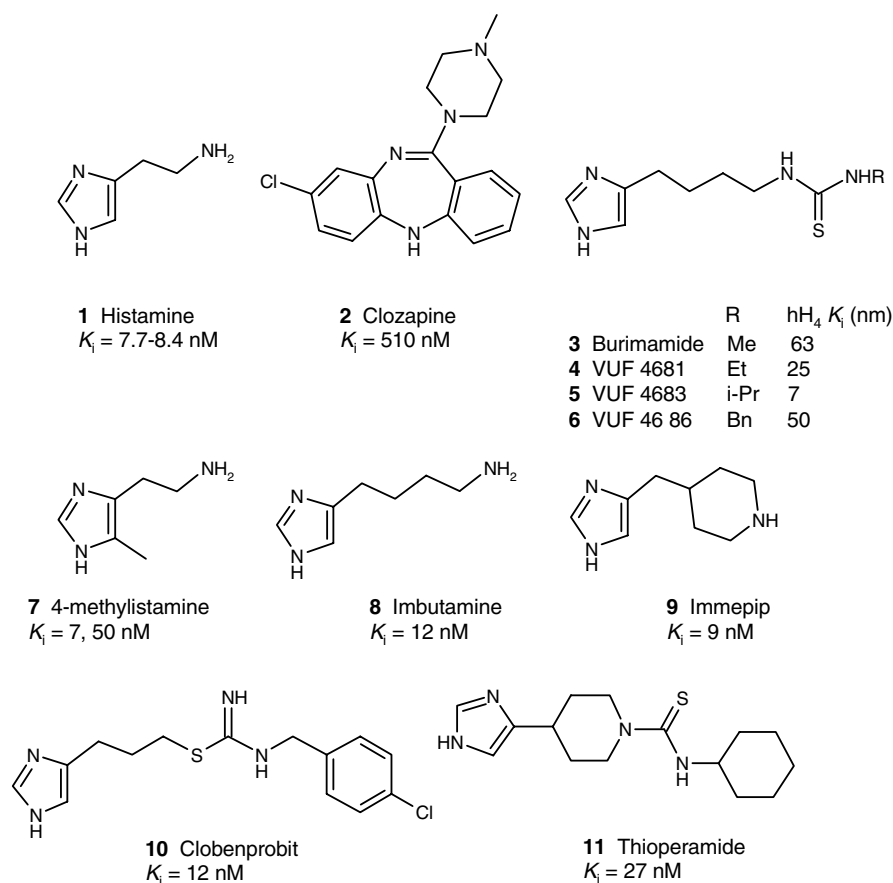


Figure 1. Activity of known histaminergic ligands for the histamine H_4 receptor.

Medicinal chemistry efforts have led to several recent publications detailing the discovery of novel, selective modulators of the human H_4 R. The first series of selective antagonists of the H_4 R, including the indolylpiperazine JNJ 7777120 ($K_i = 4$ nM, **12**; **Figure 2**), was disclosed in 2003 [37]. This compound was developed from a high throughput-screening hit and the analogues synthesised demonstrated the importance of an *N*-methylpiperazine terminus as well as allowing substitution of the indole ring. A follow up to this publication in 2005 [38] describes modifications made to the heterocyclic nucleus of the pharmacophore with the intent of maintaining activity at the H_4 R as well as exploring effects on the metabolic and pharmacokinetic parameters. This led to the development of two new H_4 R antagonists, the thienopyrrole (**13**) and the benzimidazole analogue JNJ 10191584 (**14**; also known as VUF 6002) [38,39]. Both JNJ 7777120 and JNJ 10191584 are neutral antagonists of the H_4 R [1] and have demonstrated inhibition of human eosinophil and murine bone marrow-derived mast cell chemotaxis in response to histamine [35,38]. The benzimidazole carboxamide **14** was also described by Terzioglu *et al.* [39] as a potent and selective H_4 R

antagonist during their investigation based on the indolylpiperazine lead **12**. A novel histamine H_4 R agonist OUP-16 (**15**) has also been described. Modification of the H_3 R agonist imfuramine resulted in compound **15**, which was found to display full agonism at the H_4 R, with moderate selectivity (40-fold) over the H_3 R when compared with the data for 4-methylhistamine [40,41].

The recent disclosures of selective modulators can be found in the patent literature. Investigators from Bayer have described substituted 2-aminopyrimidines (**16**, **17**) with certain aryl and diamine appendages as potent ligands for the H_4 R, with some having median inhibitory concentration (IC_{50}) values of < 20 nM [201,202]. A series of quinoxaline-2-ones was also recently disclosed, and are described as having K_i values in the range of 4 – 600 nM as exemplified by compound **18** ($K_i = 4$ nM) [203]. There have been two additional novel pharmacophores containing a 2-arylbenzimidazole and 2-arylimidazole cores with a basic amine side chain that were described as ligands for the H_4 R [204,205]. Potencies for these compounds are exemplified by ligands **19** and **20**, which exhibit K_i values of 58 and 158 nM, respectively.

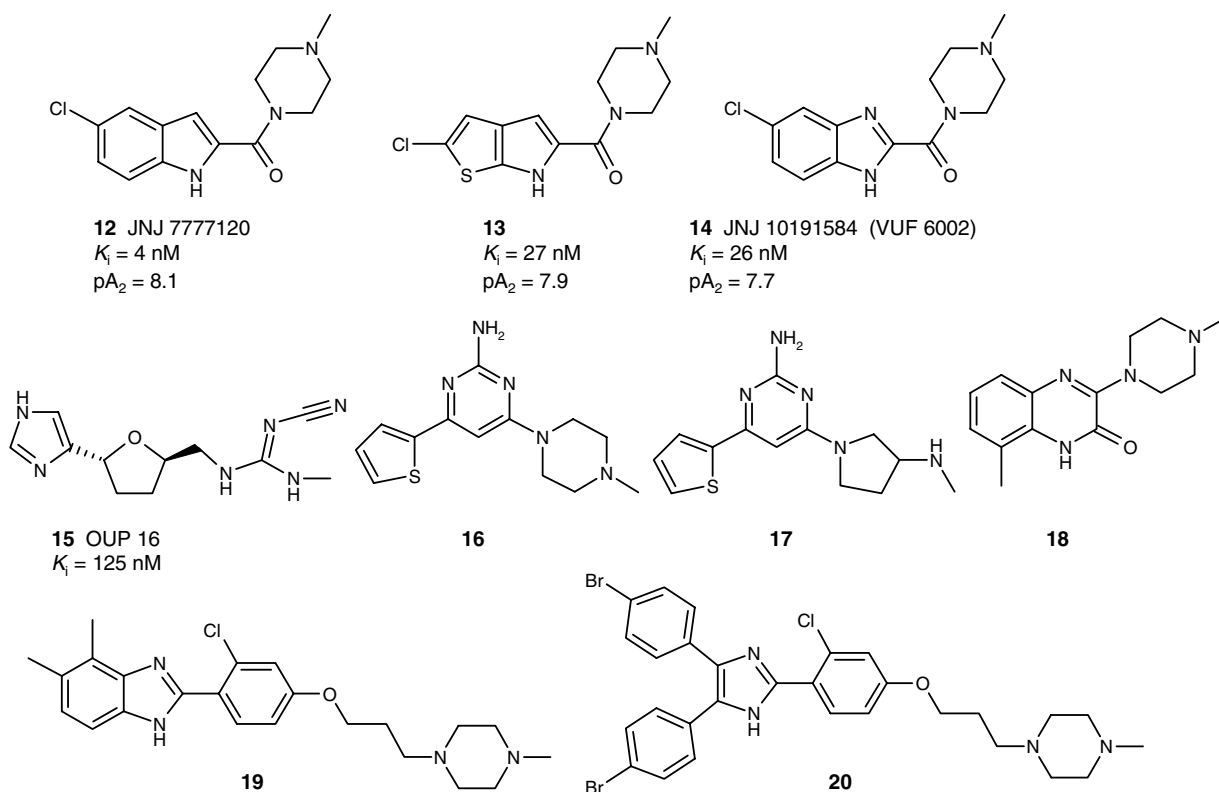


Figure 2. Novel, selective histamine H₄ receptor modulators.

3. Function of the histamine H₄ receptor

The expression pattern of the H₄R implies that it has a role in immune and inflammatory responses. The clearest expression has been in eosinophils, mast cells and dendritic cells, and most of the current literature addresses function in these cell types. Furthermore, the development of selective H₄R ligands such as JNJ 7777120 has enabled the assessment of the receptor function in a number of animal models.

One of the first functions discovered for the receptor *in vitro* was in mediating chemotaxis. Cell migration is an important event during cell maturation/differentiation, recruitment to inflammation sites and homing to draining lymph nodes. Histamine-induced chemotaxis of mast cells *in vitro* can be blocked by H₄R antagonists and is not evident in mast cells derived from H₄R-deficient mice [18]. In addition, 4-methylhistamine (a H₄R agonist) can also induce chemotaxis further proving a role for the H₄R in this process [35]. Evidence has also been provided that this chemotaxis may have *in vivo* relevance by showing aerosolised histamine-induced subepithelial mast cell accumulation in the trachea of mice and that this could be inhibited by JNJ 7777120 [19]. As for mast cells, histamine or 4-methylhistamine can induce chemotaxis of eosinophils and, once again, these responses are blocked by H₄R antagonists [22,26,35]. In

addition to being a direct mediator of eosinophil chemotaxis, histamine (acting through the H₄R) appears to synergise with other chemoattractants and, therefore, may amplify more long-range chemotactic responses [22,26]. Other important changes necessary for cell migration – such as actin polymerisation, shape change and upregulation of adhesion molecules CD11b/CD18 (Mac-1) and CD54 (intercellular adhesion molecule-1) – are also modulated by the H₄R [22,26]. The H₄R has also been implicated in dendritic cell chemotaxis. Dendritic cell migration and F-actin polymerisation can be induced by histamine and H₄R agonists, indicating that the H₄R modulates dendritic cell trafficking function [24]. The fact that the H₄R affects chemotaxis in at least three immune cell types suggests that it is potentially involved in multiple aspects of the immune response.

In addition to cell migration, the H₄R has effects on other cell functions such as inflammatory mediator production. Dendritic cells, as professional antigen-presenting cells, play a pivotal role in adaptive immunity. The production of IL-12p70 (a key T_H1 cytokine from human monocytes-derived dendritic cells) can be inhibited by H₂R or H₄R stimulation [24,42]. Similar effects of H₄R on mediator production were also demonstrated in mouse dendritic cells. Following stimulation with various Toll-like receptor ligands, H₄R-deficient dendritic cells and H₄R antagonist-pretreated

dendritic cells display diminished production in IL-6, keratinocyte-derived chemokine (KC) and macrophage inflammatory protein-1 α [43]. Furthermore, disruption of H₄R signalling on dendritic cells led to defective activation of T_H2 T cells [43]. These studies suggest a possible role for histamine signalling via the H₄R on dendritic cells that could affect dendritic cell functions, including antigen presentation and T-cell priming.

The H₄R also has a direct effect on T cells. IL-16 is a cytokine that can induce chemotactic and immunomodulatory responses of CD4⁺ T cells, monocytes and eosinophils, and its production from CD8⁺ T cells can be induced by histamine. This cytokine production process and IL-16-mediated CD4⁺ T-cell migration are modulated by both H₄R and H₂R [27].

Leukotriene production has also been reported to be mediated by the H₄R. *In vivo*, the production of leukotriene B₄ in response to zymosan injection is reduced by thio-peramide treatment [44]. Not only leukotrienes but also COX-2 levels and prostaglandin synthesis can be affected by the H₄R as examined in colon tumour cell lines [29]; however, the H₄R does not seem to affect mast cell degranulation, leukotriene B₄ or prostaglandin production following *in vitro* IgE receptor crosslinking of mouse bone marrow-derived mast cells [18].

The effects of the H₄R on various immune cells described in this section provide evidence that the receptor may be involved in inflammatory responses *in vivo*. The development of selective ligands along with the availability of H₄R-deficient mice has allowed the testing of this hypothesis. Indeed, H₄R antagonists have shown effects in inflammation models that are mast cell dependent such as neutrophil infiltration induced by zymosan. In both zymosan-induced pleurisy and peritonitis models, pretreatment of animals with H₄R antagonists led to a 50% reduction in the number of infiltrating neutrophils [19,44]. The partial efficacy is consistent with the partial reduction seen in mast cell-deficient animals. H₄R antagonists have shown efficacy in an experimental model for inflammatory bowel disease induced by hapten, trinitrobenzene sulfonic acid. Blocking the H₄R diminished macroscopic injury, inhibited the increase in colonic myeloperoxidase and reduced body weight loss and tissue TNF- α levels [45,46]. These results clearly indicate the anti-inflammatory potential of H₄R antagonists *in vivo*.

In a recent publication, the effect of the H₄R has also been illustrated using a mouse asthma model [43]. In this study, the H₄R was shown to play an important role in airway inflammation. Following allergen challenge there was significantly less inflammatory cell accumulation in bronchoalveolar lavage fluid and decreased antigen-specific antibodies in H₄R antagonist-treated or H₄R-deficient mice. *Ex vivo* draining lymph node restimulation suggested that blocking the H₄R impaired T-cell activation as evidenced by reduced IL-4, -5, -6, -13 and -17 production, but there was no effect on proliferation. Efficacy with the H₄R antagonist could be achieved by

administering the compound during the effector phase of the model, suggesting a potential therapeutic role in asthma. Interestingly, *in vivo* administration of a H₄R antagonist during the sensitisation stage was also effective. Coupled with the effects on antibody levels, T_H2 cytokine production and the *in vitro* dendritic cell stimulation, this data suggests a crucial role for the H₄R in T-cell priming. This study proposes an important function of the H₄R in modulating dendritic cell-T cell interaction in allergic responses but also opens the possibility that it could be important in autoimmunity.

4. Histamine and mast cells in autoimmune disease

Autoimmune diseases are defined by aberrant immune responses directed against self. The role of dendritic cells and T cells in these diseases and how to inhibit their action has been extensively reviewed [47-50]. The roles of these cells in driving autoimmune diseases such as rheumatoid arthritis is supported by the accumulation of T cells in rheumatoid arthritis synovium [51] and by the strong link between the major histocompatibility complex haplotype and the development of the disease [52]. In addition, cytotoxic T lymphocyte-associated antigen 4-Ig (abatacept), which directly targets dendritic cell-T cell interactions, has recently been approved for the treatment of rheumatoid arthritis and is currently being investigated for use in other autoimmune diseases [53,54]. Given the putative importance of dendritic cells and T cells in autoimmune disease, the effects of the H₄R on dendritic cell migration and cytokine production as well as those on T-cell activation [24,42,43] could point to a role for this receptor in autoimmune disease initiation and progression.

Histamine and its main producers, mast cells and basophils, have a well-characterised role in allergic responses and T_H2-mediated diseases. Traditionally, histamine has not been thought to be important in T_H1 conditions such as autoimmune diseases; however, there has recently been a recognition that the distinction between T_H1 and 2 (i.e., allergic versus autoimmune) may not be very clear [55-58]. Indeed, Jutel *et al.* [59] have shown that histamine can enhance T_H1 responses via H₁R activation on T cells and inhibit both T_H1 and T_H2 responses through the H₂R. Histamine levels have been shown to increase in multiple sclerosis [60] and in involved psoriasis skin [61]. Both plasma and synovial fluid of rheumatoid arthritis and plasma of psoriatic arthritic patients have increased histamine levels [62,63]. In Crohn's disease and ulcerative colitis higher levels of histamine metabolites have been found and this correlates with disease severity [64-66]. Furthermore, there was a recent report linking a polymorphism in the histamine-metabolising enzyme, amiloride-binding protein 1 (ABP1), to the severity of ulcerative colitis [67]. Animal models have also indicated a role for histamine in autoimmune diseases. Histidine decarboxylase (HDC) is required for the biosynthesis of histamine and,

therefore, HDC^{-/-} mice lack histamine. In these mice there is a partial protection in dextran sodium sulfate-induced colitis [68]. On the other hand, experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis, showed a more severe disease onset and greater cytokine production (IFN- γ , TNF- α and monocyte chemoattractant protein-1 [MCP-1]) in these mice, suggesting a role of endogenous histamine in limiting this autoimmune disease [69]. The presence of histamine receptors in myocardium from mice with autoimmune myocarditis and the effect of histamine on heart contractility in these mice is another example of the potential role of histamine in autoimmune diseases [70-72]. In spite of the evidence for histamine involvement in a variety of autoimmune diseases, there is little (if any) evidence that H₁R and H₂R antagonists are useful in the treatment of these conditions. Given the lack of efficacy of H₁R and H₂R antagonists, coupled with circumstantial data linking histamine with disease pathology, perhaps there is a role for the H₄R in mediating the histamine responses in autoimmune disease.

In addition to histamine, mast cell numbers are increased in many autoimmune conditions; for example, mast cells are found in increased numbers in the brains of patients with multiple sclerosis and, in particular, they appear to be associated with demyelinated plaques [73-76]. Furthermore, mast cell-deficient mice exhibit significantly reduced onset and severity of the disease in an EAE model [77,78]. Mast cells are also thought to play a role in rheumatoid arthritis [79]. They are found in synovial fluid from rheumatoid arthritis patients and there appears to be a correlation between mast cell density and inflammation score [80-85]. There is also evidence that these mast cells are more easily activated and accumulate in areas of cartilage erosion and active fibrosis [84-87]. Evidence for mast cell degranulation is observed in active regions of ulcerative colitis or Crohn's disease [88-91]. The involvement of mast cells in other conditions that may have autoimmune components (such as chronic urticaria [92,93], Sjogren's syndrome [94] and systemic sclerosis [95]) has also been reported. Although the exact role for mast cell involvement in autoimmune diseases is not yet clear, several possible mechanisms have been suggested: mast cells may function by inducing recruitment of T cells and polymorphonuclear leukocytes by mediator release; may present antigens to T cells and have a role in T-cell polarisation; may induce endothelial cells to express adhesion molecules; or they may secrete profibrotic or matrix-degrading factors [58]. Basophils are also important producers of histamine but there is little (if any) literature data on their role in autoimmune disease, which may only reflect the difficulty in studying this cell type.

In most allergic reactions, degranulation of mast cells and basophils occur via antigen crosslinking of IgE bound to Fc ϵ RI. However, degranulation can also be triggered by IgG crosslinking, complement proteins, chemokines, Toll-like receptor ligands, superoxides and neuropeptides and, therefore, does not have to be restricted to T_H2-type diseases.

In addition, it should be noted that although mast cells and basophils store histamine, many cell types have the ability to produce it. Dendritic cells, T cells and macrophages can all produce and release histamine following stimulation [43,96-101]. Although this *de novo* production may result in lower histamine levels than that produced by mast cell or basophil degranulation, it may be especially relevant for H₄R function because the receptor has a high affinity for histamine when compared with H₁R or H₂R. Blocking this endogenous histamine synthesis can reduce activation marker upregulation and cytokine production in dendritic cells and T cells [99,101]. Furthermore, it has been shown that histamine secreted by dendritic cells can potentiate IL-6, KC and macrophage inflammatory protein-1 α production induced by Toll-like receptor stimulation and that this effect is mediated via the H₄R [43].

5. Conclusions

In summary, it has been shown conclusively that the H₄R is expressed on mast cells, dendritic cells, basophils and T cells. The receptor modulates the chemotaxis of several of these cell types and also modulates cytokine production. Furthermore, recent evidence suggests that the receptor plays a role in T-cell activation. Antagonists for the receptor are clearly anti-inflammatory *in vivo* and are efficacious in animal models of asthma and colitis. Although H₄R antagonists have not been tested for efficacy in autoimmune disease, the emerging role of histamine and mast cells suggest that they may be useful. In addition, there are a number of studies showing that histamine acting through H₁R and H₂R receptors can have a variety of effects on immune responses [102]; therefore, it is possible that a compound that is an antagonist against more than one histamine receptor may have additional benefits. Taken together, the data suggest that it is plausible that the H₄R may play an important role in autoimmune diseases and that antagonists for the receptor may open new avenues for treating such conditions.

6. Expert opinion

Although histamine has mainly been associated with allergic T_H2-type conditions, there is emerging evidence that it (and the cells that produce it) may be important in autoimmune diseases. One has to be careful when judging the role of histamine in these diseases or any other condition, because it has largely been defined by the efficacy (or lack of efficacy) of traditional antihistamines that target the H₁R and H₂R. The recent discovery of the H₄R may change some of these assumptions. Although there are no reports of clinical data with H₄R antagonists, preclinical data in animal models suggest that such antagonists are anti-inflammatory *in vivo*. The receptor appears to be expressed in synovial cells from rheumatoid arthritis patients but the functional consequence of this is not known [25]. The effects of the H₄R in dendritic cells

and on T-cell activation have mainly been focused on T_H2 conditions but it is possible that effects could also be seen under T_H1 conditions; for example, Dunford *et al.* [43] have shown that the H_4R is involved in cytokine and chemokine production by dendritic cells when stimulated with Toll-like receptor agonists, which are usually associated with T_H1 responses. In addition, there is accumulating evidence that increased production of histamine and increases in mast cell numbers, the main source of histamine in tissues, are associated with many autoimmune diseases such as rheumatoid arthritis. However, in general, these findings have not been considered particularly important for understanding the pathology of autoimmune disease, mainly because drugs that target H_1R and H_2R do not seem to have any efficacy. The authors suggest that the discovery of the H_4R will lead to a

reassessment of these conclusions; therefore, in autoimmune diseases, histamine is known to be present and can be produced either by mast cells and basophils in an IgE-independent fashion or by other cells such as dendritic cells or T cells. The presence of histamine activates the H_4R and could drive processes such as recruitment and activation of mast cells, dendritic cells, neutrophils and T cells that are essential in the pathogenesis of the disease. In particular, it is possible that the H_4R on dendritic cells could directly influence T_H1 T-cell development as has been shown for T_H2 cells. The current evidence points to the use of antagonists of the H_4R for the treatment of autoimmune diseases. However, this will have to await proof that H_4R antagonists can have efficacy in animal models of autoimmune disease and, ultimately, whether they have use in the clinic.

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Patents

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