Does the Histamine H₄ Receptor Have a Pro- or Anti-Inflammatory Role in Murine Bronchial Asthma?

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Key Words

Pro-inflammatory role • Anti-inflammatory role •
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Abstract

The histamine H₄ receptor is expressed preferentially on immune cells, indicating a possible role of the H₄ receptor in inflammation. Studies of inflammation in several animal models point to a pro-inflammatory function of the H₄ receptor. However, studies on experimental murine bronchial asthma yielded conflicting results, a fact which is neglected in most H₄ receptor publications. Therefore, the present review critically analyzes available data on the role of the H₄ receptor in the murine bronchial asthma model.

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Introduction

The biogenic amine histamine is an important mediator involved in various (patho-)physiological processes. For example, histamine induces contraction of smooth

muscle cells, mucus production in goblet cells, and nitric oxide production of endothelial cells [1]. Furthermore, histamine regulates gastric acid secretion and the recruitment of immune-competent cells to the site of infection [2]. These and other effects are mediated by histamine-specific receptors expressed on the respective target cells. So far, four histamine receptors have been characterized and cloned in humans and mice, referred to as histamine H₁ receptor (H₁R), H₂R, H₃R, and H₄R, respectively [3–6]. These receptor subtypes display homologies of just about 20% within a species and of about 70–95% of a given receptor subtype between humans and mice [1, 3, 7]. Histamine receptors belong to the family of seven-transmembrane receptors, signaling via the activation of specific G proteins.

H₄R was identified in 2000/2001 by several groups [4–6], displaying moderate structural homology (~40%) to H₃R. It couples to pertussis-sensitive G_i proteins, resulting in the inhibition of adenylyl cyclase activity. More importantly, via the βγ subunits of G_i proteins, H₄R activates phospholipase C followed by an increase in intracellular calcium concentration [6, 8], which may result in the activation of mitogen-activated protein kinase

(MAPK) cascades. H₄R is expressed preferentially in hematopoietic cells, specifically in the immune cells. Deduced from its expression pattern, it was postulated that H₄R is involved in immunoreactions. This hypothesis has been studied in several models, e.g. experimental mouse models comprising those for airway inflammation [9, 10], pruritus [11–13], and peritonitis [14–16]. These models mostly rely on the use of the dual H₃R/H₄R antagonist thioperamide [14, 15], the H₄R-selective antagonist JNJ 7777120 (1-[(5-chloro-1H-indole-2-yl)carbonyl]-4-methylpiperazine) [16], the assumed H₄R-selective agonist 4-methylhistamine (4MeHA) [17], or on the H₄R^{-/-} mouse [8]. All of the above-mentioned mouse-based studies point to a pro-inflammatory function of H₄R, since disease symptoms were ameliorated by treating the animals with H₄R-antagonistic JNJ 7777120 or thioperamide or were reduced in H₄R^{-/-} mice. However, an exception to this general assumption are the studies on airway inflammation, i.e. experimental asthma [9, 10], which resulted in conflicting conclusions.

In addition to other disadvantages of mouse models for human bronchial asthma, analyzing H₄R in mouse models is even more complicated. Specifically, human and mouse H₄R share only 68% homology in their amino acid sequences, which is, for example, reflected by substantial differences in their affinities for [³H]histamine [K_D: 5 nmol/l (human) vs. 136 nmol/l (mouse)] and in their functional activities and pharmacological profiles [7, 18, 19]. The still rather incomplete pharmacological characterization of mouse H₄R in comparison to human H₄R points to major differences between the 2 receptors [7, 18, 19]. This has to be taken into account when interpreting *in vivo* experiments exploring H₄R. The studies become even more difficult to interpret when considering the possibility of constitutive, i.e. agonist-independent, activity of 1 of the 2 receptors [20] or of differing, species-specific activities of H₄R ligands [7, 19].

Several excellent reviews on H₄R, especially with respect to medicinal chemistry aspects, are presently available [1, 21–25]. In contrast to previous reviews, the present one just focuses on the role of H₄R in the mouse model of bronchial asthma.

Histamine and Asthma

A widely accepted model of acute airway inflammation is the mouse model of ovalbumin (OVA)-induced allergic asthma [26]. Functionally, this model is divided into two phases, i.e. sensitization (fig. 1) and provocation.

In the sensitization phase, the experimental allergen OVA is taken up by antigen-presenting cells such as dendritic cells (DCs), processed, and presented to Th0 cells. These Th0 cells then polarize into Th2 cells due to the presence of interleukin (IL)-4 and into regulatory T cells (Tregs). Activated Th2 cells mainly produce the cytokines IL-4, IL-5, and IL-13, which, besides having other functions, support the differentiation of B cells into immunoglobulin (Ig)-secreting plasma cells. Tregs, upon proper stimulation, can efficiently inhibit the activity of Th2 cells by the release of IL-10 and transforming growth factor β . The allergen-specific Igs produced in allergy are mainly of the IgE isotype. The IgE molecules diffuse in the body and enter peripheral tissues, where they bind to IgE-binding receptors (Fc ϵ R) on mast cells and basophils.

After the sensitization, the subsequent administrations of the allergen are referred to as provocation. Provocation induces an acute allergic reaction due to the uptake of OVA in peripheral tissues and direct binding to the cell-bound OVA-specific IgE. By this mechanism, multiple IgE molecules are cross-linked, followed by cellular activation and degranulation. This results in the rapid and massive release of bioactive mediators such as histamine and leukotrienes, which are responsible for the early clinical allergic symptoms. In parallel, OVA is presented to Th2 cells by DCs, again leading to the production of IL-4, IL-5, and IL-13, promoting the recruitment of eosinophils and airway hyperresponsiveness.

Although histamine is massively released topically in allergic reactions like asthma, rhinitis, or conjunctivitis, only the latter two conditions can be effectively controlled clinically by antagonists blocking H₁R, whereas such drugs at therapeutically relevant doses are ineffective in human bronchial allergic asthma as well as in the murine model [27]. However, deletion of the histamine-forming enzyme L-histidine decarboxylase [28–30], or of H₁R [27] in mice, both provide beneficial effects on the induction of experimental asthma. These data clearly point to a role for histamine also in bronchial asthma, at least in the murine model. Thus, it is most likely that histamine receptors other than, or in addition to, H₁R are involved in the asthmatic reaction.

H₂R is expressed mainly on parietal cells in the gastrointestinal tract, where it is involved in the regulation of gastric acid release and serves as an important pharmacological target. In addition to this well-known and clinically relevant function, H₂R is also expressed and active on T cells. Here, its activation reduces both Th1- and Th2-type immunoreactions by reducing the expression

Fig. 1. Schematic representation of the cellular interplay in the sensitization reaction in OVA-induced allergic asthma and hypothetical function of the H₄R ligands 4MeHA and JNJ 777120.

of specific cytokines [31]. Moreover, the activation of neutrophils is reduced by histamine via H₂R [32].

H₃R is found mainly, if not exclusively, on cells of the nervous system. It offers pharmacological potential for the treatment of, for example, cognitive disorders, obesity, or epilepsy. Clinical trials using several ligands for H₃R are being performed; however, approved drugs are not yet available [33].

H₄R and Murine Asthma

H₄R is the most likely candidate receptor involved in histamine actions in bronchial asthma. First hints for such an involvement were provided by Hofstra et al. [8] who demonstrated that H₄R mediates histamine-induced calcium mobilization from intracellular stores and chemotaxis in murine mast cells, a cell type critically in-

involved in acute allergic reactions. Both effects of histamine were efficiently blocked by the H₄R-selective antagonist JNJ 777120 [16]. It is worth noting that Hofstra et al. [8] also demonstrated that histamine does not induce degranulation or the synthesis of inflammatory mediators in mast cells. Thus, in the situation of an allergic reaction such as an acute asthmatic response, the allergen-induced release of histamine from mast cells or basophils probably auto-amplifies the reaction by inducing the redistribution of mast cells leading to the accumulation of additional mast cells at the site of the allergic inflammation. These cells, however, still need to be activated for mediator release, either preformed or de novo synthesized, by mechanisms other than histamine. These activating mechanisms could be either an allergen in combination with allergen-specific IgE, or unspecific stimuli, such as physical or chemical triggers.

Genetic Deletion of Mouse H₄R and Studies with JNJ 7777120

More direct approaches addressing the involvement of H₄R in murine experimental asthma were conducted using the OVA-induced asthma mouse model. There are just 2 original H₄R asthma reports [9, 10], but 5 reviews [1, 22, 23, 34, 35] discussing both original H₄R papers, and another 15 reviews citing 1 of the 2 asthma papers (ISI Web of Knowledge, January 14, 2010). This situation highlights the paucity of experimental data, the interest in the link between H₄R and asthma, but also the biased citation of the studies.

In both original articles, experimental asthma in Balb/c mice was induced using a very similar protocol. The first paper takes advantage of the H₄R^{-/-} mouse and the antagonistic H₄R-selective ligand JNJ 7777120 [9]. In this study, the parameters of experimentally induced asthma were reduced in animals from the H₄R^{-/-} strain as compared to wild-type mice. However, the H₄R^{-/-} strain has not yet been characterized with respect to the development and function of the immune system, susceptibility to diseases of the immune system, and tumors. Thus, formally, it cannot be ruled out that adaptive processes occurred in this strain, leading to alterations in the equilibrium between DCs, Th2 cells, and Tregs. This may result in the predominance of Tregs, leading to the reduced asthmatic phenotype (fig. 1).

In addition, in wild-type mice, systemic administration of JNJ 7777120 reduced asthma-like parameters as observed in H₄R^{-/-} mice [9]. Surprisingly, data describing the effect of JNJ 7777120 administration on lung function are missing in the original publication but are briefly mentioned in a review [25]. Certainly, the inclusion of lung function parameters into the original paper would have bolstered the concept of a pro-inflammatory role of H₄R in asthma very substantially, which is emphasized in all H₄R reviews. The beneficial effects of JNJ 7777120 on asthma were independent of the presence of mast cells, since similar results were obtained in mast cell-deficient and wild-type mice [9]. Thus, the above-discussed stimulatory function of H₄R in mast cells [8] does not account for this setting. This, however, is not surprising since in the mouse asthma model, mast cells are not required for disease symptoms despite the induction of increases in lung resistance [36, 37]. JNJ 7777120 produces beneficial effects in murine experimental asthma in both cases, when administered during the sensitizing phase or during the challenging phases. Its efficacy when applied during the sensitization phase points to an activity on the DC-T cell axis in the initial immunoreac-

tions, i.e. the proper polarization of Th0 cells into Th2 cells (fig. 1).

Indeed, lymph node cells from JNJ 7777120-treated mice produce less Th2-specific cytokines upon in vitro restimulation when compared to those obtained from vehicle-treated mice, probably due to the H₄R-dependent alterations of DC activity. The capacity to produce Th2-specific cytokines is also reduced in lymph node cells from mice treated with JNJ 7777120 during the challenging phase. Thus, also in this state, DCs and/or T cells appear to be the major targets for H₄R-selective intervention. Additionally, the fact that antagonism at the H₄R reduces the activation of CD8⁺ T cells by soluble OVA, a process mediated by DCs, which is referred to as cross-presentation, points to DCs as the cells mainly reactive to histamine via H₄R [38].

Studies with 4MeHA

In the second study examining the role of H₄R in the murine asthma model, the authors, instead of antagonizing the function of H₄R, stimulated H₄R topically in the challenging phase by intratracheal administration of the supposedly H₄R-selective ligand 4MeHA [10]. This administration resulted in the reduction of asthma-like symptoms including those directly relating to lung function, and can be attributed to the enhanced migration of CD4⁺ CD25⁺ FoxP3⁺ Tregs to the site of inflammation, where the accumulated cells release large amounts of the anti-inflammatory cytokine IL-10 (fig. 1). However, although 4MeHA instillations in asthmatic mice lead to elevated Treg numbers and IL-10 levels in bronchoalveolar lavage fluids, direct evidence for 4MeHA-induced migration of Tregs and synthesis of IL-10 was provided in this publication only for human Tregs, but not for their murine counterparts.

Due to the absence of available literature, it cannot be ruled out that human and mouse Tregs respond in different manners to the stimulation of H₄R. Thus, it is tempting to speculate that 4MeHA did not induce the expected effects in mouse Tregs but did so in human cells, and only the latter data were reported. Moreover, 4MeHA had originally been described as a selective H₂R agonist [39, 40], since H₄R had not been identified at that time. In fact, its affinity for human H₄R is about 100-fold higher than that for H₂R [17], while for murine H₂R and H₄R such data, to the best of our knowledge, are not available. Nevertheless, at 50 µmol/l, the concentration used in the migration assay, 4MeHA is fully active not only at human H₄R, but also at human H₂R and human H₃R [17]. Therefore, it is questionable whether the observed effects can

be attributed exclusively to H₄R given that the study does not include data derived from the use of selective histamine receptor antagonists, which are superior to agonists for determining receptor subtype-specific functions. Although this publication presented data which give rise to some concerns regarding the identity of the histamine receptors involved, the paper by Morgan et al. [10] nonetheless points to an anti-inflammatory function of H₄R. It also cannot be ruled out that the anti-inflammatory effect of 4MeHA in the study by Morgan et al. [10] is due to the activation of anti-inflammatory H₂R.

In any case, this paper has been overlooked by most of the subsequent publications on H₄R, which nearly all point to a pro-inflammatory role of H₄R. In fact, the paper by Morgan et al. [10] is cited in only 14 publications, including 7 reviews, while at the same time the publication by Dunford et al. [9], which points to a pro-inflammatory function of H₄R in murine experimental asthma, is discussed in 50 papers, including 13 reviews (ISI Web of Knowledge, January 14, 2010).

H₄R and H₁R and Murine Asthma: Kinetic Effects of Ligands

Thus, in the 2 papers discussed above, conflicting effects of H₄R in experimental asthma are described: asthma-like symptoms are ameliorated upon systemic reduction or elimination of H₄R activity as well as upon local enhancement of H₄R activity. Whether this is just an effect of the route of application or of the dosing used remains to be clarified, since Dunford et al. [9] did not use a local route of JNJ 7777120 application and Morgan et al. [10] failed to apply 4MeHA systemically. Moreover, dose-response experiments are missing in both publications.

We reproduced the ameliorating effect of systemically applied JNJ 7777120 at 20 mg/kg on the outcome of OVA-induced allergic asthma in mice [41]. In addition, we have shown that JNJ 7777120 and the H₁R antagonist mepyramine, when administered in combination at the time of sensitization, ameliorate asthma-like symptoms in a synergistic fashion. This observation implies a cross talk between H₁R and H₄R in the cell type responsible for the antiasthmatic effect. As deduced from the papers discussed above [9, 10], those cells are most likely of DC and/or Th cell origin. While in mouse DCs the expression of both H₁R and H₄R was demonstrated [38], in mouse T cells only the expression of H₁R has been directly shown [31]. Besides clear indications as discussed above, defini-

tive proof of an H₄R expression in mouse T cells remains to be provided (fig. 1).

Still, the question remains whether H₄R possesses anti- or pro-inflammatory properties. Using the H₄R-selective ligand JNJ 7777120 as an antagonist in human and murine experimental systems, several reports classify H₄R as pro-inflammatory [1, 22, 23, 25], while another study using a conjunctivitis model in rats points to an anti-inflammatory function of H₄R as well [42]. The definitive function of JNJ 7777120 on mouse H₄R as a partial agonist or as a truly neutral antagonist on a molecular level, however, is still elusive. Thus, the possibility remains that in mice JNJ 7777120 behaves as a partial agonist, at least in some settings (fig. 1). In the latter case, whether JNJ 7777120 acts agonistically or antagonistically in mice depends on the local concentrations of histamine in relation to that of JNJ 7777120, but exact determinations of these ligand concentrations have not yet been performed. Consequently, the data obtained from mice using JNJ 7777120 could also be interpreted as a result of (partial) activation of H₄R. In this case, both reports analyzing the function of H₄R in murine OVA-induced asthma [9, 10] would point to an anti-inflammatory function of H₄R (fig. 1). In order to finally solve this intriguing question, we urgently need H₄R-specific neutral antagonists for both human and mouse H₄R.

Conclusion

The general tenor of H₄R reviews suggests that H₄R has a pro-inflammatory role in asthma. However, closer analysis of the data available so far concerning the function of H₄R in murine experimental asthma reveals that this is a premature conclusion. To the best of our knowledge, there is no study on the role of H₄R in human asthma; a pro-inflammatory role of H₄R in human asthma is only predominantly implicated in mice in the study by Dunford et al. [9]. Thus, when planning to examine H₄R in a clinical setting in order to treat bronchial asthma, it remains unclear whether an agonistic or an antagonistic ligand should be used. This is furthermore complicated by the commonly known fact that the standard mouse models used in basic research do not reliably reflect characteristic human bronchial asthma [43]. In addition, the interplay between H₄R and other histamine receptors, mainly H₁R, in bronchial asthma is an interesting, but still open question. Since some classic H₁R antagonists do also block H₄R at higher concentrations [41], it cannot be ruled out that the beneficial effects of H₁R antagonists

observed at high doses in asthma [1] are due to a dual H_1R/H_4R blockade. In conclusion, much more basic research is needed in order to finally understand the function and mechanism of H_4R in bronchial asthma and to translate it from mouse experiments to clinical use in humans.

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