



Perspective

The histamine H₄ receptor: Targeting inflammatory disorders

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ABSTRACT

The discovery of the histamine H₄ receptor has added a new chapter to the century of extensive biogenic amine research. The human histamine H₄ receptor is mainly expressed in cells of the human immune system (e.g. mast cells, eosinophils, monocytes, dendritic cells, T cells) and mediates several effects on chemotaxis with numerous cell types. The distinct expression pattern and the immunomodulatory role highlight its physiological relevance in inflammatory and immunological processes. Inflammatory conditions, e.g. allergy, asthma and autoimmune diseases, were for a long time thought to be mainly mediated by activation of the histamine H₁ receptor subtype. However, in the treatment of diseases as chronic pruritus, asthma and allergic rhinitis the use of histamine H₁ receptor antagonists is unsatisfying. Selective H₄ receptor ligands and/or synergism of histamine H₁ and H₄ receptor modulation may be more effective in such pathophysiological conditions. Promising preclinical studies underline its role as an attractive target in the treatment of inflammatory and autoimmune disorders. Meanwhile, first histamine H₄ receptor antagonist has reached clinical phases for the treatment of respiratory diseases.

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1. History

Histamine plays an important role as neurotransmitter and chemical mediator in a multitude of central and peripheral (patho) physiological processes. In the last century extensive study of its actions in the human body, resulted in detection of four G protein-coupled receptor subtypes (histamine H₁–H₄ receptors) (Parsons and Ganellin, 2006). In 1994, Raible and co-workers identified histamine induced pertussis toxin-sensitive cytosolic calcium²⁺ increase in eosinophils, which could be inhibited by histamine H₃ receptor inverse agonist thioperamide and induced by (R)- α -methylhistamine (agonist) in lower potency (Raible et al., 1994). Histamine H₃ receptor independent uptake and release of histamine by hematopoietic progenitor cells was unaffected by histamine H₃ receptor agonists, indicating a further histamine receptor subtype (Corbel et al., 1997). First, the long-awaited cloning of the histamine H₃ receptor gene in 1999 enabled detection and proof of a fourth histamine receptor responsible for the observed effects. In 2000–2001 several research groups independently identified an unexplored sequence in the human genome as new histamine H₄ receptor (cf. Zampeli and Tiligada, 2009). The subsequent discovery of the selective acting inverse agonist/antagonist JNJ777120 (Jablonowski et al., 2003) give an important pharmacological tool for the characterization of the receptor and enabled the investigation of its pathophysiological role in the development of various diseases. Lately, findings concerning

partial agonism of JNJ777120 (Rosethorne and Charlton, 2010) and functional selectivity of the receptor have challenged its use as “standard” histamine H₄ receptor antagonist (Seifert et al., 2011). Since the cloning and pharmacological characterization of the histamine H₄ receptor, preclinical and clinical studies underlined its role as an attractive target in the treatment of inflammatory and autoimmune diseases (Tiligada et al., 2009; Vives et al., 2010).

2. Molecular structure

The human histamine H₄ receptor gene, encoding for a 390 amino acid protein, is localized on chromosome 18 and contains three exons, interrupted by two introns. Whereas such intron–exon distribution resulted in a multitude of histamine H₃ receptor isoforms, so far only three non-signaling H₄ receptor isoforms have been reported, possibly acting as negative regulatory element on full-length receptor function (van Rijn et al., 2008). The histamine H₄ receptor protein possesses all consensus motifs identified for class A rhodopsin-like G protein-coupled receptors similar to the other histamine receptor subtypes. So far, structure-based as well as computer-aided investigations revealed some similarities in ligand–receptor interactions of histamine H₃ and H₄ receptor, leading to dual acting imidazole-containing histamine H₃/H₄ receptor ligands (Kottke et al., 2011). Due to structural relatedness imidazole-containing compounds and the endogenous ligand histamine bind in a comparable manner to both targets (Jongejan et al., 2008; Schlegel et al., 2007). Scaffold optimization of diaminopyrimidines led to functional-varying histamine H₄ receptor ligands (Sander et al., 2009) based on their receptor binding mode (Werner et al., 2010). Depending on the identification of the human

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H₄ receptor, cDNA of mouse, rat, guinea pig, pig, dog and monkey histamine H₄ receptors were cloned, sharing only moderate sequence homology to the human receptor (67–72%; except monkey histamine H₄ receptor 92%) (cf. Leurs et al., 2009). This results in substantial differences in ligand binding efficacies and complicates the preclinical investigation of the human histamine H₄ receptor function due to lack of reliable animal models. However, comparable tissue distribution of the histamine H₄ receptor in different species suggests its responsibility for common physiological processes among these species.

3. Cellular distribution

Expression of human histamine H₄ receptors was detected at mRNA levels in bone marrow, peripheral blood, spleen, thymus, small intestine, colon, heart and lung. Highest expression levels were found in tissues involved in immune responses, i.e. bone marrow, lung and spleen (Zampeli and Tiligada, 2009). Additionally, the expression of the histamine H₄ receptor is inducible in response to inflammatory stimuli. Histamine has regulatory functions in hematopoiesis, which is partly mediated by histamine H₄ receptor signaling (Schneider et al., 2011). The majority of histamine H₄ receptor expressing cells indeed belongs to the hematopoietic system (neutrophils, mast cells, eosinophils, basophils, dendritic cells, monocytes and T cells). Furthermore, the histamine H₄ receptor was detected in endocrine cells in the gastrointestinal tract, on dermal fibroblasts and nerves of the human nasal mucosa as well as in the enteric and the central nervous system (cf. Leurs et al., 2009).

4. Cell Signaling

The histamine H₄ receptor activates pertussis-toxin-sensitive G $\alpha_{i/o}$ -proteins. On molecular level agonist-induced liberation of G $\alpha_{i/o}$ -proteins inhibited adenylyl cyclase activity. Receptor activation modulates protein kinase A and its downstream signals such as transcription of genes regulated by cAMP-responsive elements (Leurs et al., 2009). Signaling via mitogen-activated protein kinase activates transcription factor activator protein-1 in monocyte-derived dendritic cells (Gutzmer et al., 2005). Calcium²⁺ mobilization is mediated by the

G $\beta\gamma$ subunit through phospholipase C activation (Hofstra et al., 2003). Increased intracellular calcium²⁺ leads to actin polymerization, change in cell shape and resulting migration of mast cells, eosinophils and monocyte-derived dendritic cells into sites of inflammation.

The histamine H₄ receptor controls pro-inflammatory responses by regulation of autocrine and paracrine histamine-induced processes (Fig. 1). Increased expression of adhesion molecules as well as cell shape change and rearrangement of the actin cytoskeleton lead to histamine H₄ receptor-mediated cell movement of eosinophils (Barnard et al., 2008; Ling et al., 2004), partly mediated by CCL-16 (Nakayama et al., 2004). Eosinophil and neutrophil recruitment are supported by leukotriene C₄ and B₄ (Ling et al., 2004; Takeshita et al., 2003). In bone marrow-derived mast cells accumulation of histamine vesicles is induced by B cell-derived immunoglobulin E (Tanaka et al., 2002). Mast cells are major players in immune responses controlling the production, storage and liberation of histamine and other inflammatory mediators and chemoattractants (Marshall, 2004). During the sensitization phase of immune response histamine, interleukin-4 and prostaglandin D₂ are liberated by mast cells, starting the CD4⁺ T cell polarization. During the effector stage mast cells are themselves attracted due to activation by histamine, liberated by dendritic cells. Histamine H₄ receptor activation on mast cells results in calcium²⁺ mobilization as well as chemotaxis, without affecting degranulation, which enables selective recruitment of effector cells and amplification of histamine-induced processes (Hofstra et al., 2003). Histamine H₄ receptor agonist-mediated migration of dendritic cells and Langerhans cells was detected (Bäumer et al., 2008; Gschwandtner et al., 2010). The interplay of histamine H₄ and H₂ receptor controls histamine-induced interleukin-16 release from human CD8⁺ T lymphocytes (Gantner et al., 2002), acting as chemoattractant for naive CD4⁺ T cells. Histamine H₄ receptor activation on dendritic cells results in actin polymerization and cell movement of CD4⁺ T cells (Fig. 1) (Gutzmer et al., 2005). T lymphocyte activation is mediated by dendritic cells. T cell polarization is adjusted by the histamine H₄ receptor via modulation of cytokine production. Histamine-mediated T helper (T_H) cell responses are modulated in cooperation of histamine H₁, H₂ and H₄ receptors (Jutel et al., 2001). Histamine H₄ receptor activation reduces T_H1 cell-associated interleukin-12p70 concentration (Dijkstra et al., 2008; Gutzmer et al.,

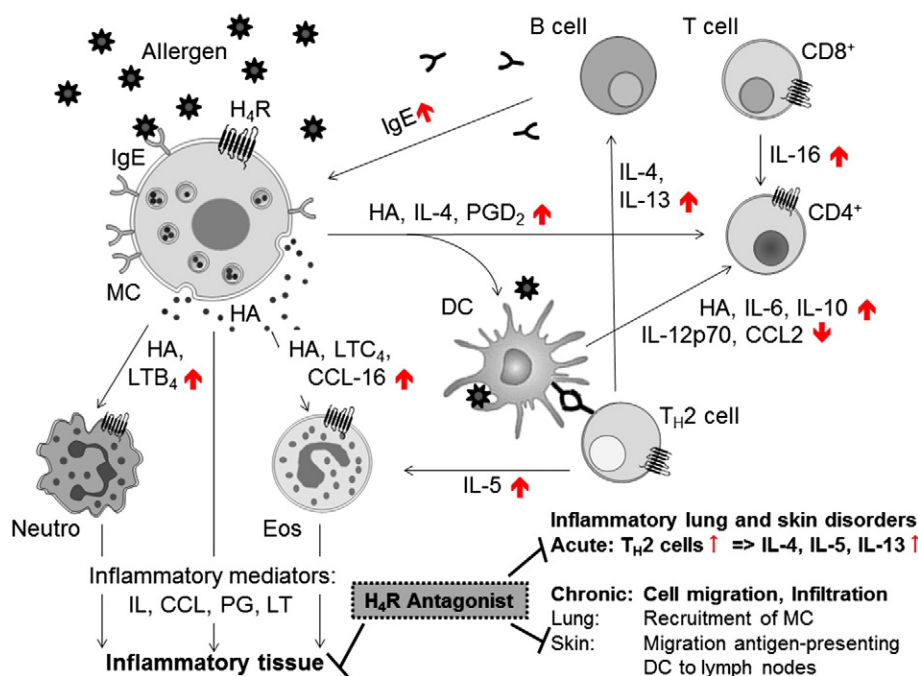


Fig. 1. Histamine H₄ receptor involvement in immune response. Abbreviations: CCL, Chemokine ligand; DC, Dendritic cell; Eos, Eosinophil; HA, Histamine; H₄R, Histamine H₄ receptor; Ig, Immunoglobulin; IL, Interleukin; LT, Leukotriene; MC, Mast cell; Neutro, Neutrophil; PG, Prostaglandin; TH2, T helper type 2 cell.

2005), whereas expression of interleukin-10 and interleukin-6 is increased after Toll-like receptor activation resulting in development of T_H2 cells (Dunford et al., 2006). Controlling T_H2 cell polarization histamine H_4 receptor activation reduces synthesis and secretion of chemokine ligand 2 (Dijkstra et al., 2007), leading to decreased monocyte chemotaxis and enhanced T_H1 cell response. This negative feedback mechanism takes part in the switch from humoral to cellular immune response, attenuating the acute state of disease. The histamine H_4 receptor is functionally higher expressed on T_H2 cells than on T_H1 cells and native T cells (Gutzmer et al., 2009) and leads to upregulation of activator protein-1 and interleukin-31 (Dillon et al., 2004), associated with atopic dermatitis and pruritus (Raap et al., 2008; Tey and Yosipovitch, 2011). The involvement of histamine H_4 receptors in diseases, where T_H2 cells are overexpressed, was demonstrated. Whether drugs that modulate this interplay are useful strategies to treat inflammatory conditions has to be proven in further investigations.

5. Preclinical and Clinical Effects

The involvement in chemotaxis and cytokine release as well as its defined expression pattern in organs of the immunological system indicates the pathophysiological importance of the histamine H_4 receptor in inflammatory conditions. Elevated histamine levels correlate with the severity of inflammatory diseases like allergy, asthma or arthritis. Depending on the pro-inflammatory role of the receptor, demonstrated in several animal models, the use of histamine H_4 receptor antagonists represents a new therapeutic option to treat inflammatory disorders (Fig. 1). Modulation of histamine H_4 receptor signaling on cellular levels showing immune regulatory effects in the initial phase and under long term conditions of inflammation (Thurmond et al., 2008).

In inflammatory lung disorders histamine mediates both the acute (airway hyper-responsiveness) and chronic phase (cytokine, chemokine release and cell migration). According to allergen exposure in lung histamine H_4 receptor induces redistribution and recruitment of mast cells in mucosal epithelium, leading to amplification of allergic symptoms and maintaining of chronic inflammatory conditions. Additionally, the histamine H_4 receptor mediates the synergistic action of histamine and chemokine CXCL12, which act as chemoattractant for mast cell precursors (Godot et al., 2007). Aberrant T_H2 cell response with overproduction of interleukin-4, interleukin-5 and interleukin-13 plays a key role in airway inflammation (Busse and Lemanske, 2001). Histamine H_4 receptor-mediated decrease in cytokine and chemokine production in dendritic cells leads to $CD4^+$ T cell activation (Dunford et al., 2006). Allergen-specific T_H2 cell response was inhibited by histamine H_4 receptor antagonism (Lundberg et al., 2011). Studies on inflammatory models mostly point to a pro-inflammatory role of the histamine H_4 receptor. However, conflicting results were obtained in the murine bronchial asthma model (Neumann et al., 2010). Besides reducing asthma parameters by systemic administration of the antagonist JNJ7777120, in another study decrease in asthma symptoms was achieved by intratracheal application of the agonist 4-methylhistamine. These findings underline the need for further basic research, especially concerning reliable animal models and the histamine receptor subtype interplay. The first clinical candidate UR-63325 has completed clinical phase I studies, offering good safety, pharmacokinetic and -dynamic data (Vives et al., 2010). Proof-of-concept phase II study in allergic rhinitis induced by allergen challenge (completion date: March 2011) has compared UR-63325 with fluticasone and placebo (<http://clinicaltrials.gov/ct2/show/NCT01260753?term=UR-63325&rank=1>, 2010). Additionally, CZC-13788 and PF-2988403 demonstrate promising preclinical data for treating asthma and allergic rhinitis (Clarke et al., 2008; Lock et al., 2007).

Chronic pruritus displays a major symptom in dermatological and systemic diseases characterized by diverse pathogenesis and involvement of a complex network of cutaneous and neuronal cells (Greaves, 2010).

Lately, many itch-specific mediators and receptors, such as histamine, interleukin-31 as well as histamine H_1 , H_3 and H_4 receptor and proteinase-activated receptor 2, were identified (Tey and Yosipovitch, 2011). The histamine H_4 receptor is expressed in human skin mast cells, inflammatory dendritic epidermal cells and dermal fibroblasts (Zampeli and Tiligada, 2009). Different animal models support the involvement of histamine H_4 receptor in T_H2 cell-dependent skin inflammations. Decreased activation of T_H2 cells leads to reduced migration of antigen-bearing dendritic cells to the lymph nodes (Cowden et al., 2010). Skin inflammations, such as atopic dermatitis, offer an initial acute phase with an increased number of T_H2 cells secreting interleukin-4, interleukin-13 and interleukin-5 and the later chronic phase characterized by infiltration of inflammatory dendritic epidermal cells, macrophages and eosinophils. According to a specific T_H2 cell milieu, reflecting the acute phase of atopic dermatitis, stimulation of T cells leads to an increase in histamine H_4 receptor expression. Interferon gamma, a marker for the chronic phase, up-regulates the receptor expression on dendritic cells (Mommert et al., 2011). Histamine promotes skin inflammation probably via histamine H_4 receptor acting on T_H cells releasing pro-inflammatory cytokines and on antigen-presenting cells as potent chemoattractant. Otherwise, inflammation is controlled by suppression of cytokine and chemokine production in antigen-presenting cells influencing T_H cell polarization. Pre-clinical investigations of UR-65318 as first histamine H_4 receptor antagonist for atopic dermatitis were at present in advanced stages (<http://palaupharma.com/media/uploads/pipeline/6/Factsheet%20UR-65318%20Autumn%202010.pdf>, 2010). Administration of histamine H_1 and H_4 receptor antagonists failed to prevent atopic dermatitis in a dog model (Bäumer et al., 2011). In a model of allergic contact dermatitis JNJ7777120 could not reduce inflammatory response but inhibits allergen-induced scratching notably in combination with histamine H_1 receptor antagonism (Roßbach et al., 2008).

Vernal keratoconjunctivitis as chronic ocular allergic disease is characterized by T_H2 cell and eosinophil infiltration. Beside the histamine H_1 and H_2 receptor also the H_4 receptor was detected in normal conjunctiva and an extensive upregulation was found in inflamed tissue (Leonardi et al., 2011).

Additionally, in an experimental colitis model in rat acute colonic inflammation JNJ7777120 reduced the response to the trigger and point to further potential indications of the receptor in Crohn's disease and ulcerative colitis (Zampeli and Tiligada, 2009).

Histamine is involved in pathogenesis of autoimmune diseases, such as rheumatoid arthritis characterized by a synovial tissue inflammation (Woolley and Tetlow, 1997). Synovial cells of patients show elevated levels of histamine and histamine H_4 receptor expression correlates with disease severity and duration. Additional detection of the histamine H_4 receptor in fibroblasts and macrophage-like cells in synovial tissue indicates its involvement in disease progress (Zampeli and Tiligada, 2009). Evidence for involvement of histamine H_4 receptors in systemic lupus erythematosus was found by investigating the copy number of histamine H_4 receptor in the genome and its mRNA expression in patients (Yu et al., 2010).

6. Conclusion and Future Perspective

Despite the long term *in vitro* characterization and the large number of animal studies the indications for the histamine H_4 receptor remain speculative. Its (patho)physiological role and reliable animal models with high predictive value have to be further investigated. Based on preclinical studies, the histamine H_4 receptor is a promising target in (chronic) inflammatory conditions, such as inflammatory skin diseases (e.g. pruritus, atopic dermatitis) and respiratory disorders (e.g. asthma, allergic rhinitis). Meanwhile, the first clinical candidate has completed clinical phase II for the treatment of allergic rhinitis. Beside the local application, systemic effects concerning autoimmune or arthritic diseases as well as the treatment of pain conditions are conceivable indications. So far, the physiological role of the histamine H_4 receptor

was mainly restricted to its pro-inflammatory actions. Concerning controversial findings in a murine bronchial asthma model, the need for further investigations to fully understand its function becomes evident. Beside the histamine H₄ receptor also subtypes H₁ and H₂ are at least involved in the immune response to a comparable extent. Their interplay in inflammatory processes suggests a potential synergistic benefit of combined histamine H₁–H₄ receptor antagonism, especially in chronic allergic conditions. Additionally, the combination of histamine H₃ and H₄ receptor properties demonstrates a potential treatment approach in neuropathic pain and itch. The histamine H₄ receptor is still underestimated in its influence on immunomodulatory states, offering a great potential for new therapeutic strategies for unmet medical needs. Nevertheless, effects on other regulatory systems cannot be ruled out. Dealing with arising adverse reactions might be challenging for the development of clinical useful histamine H₄ receptor ligands. The therapeutic utility of the histamine H₄ receptor has to be proven in further preclinical and clinical investigations.

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