The role of histamine H4 receptors as a potential targets in allergic rhinitis and asthma

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ABSTRACT

Histamine—the main product of mast cells plays critical role in the pathogenetic pathways of both allergic rhinitis and asthma. The novel concept of the unique airway diseases its only supported by the similarities within pathogenetic process. Antagonists of H1 and H2 receptors are quite effective in allergic rhinitis, but not effective enough in asthma. In an era of corticosteroids, leucotriene antagonists and Anti-IgE treatment, there is still a challenge to search for more effective, more accurate and more safe treatment option. Antagonists (inverse agonists) of histamine receptors H4 seems to be one of the promising targets in the allergic rhinitis and asthma treatment. The first H4 antagonist entered to clinics and the results from a proof-of-concept Phase II clinical study is expected to be disclosed soon. This review article summarizes current knowledge on H4R that have been collected in various studies sharing evidences about efficacy of H4R as a reasonable target for diseases with histamine involved pathogenetic pathways.

Keywords: Allergic Rhinitis; Asthma; Histamine; H4R; Novel Drug Target

1. INTRODUCTION TO THE TOPIC

The increasing recognition over the last 50 years that allergic rhinitis and allergic asthma frequently co-exist, has led to the concept that these seemingly separate disorders are possibly the same disease, with symptoms occurring to a greater or lesser extent in the upper airways (rhinitis) or lower airways (asthma). When patients with either allergic rhinitis or allergic asthma are thoroughly investigated, it is frequently found that they have allergic inflammation and airway sensitivity throughout all of the airways [1].

One of the important biological signals involved in the pathogenesis of both of them is histamine, which is released after relevant antigenic stimulation of sensitized subjects, initiating the early phase of allergic reaction [2]. Many patients with allergic rhinitis and asthma could be managed quite easily, mainly if they respond to the treatment in an expected pattern. But still, there are challenges to find better treatment targeting the pathogenetic pathways more accurately, more effectively and more safely. In an era of local or systemic corticosteroids, antihistamines and antileukotrienes and new class of anti-allergy drugs, anti-IgE antibodies, there is still a need and provocation to search novel, possibly effective treatment options. This review article analyzes the role of H4 receptors in pathogenesis of allergic rhinitis and asthma and possible clinical applications of H4 antagonists.

2. HISTAMINE AND ITS MAIN BIOLOGICAL ACTIVITY

Histamine, is biogenic amine, that was isolated from the mould ergot in 1910 by Sir Henry Dale and his colleagues at the Wellcome Laboratories. Very early, in 1924, Lewis described the classic “triple response” to histamine consisting of a red spot due to vasodilatation, a wheal which was the consequence of increased permeability and flare due to an axon reflex [3]. Since that time a lot of knowledge had been collected about histamine and its action in various system of human body concerning gastrointestinal, cardiovascular and respiratory systems [4,5]. Later this amine was found to be a natural constituent of the body, hence, the name histamine was given after the Greek word for tissue, histos.

Nowadays we know, that histamine belongs to the biogenic amines and is synthesized by the pyridoxal phosphate (vitamin B-6)–containing 1-histidine decarboxylase (HDC) from the amino acid histidine [6]. Gastric enterochromaffin-like cells, histaminergic neurons as well as mast cells and basophils are classical cellular sources of histamine, where it is stored intracellularly in vesicles and released on stimulation [7]. De novo histamine synthesis has also been shown in other cell types, such as platelets, monocytes/macrophages, dendritic cells,
neutrophils and lymphocytes [8-10].

Histamine is a potent mediator of numerous biologic reactions. Besides the well-known triggering of degranulation of mast cells by crosslinking of the FcεRI receptor by specific allergens, several other nonimmunologic stimuli, such as neuropeptides, substance P, complement factors (i.e., C3a and C5a), cytokines (IL-1, IL-3, IL-8, GM-CSF), platelet-activating factor (PAF), hyperosmolarity, lipoproteins, adenosine, superoxide dismutase [11]. Hypoxia, chemical and physical factors (e.g., extreme temperatures, trauma, vibration) [12] or alcohol and certain food and drugs, may activate mast cells thus releasing histamine [7,13]. The pleiotropic effects of histamine are triggered by activating through one or several histamine receptors on different cells. Four subtypes of receptors (histamine 1 receptor (H1R), histamine 2 receptor (H2R), histamine 3 receptor (H3R), and histamine 4 receptor (H4R)) have been described. All these receptors belong to the G-protein-coupled receptor family. They are heptahelical transmembrane molecules that transduce the extracellular signal by using G-proteins and intracellular second messenger systems [14]. Differences in the affinities of these receptors are highly decisive on the biological effects of histamine and agents that target the active and inactive states of HRs exist in equilibrium. However, it has been shown in recombinant systems that HRs can trigger downstream events in the absence of receptor occupancy by an agonist, which accounts for constitutive spontaneous receptor activity [15]. HR agonists stimulate the active state in the receptor and inverse agonists stimulate the inactive one. An agonist with a preferential affinity for the active state of the receptor stabilizes the receptor in its active conformation leading to a continuous activation signal. An inverse agonist with a preferential affinity for the inactive state of the receptor stabilizes the receptor in this conformation and consequently induces an inactive state, which is characterized by blocked signal transduction via the HR [16]. HRs form dimers and even oligomers, which allow cooperation between HRs and other G-protein-coupled receptors. The affinity of histamine binding to different HRs varies significantly, with Ki values ranging from 5 - 10 nM for the H3 and H4 receptors to 2 - 10 mM for the H1 and H2 receptors [6,17]. Specific activation or blockade of HRs showed that they differ in expression, signal transduction or function and improved the understanding of the role of histamine in physiology and disease mechanisms [18]. Histamine can act not only on cell surface receptors (H1, H2, H3 and H4 receptors), but may also bind to some intracellular receptors such as cytochrome p450 and cytochrome c [19,20] and high-affinity lipocalins isolated from the saliva of ticks [21].

Histamine causes smooth muscle cell contraction, vasodilatation, increased vascular permeability and mucus secretion, tachycardia, alterations of blood pressure, and arrhythmias, and it stimulates gastric acid secretion and nociceptive nerve fibers. In addition, histamine has been known to play various roles in neurotransmission, immunomodulation, hematopoiesis, wound healing, day-night rhythm, and the regulation of histamine- and polyamine-induced cell proliferation and angiogenesis in tumor models [22,23] and intestinal ischemia [24]. The important roles of histamine in body physiology and various pathologic events have been well established, whereas new and exciting findings are still being uncovered.

The major routes of histamine inactivation in mammals are methylation of the imidazole ring, catalyzed by histamine N-methyltransferase (HNMT), and oxidative deamination of the primary amino group, catalyzed by diamine oxidase (DAO) also known as histaminase [25]. The DAO protein is stored in plasma membrane-associated vesicular structures in epithelial cells and is secreted into the circulation on stimulation [26].

3. H4 RECEPTOR—BIOLOGICAL AND CLINICAL RELEVANCE FOR THE H4 ANTAGONISTS USE

Histamine has long been known to mediate inflammatory, and allergic responses acting predominately through H1 receptors and H1 receptor antagonists have been used to treat allergies for many years [27]. Accumulating evidence derived from diverse in vivo and in vitro studies using animal models of disease and human biological samples substantiates the fundamental role of the H4 receptor in histamine-induced chemotaxis of mast cells, eosinophils and other immune cells [17,28,29]. In addition, the presence of H4 receptors mostly in immune system organs and their immunomodulatory role in cytokine production [30-32] argue for the pathophysiologic significance of H4 receptors in inflammatory conditions that are characterized by increases in immune cell numbers, such as asthma, allergic disorders and autoimmune diseases and imply their contribution not only in the histamine-mediated initial inflammatory signal but also in the maintenance of inflammation [17,33-35]. At the end of 2000, both Oda et al. [2000] [36] and Nakamura et al. [2000] [14] reported the cloning of the human H4 receptor cDNA from fetus and leukocyte cDNA, respectively. Subsequently, six other laboratories reported the same finding [37-42]. The gene encoding the H4 receptor is on chromosome 18q11.2, spans > 20.6 kb and has a similar intron-exon arrangement as the gene encoding the H3 receptor [42]. The human H4 receptor is related most closely to the human H3 receptor, which shares 31% sequence identity at the protein level. In the transmembrane domains, the sequence identity with the H3 receptor increases to 54%, whereas, taking into account the similarities in physico-chemical properties of
the different amino acids, the similarity in the trans-
membrane region is even higher (68%). Sequence identi-
ity with the H1 receptor and H2 receptor is 23% and 22%,
respectively [36,37]. Following the cloning of the human
H4 receptor, cDNAs that encode the H4 receptor were
cloned from mouse, rat, guinea pig and pig [43,44].

The H4R couples to members of the PTX-sensitive
Gi/o proteins (Figure 1). Thus, activation of the H4R
reduces cAMP formation and further downstream events
like CREB-mediated gene transcription [45]. In addition,
the H4R can activate the MAPK pathway via PTX-sensi-
tive mechanisms [39]. Furthermore, activation of H4R in
mast cells and eosinophils leads to a mobilization of
intracellular Ca2+. An increase in [Ca2+] is
sensitive to PTX and PLC inhibitors, indicating that PLC
is activated by the dissociated G βγ subunit after H4R
activation [48]. Recently, signaling of the H4R, presuma-
ably via a G protein-independent β-arrestin pathway,
resulting in a phosphorylation of ERK 1/2 in U2OS cells
has been reported [49,50]. The H4R exerts high levels of
constitutive activity [39,51].

H4R expresses on the surface of various hematopoietic
cells including T cells [31,53,54], B cells [37], mast cells
[17,41,47,55,56], eosinophils [36,46,57], dendritic cells
[37,58], monocytes [36,37], neutrophils [36,39] and
natural killer (NK) cells [58] and also on the surface
of non-hematopoietic cells such as fibroblasts [59] and
endocrine cells in gastrointestinal tract [60]. There are
controversial reports about H4R expression in neutro-
phils, spleen, thymus, lymph node, kidney, testis, brain,
lung, liver, placenta, heart, skeletal muscle and pancreas
[14,61].

The H4 receptor shows little homology to the classical
proinflammatory H1 receptor or the H2 receptor. H3 and
H4 receptors are most closely related to each other, and
they have a closer phylogenetic relationship with peptide
ligand GPCRs, while they are remotely related to other
biogenic amine receptors, including H1 and H2 receptors
[62]. The H4 receptor appears to have higher affinity for
histamine compared with the H1 receptor, activation
leading to leukocyte chemotaxis to sites of inflammation
via Gi/o proteins and increases in intracellular Ca2+
concentration [47,48]. In addition to histamine, liver-
expressed chemokine LEC/CC16 has been reported to
be a non-histamine endogenous H4 receptor agonist, de-
monstrating additive effects with histamine and involved
in eosinophil trafficking [62].

H4 receptors control leukocyte trafficking and pro-
inflammatory responses. It is caused by H4 receptor-
ediated histamine-induced activation of eosinophils, in-
eased expression of adhesion molecules like CD11b/
D18(Mac1) and CD54(ICAM-1) and rearrangement of
the actin cytoskeleton leading to eosinophil migration
from the bloodstream into the sites of inflammation
[41,46,57,63].

Human mast cells constitutively express H4 receptors
that govern autocrine and paracrine histamine-induced
processes [56]. H4 receptor activation mediates chemo-
taxis and intracellular Ca2+ mobilization in murine mast
cells, without affecting degranulation, thus providing a
mechanism for the selective recruitment of these effector
cells into the tissues and the amplification of the his-
tamine-mediated reaction eventually leading to chronic
allergic inflammation [47]. Supportive evidence for an
autoregulatory function of the mast cell-expressed H4
receptor comes from its critical role in zymosan-induced
recruitment of neutrophils in vivo, possibly via regulation
of leukotriene B4 release from mast cells [17,64].

The H4 receptor expressed on dendritic cells, CD4+
and CD8+ T cells appears to control cytokine and che-
mosine production. In general, histamine can enhance
TH1 responses through H1 receptor activation and
negatively regulate both TH1 and TH2 responses by
acting on H2 receptors. H4 receptor, which alongside H1
and H2 receptors, modulates cytokine secretion during
the integration of TH1/TH2 differentiation [65]. Cyto-
kines mediate their effects via the signal transduction and
activators of transcription (STAT), with STAT6 activa-
tion causing a shift towards the TH2 response imp-
licated in allergic state development and STAT1 and
STAT4 playing a role in the pathogenesis of asthma with
distinct responses existing in non-atopic and atopic states.
Histamine acting on the H4 receptor has been reported to
suppress ex vivo the mitogen-induced STAT1 phos-
phorylation and its specific interaction with DNA in per-
ipheral blood mononuclear cells derived from non-atopic
individuals [53], while the H4 receptor antagonist
JNJ7777120 inhibited STAT6 DNA binding in cells
derived from atopic subjects [54]. Additional evidence
for the immunomodulatory function of the H4 receptor
is provided by its involvement in the release of the CD4+
cell chemoattractant interleukin (IL)-16 from human
CD8+ T-lymphocytes in vitro [31], the influence on

Figure 1. Signal transduction pathways activated by the H4R
stimulation [52].
mouse CD4+ T cell activation possibly via signalling in dendritic cells [29], as well as by its up-regulation during monocyte differentiation, suppression of IL-12p70 production and chemotraction of human monocyte-derived dendritic cells [32]

A reciprocal crosstalk between histamine and cytokines or chemokines involving the H4 receptor seems to be in operation. Interferon (IFN)-γ up-regulates H4 receptor expression in human peripheral blood monocytes/CD14+ [66] and in inflammatory dendritic cells from atopic dermatitis skin [67]. The H4 receptor-mediated induction of Ca2+ mobilization and down-regulation of synthesis and release of the TH2-linked chemokine CCL2 from monocytes is indicative of a negative feedback mechanism that would avoid the TH2 environment in case of high histamine levels in allergic inflammation and contribute to the shift to TH1 that is observed in the transition from acute to chronic allergic inflammation [66]. Comparably, H4 receptor stimulation down-regulates the production of the TH1 cytokine IL-12 and that of CCL2 in human monocyte-derived inflammatory dendritic epidermal cells, the latter leading to decreased monocyte migration [67].

4. EVIDENCES FOR H4 RECEPTORS INVOLVEMENT IN ALLERGIC AIRWAY INFLAMMATION

Asthma

Histamine has been closely associated with pathophysiology of asthma. Histamine is a known airway constrictor and increased levels have been found in airways and plasma of asthma patients following antigen challenge [68]. Many cell types associated with asthma express histamine receptors, most notably the H1R, H2R and H4R. Eosinophils, T cells, mast cells and smooth muscle cells have all been shown to express both H1R and H2R and these receptors can mediate cytokine and chemokine secretion [69].

H1 antagonists were shown to be effective only when given during sensitization, but not during the antigen challenge phase. Despite the clinical data, currently H1 antagonists are not a front-line treatment for asthma and indeed a meta—analysis of clinical trial data indicates that H1 antagonists are not effective in treating asthma [70]. H2R antagonists have largely had no efficacy in asthma [71].

The identification of H4R has offered new insights into the effect of histamine and histamine receptors in asthma. The H4R is expressed in many important immune cells involved in pathophysiology of asthma. It is present in low amounts in the lung, where its expression in bronchial epithelial and smooth muscle cells and microvascular endothelial cells [31] may contribute to the airway disease phenotypes in various ways. The general tenor of H4R reviews suggests that H4R has a pro-inflammatory role in asthma [72].

For example, mast cells are main source of histamine in the lung and it has been shown, that histamine enhances mast cells chemotaxis via the H4R [47]. The H4 receptor mediates redistribution and recruitment of mast cells in the mucosal epithelium in response to allergens, thus amplifying allergic symptoms and maintaining chronic inflammation [17]. Supportive evidence is derived from the H4 receptor-mediated synergistic sequential action of histamine and CXCL12, the chemokine that is constitutively expressed in skin and airway epithelium and plays a key role in allergic airway disorders, to induce migration of mast cells precursors in vitro [55]. Moreover, the H4 receptor seems to regulate only locally mast cell redistribution in the oesophageal mucosal epithelium followed by infiltration of eosinophils in ovalbumin-challenged guinea pigs [73].

H4R—deficient mice and mice treated with H4R antagonists exhibited decreased allergic lung inflammation, with decreases in Th2 responses, including decreases in IL-4, IL-5, IL-13, IL-6 and IL-17 levels. H4 receptor play a role in modulating TH2 allergic responses, by influencing CD4+ T cell activation attributed to decreased cytokine and chemokine production by dendritic cells [29]. Cowden et al. (2010) [74] demonstrated, that therapeutic H4R antagonism can significantly ameliorate allergen induced, Th2 cytokine driven pathologies such as lung remodeling and airway dysfunction. In the mice sensitized to ovalbumin, therapeutic H4R antagonism inhibited T cell infiltration in to the lung and decreased Th2 cytokines IL-13 and IL-5, IL-13 dependent remodeling parameters, such as goblet cell hyperplasia and lung collagen were reduced. Intervention with H4R antagonist also improved measures of central and peripheral airway dysfunction. Most recently the H4R has been shown to by functionally expressed on human Th2 cells and the expression level is upregulated by IL-4. In another study, inhibition of airway resistance and inflammation, mediated through the recruitment of CD25 + FoxP3+ T regulatory (Treg) cells was observed by using the selective H4 receptor agonist 4-methylhistidine administered intratracheally into the lungs of asthmatic mice [75].

In contrast to H1R antagonists, H4R antagonists were equally effective during the sensitization and the allergen challenge phase of a mouse asthma model [29]. The H4R may account for effects of histamine that are not blocked by H1R antagonists an asthmatic responses and, in addition, there may been interaction between the two receptors [76]. Increased eosinophile numbers are found in asthmatic lungs and the H4R has been shown to mediate eosinophil chemotaxis [63]. A recent study
demonstrated, that in an acute mouse asthma model, the H1R antagonist mepyramine and the H4R antagonist JNJ7777120 exhibited synergistic inhibitory effects on eosinophil accumulation in bronchoalveolar lavage fluid [77].

The H4R may have other effects that could contribute to asthma. In mice, the H4R mediates IL-4 and IFN-γ production from invariant NK T cells and such cells have been implicated in the pathogenesis of asthma in humans [78].

The H4R mediates the migration of lung fibroblasts, which are important contributors of lung remodeling and other fibrotic lung disorders. Histamine augmented the migration of human fetal lung fibroblasts induced by fibronectin and this effect could be blocked by the H4R antagonist JNJ7777120 [79].

5. ALLERGIC RHINITIS

Histamine plays an important role in eliciting nasal symptoms of allergic rhinitis, such as sneezing, itch, rhinorrhea and nasal obstruction [80]. All histamine receptor subtypes (H1, H2, H3 and H4) play a role in allergic rhinitis. Nakaya et al. [81] demonstrated, that in human nasal mucosa, H1R was localised primarily in the epithelium, vessels and nerves, H2R was localized primarily in the epithelium and the glands, and the H3R and H4R were localized primarily in the nerves. Table 1. summarize location, activities of various histamine receptor subtypes in relationship to nasal symptoms of allergic rhinitis. Histamine H1 receptor antagonists, such as chlorpheniramine and ketotifen, have been used as the first choice in the treatment of nasal allergy. Although histamine H1 receptor antagonists inhibited nasal symptoms induced by antigen-antibody reaction in rats and mice [82], it has been pointed out that these histamine H1 receptor antagonists did not completely inhibit nasal symptoms [83]. JNJ7777120 is reported to be a selective histamine H4 receptor antagonist from the findings that the compound showed at least 1000-fold selectivity over other histamine receptors [17]. Repeated intranasal administration of JNJ7777120 significantly inhibited nasal symptoms of allergic rhinitis in mice. Single and repeated oral administrations of JNJ7777120 also significantly inhibited nasal symptoms. In addition, repeated oral administration significantly decreased serum total IgE. Shapira et al. (1991) reported that IL-4 induced B cells to switch to IgE production. On the other hand, IFN-γ is known to inhibit the switching of B cells to IgE production. JNJ7777120 caused a significant decrease in the levels of IL-4 and a significant increase in the levels of IFN-gamma in nasal lavage fluid. JNJ 7777120, could relieve symptoms and inflammatory conditions in allergic rhinitis in rat, the effect was weak compared with H1 receptor antagonist—Loratadine [84].

6. CONCLUDING REMARKS

Histamine plays an important role as neurotransmitter and chemical mediator in multiple physiological and pathophysiological processes in central and peripheral tissues. In the last century the extensive study of its

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<th>Receptor</th>
<th>Location</th>
<th>Activities</th>
<th>Nasal symptoms produced</th>
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<tr>
<td>H1</td>
<td>Blood vessels, sensory nerves (smooth muscle bronchi, GI tract, cardiac tissue, endothelium, CNS)</td>
<td>Increases vascular permeability, stimulation sensory nerves of airways, eosinophil chemotaxis, smooth muscle contraction in bronchi and GI tract, stimulation of vagal nerve receptors producing reflex smooth muscle contraction in airways, decreased AV node conduction time, enhancement of release of histamine and arachidonic acid derivatives, nitric oxide formation</td>
<td>Sneezing, itching, rhinorrhea, and perhaps some degree of nasal congestion via increased vascular permeability with leakage of fluid into the tissues and vasodilatation</td>
</tr>
<tr>
<td>H2</td>
<td>Vascular bed, epithelium of mucosa of nose, submucosal glands in nose, mucosa of stomach, CNS, cardiac tissue, uterus, smooth muscle</td>
<td>Stimulate mucous glands in airways, increases vascular permeability, direct chronotropic effect on atrium and inotropic action on ventricle, relaxation of esophageal sphincter, stimulation of suppressor T cells, decrease in neutrophil and basophil chemotaxis and activation, proliferation of lymphocytes, activity of NK cells</td>
<td>Potentially increase nasal airway swelling, producing nasal decongestion and perhaps increasing rhinorrhea</td>
</tr>
<tr>
<td>H3</td>
<td>Presynaptic nerves in the peripheralsympathetic adrenergic system, nasal submucosal glands, CNS (histaminergic nerves), airways, GI tract</td>
<td>Suppression of norepinephrine release at presynaptic nerve endings, stimulates nasal submucosal gland secretion, opposes bronchoconstriction and gastric acid</td>
<td>Can produce nasal congestion by prevention of norepinephrine after synaptic release</td>
</tr>
<tr>
<td>H4</td>
<td>Eosinophils, mast cells, basophils neutrophils, nasal turbinates (nerves), lung colon, epicanthus, bone marrow, spleen, live</td>
<td>Chemotaxis and chemokinesis of mast cells and eosinophils, enhancement of the activity of other chemomediators (e.g., chemokines) on eosinophils, upregulation of adhesion molecules</td>
<td>Could enhance the inflammatory response to nasal allergen exposure</td>
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actions in the human body, resulted in the identification of four G protein-coupled receptor (GPCR) subtypes (H1R-H4R), mediating numerous effects. The successful application of H1R and H2R antagonists/inverse agonists in the treatment of allergic conditions and gastric ulcer proved that these two receptors are excellent drug targets.

Growing pool of evidences about action and efficacy of H4R antagonists makes it very interesting to wait for the results of clinical trials. As it could be seen from the literature and novel patent applications there is huge reinforcement of H4R antagonists in inflammatory diseases such as pruritus, asthma, inflammatory pain and allergic rhinitis. Targeting histamine mediated pathways could be now more effective and influence pathomechanisms of certain diseases covering all known subtypes of histamine receptors.

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H2 receptors control histamine-induced interleukin-16 re-

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