British Journal of Pharmacology (2009), 157, 24–33

0007-1188/09
www.brjpharmacol.org

REVIEW

The role of histamine H_4 receptor in immune and inflammatory disorders

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Since its discovery at the beginning of the 20th century, histamine has been established to play a pathophysiological regulatory role in cellular events through binding to four types of G-protein-coupled histamine receptors that are differentially expressed in various cell types. The discovery, at the turn of the millennium, that the histamine H_4 receptor is largely expressed in haemopoietic cells as well as its chemotactic properties designate its regulatory role in the immune system. H_4 receptors modulate eosinophil migration and selective recruitment of mast cells leading to amplification of histamine-mediated immune responses and eventually to chronic inflammation. H_4 receptor involvement in dendritic cell activation and T cell differentiation documents its immunomodulatory function. The characterization of the H_4 as the immune system histamine receptor directed growing attention towards its therapeutic exploitation in inflammatory disorders, such as allergy, asthma, chronic pruritus and autoimmune diseases. The efficacy of a number of H_4 receptor ligands has been evaluated in *in vivo* and *in vitro* animal models of disease and in human biological samples. However, before reaching decisive conclusions on H_4 receptor pathophysiological functions and therapeutic exploitation, identification of genetic polymorphisms and interspecies differences in its relative actions and pharmacological profile need to be addressed and taken into consideration. Despite certain variations in the reported findings, the available data strongly point to the H_4 receptor as a novel target for the pharmacological modulation of histamine-transferred immune signals and offer an optimistic perspective for the therapeutic exploitation of this promising new drug target in inflammatory disorders.
British Journal of Pharmacology (2009) **157**, 24–33; doi:10.1111/j.1476-5381.2009.00151.x; published online 20 March 2009

Keywords: allergy; asthma; H_4 receptor ligands; histamine; histamine H_4 receptor; immune system; immunomodulation; inflammation; pruritus; rheumatoid arthritis

Abbreviations: 4-MH, 4-methylhistamine; Ag, antigen; BM, bone marrow; DC, dendritic cell; GPCR, G-protein-coupled receptor; $H_4R^{-/-}$, H_4 receptor-deficient mice; HL60.15, eosinophilic precursor cell line; IDEC, inflammatory dendritic epidermal cells; IFN, interferon; IL, interleukin; JNJ10191584, selective H_4 receptor antagonist; JNJ7777120, selective H_4 receptor antagonist; LPS, lipopolysaccharide; MC, mast cell; Mo-IDEC, monocyte-derived IDEC; PBMC, peripheral blood mononuclear cells; RA, rheumatoid arthritis; STAT, signal transduction and activator of transcription; T_H, helper T cell; TNF-α, tumour necrosis factor-alpha; Treg, T regulatory cell; VUF6002, selective H_4 receptor antagonist

Introduction

Histamine [2-(4-imidazolyl)-ethylamine] is an endogenous short-acting biogenic amine synthesized from the basic amino acid histidine through the catalytic activity of the rate-limiting enzyme histidine decarboxylase and widely distributed throughout the body (Dy and Schneider, 2004). The pharmacological study of histamine started concurrently with its discovery by Sir Henry H Dale at the beginning of the 20th century (Barger and Dale, 1910; Dale and Laidlaw, 1910). One of the first described functions was its ability to mimic anaphylaxis and has since been demonstrated to play a major role in inflammatory processes. Following the recognition of its 'somewhat complicated action' by Dale and Laidlaw (1910), histamine has been one of the most studied substances in medicine for nearly a century, possessing a wide spectrum of activities (Figure 1) including its potent mediator role in immediate hypersensitivity reactions (Daugherty, 2004).

Undoubtedly, the fundamental pleiotropic regulatory character of histamine in cellular events is attributed to its binding to four subtypes of G-protein-coupled receptors (GPCR), designated H_1, H_2, H_3 and H_4 (Figure 1) that are differentially expressed in various cell types (Dy and Schneider, 2004; Akdis and Simons, 2006; Chazot and Tiligada, 2008). Histamine

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Received 12 November 2008; revised 8 December 2008; accepted 5 January 2009

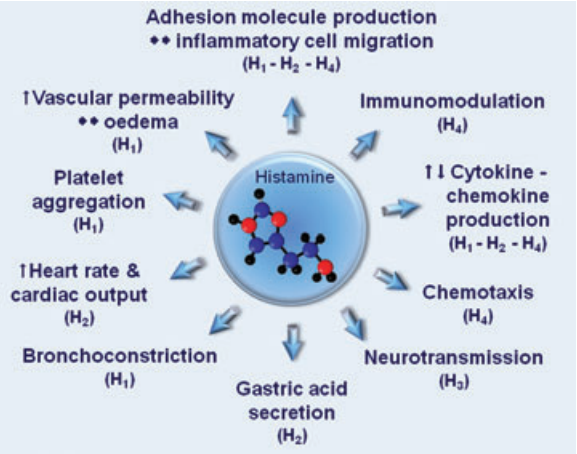

Figure 1 Indicative major effects exerted by histamine. The predominant histamine receptors, designated H_1, H_2, H_3 and H_4, eliciting the effects are shown in parentheses.

receptor diversity is supported by pharmacological evidence and by the low protein sequence homology, which is suggestive of their evolution from different ancestral genes (Leurs *et al.*, 2000). The H_4 receptor shows little homology to the classical pro-inflammatory H_1 receptor or the H_2 receptor and about 35% homology with the H_3 receptor. H_3 and H_4 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 H_1 and H_2 receptors (Nakayama *et al.*, 2004).

Histamine is synthesized in several cell types of peripheral and central tissues, while its release from repository cells is modulated by a variety of stimuli. The classical source of histamine is the pluripotent heterogeneous mast cell (MC) (Riley and West, 1952), where it is stored in cytosolic granules and released by exocytosis to exert its immunomodulatory role in response to various immunological and non-immunological stimuli, including allergens, drugs, mechanical stimulation, cold, ultra violet rays and endogenous polypeptides such as substance P and bradykinin (Kakavas *et al.*, 2006; Krishnaswamy *et al.*, 2006). Non-MC histamine is derived from numerous sources, indicative examples being gastric enterochromaffin-like cells (Prinz *et al.*, 2003), various types of blood cells, such as basophils (Falcone *et al.*, 2006), macrophages, lymphocytes (Zwadlo-Klarwasser *et al.*, 1994) and platelets (Masini *et al.*, 1998), neurons (Arrang *et al.*, 1983; Haas *et al.*, 2008), chondrocytes (Maslinska *et al.*, 2004) and tumours (Falus *et al.*, 2001). In the gastric mucosa, enterochromaffin-like cell-derived histamine acts as a paracrine stimulant to control acid secretion in response to hormonal and neural stimuli (Prinz *et al.*, 2003; Grandi *et al.*, 2008). In the brain, histamine is synthesized exclusively in histaminergic neurons of the tuberomamillary nucleus of the posterior hypothalamus that project all over the central nervous system (Haas and Panula, 2003). In a mutual interaction network with other transmitter systems, brain histamine is implicated in basic homeostatic and higher brain functions, including sleep–wake regulation, circadian and feeding rhythms, immunity, learning and memory (Haas *et al.*, 2008). Thus, in addition to the predominately H_1 receptor-mediated actions on smooth muscle, vascular permeability and modulation of allergic responses, the main functions of histamine (Figure 1) include gastric acid secretion basically via H_2 receptors (Black *et al.*, 1972), neurotransmission in the central nervous system largely via H_3 receptor signalling (Arrang *et al.*, 1983; Haas *et al.*, 2008) and modulation of immune system processes through the H_1 receptor and the recently identified H_4 receptor (Oda *et al.*, 2000; Liu *et al.*, 2001a; de Esch *et al.*, 2005).

The histaminergic system has proved to be a rich source of drugs over the last five decades with a number reaching blockbuster status. H_1 (commonly referred to as antihistamines) and H_2 receptor antagonists are widely used in the treatment of allergy and gastrointestinal disorders, respectively, while H_3 receptor antagonists may have therapeutic value in dementias, psychotic and sleep disorders as well as obesity (Hill *et al.*, 1997). Most importantly, growing attention is directed towards the therapeutic exploitation of the H_4 receptor in inflammation and cancer (Venable and Thurmond, 2006), following its cloning by several groups independently at the turn of the millennium (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Cogé *et al.*, 2001; Liu *et al.*, 2001a; Morse *et al.*, 2001; Nguyen *et al.*, 2001; Zhu *et al.*, 2001) and its subsequent characterization as the immune system histamine receptor.

Over the years, studies on the effect of histamine during the immune response have produced a number of apparently conflicting data. These inconsistencies might arise from the differential expression of histamine receptors that may vary with the experimental setup. The contribution of histamine receptors in immune responses is exemplified by the frequently stimulatory effects through H_1 receptor and inhibitory actions through H_2 receptor signalling, as well as by the regulatory role of these receptors in the balance between type I and II helper T (T_H) cells (Dy and Schneider, 2004; Akdis and Simons, 2006). The localization of H_4 receptors largely in haemopoietic cells, their distinct pharmacological profile and their role in chemotaxis and mediator release in various cell types (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Liu *et al.*, 2001a) led to the re-evaluation of many biological actions of histamine, resolved some of the inconsistencies regarding the pharmacology of histamine receptor ligands and differentiated its functional roles in physiology and pathophysiology (de Esch *et al.*, 2005; Thurmond *et al.*, 2008).

H_4 receptor: the immune system histamine receptor

Histamine H_4 receptor is a pertussis-toxin-sensitive GPCR predominantly expressed on cells of the immune system, including MCs, monocytes, eosinophils, dendritic cells (DCs), T cells and natural killer cells (Table 1); in peripheral tissues such as spleen, thymus, colon, blood leukocytes and bone marrow, its expression being induced or altered in response to inflammatory stimuli (Oda *et al.*, 2000; Cogé *et al.*, 2001; Liu *et al.*, 2001a; Morse *et al.*, 2001; Lippert *et al.*, 2004; Gutzmer *et al.*, 2005; Damaj *et al.*, 2007; Dijkstra *et al.*, 2007; 2008). The H_4 receptor appears to have higher affinity for histamine compared with the H_1 receptor, activation leading to leukocyte

Table 1 Expression and functional characteristics of the histamine H_4 receptor in cells associated with inflammatory and immune disorders

Cell type	*H_4 receptor expression, characteristics and function*	*References*
B-lymphocytes	Very low expression level (human blood)	Zhu *et al.* (2001)
Dendritic cells	mRNA expression; chemotaxis with Ca^{2+} fluxes (human blood)	Zhu *et al.* (2001); Ling *et al.* (2004); Damaj *et al.* (2007)
	Migration (guinea pig and mouse BM)	Bäumer *et al.* (2008)
	Up-regulation by IFN-γ; down-regulation of T_H2-linked chemokine CCL2 and T_H1 cytokine IL-12 (human IDECs)	Dijkstra *et al.* (2008)
	mRNA up-regulation during differentiation; suppression of IL-12p70 production; F-actin polymerization → migration (human MoDC)	Gutzmer *et al.* (2005)
Eosinophils	mRNA expression; intracellular Ca^{2+} mobilisation, actin polymerization, shape change, up-regulation of CD11b/CD18 and CD54 expression; migration into inflamed tissue (human blood)	Oda *et al.* (2000); Morse *et al.* (2001); Buckland *et al.* (2003); Ling *et al.* (2004); Barnard *et al.* (2008)
	Ca^{2+} mobilization, chemotaxis (mouse)	O'Reilly *et al.* (2002)
Fibroblasts	mRNA up-regulation by LPS and indomethacin, protein levels increased by dexamethasone (human, dermal)	Ikawa *et al.* (2008)
HL60.15 cell line	IL-5 induced differentiation → increased H_4 receptor expression	Ling *et al.* (2004)
Mast cells	H_4 receptor mRNA and protein expression (human skin)	Lippert *et al.* (2004)
	Intracellular Ca^{2+} mobilization; chemotaxis without degranulation (mouse)	O'Reilly *et al.* (2002); Hofstra *et al.* (2003); Thurmond *et al.* (2004)
	Enhancement of CXCL12 chemotactic activity on mast cell precursors (human umbilical cord blood)	Godot *et al.* (2007)
	Local mast cell regulation, redistribution in ovalbumin-challenged oesophageal mucosal epithelium → infiltration of eosinophils (guinea pig)	Yu *et al.* (2008)
Monocytes	Higher expression in resting than in activated cells; up-regulation by IFN-γ; Ca^{2+} influx, down-regulation of CCL2 synthesis and release → reduced monocyte recruitment (human blood)	Oda *et al.* (2000); Morse *et al.* (2001); Zhu *et al.* (2001); Dijkstra *et al.* (2007)
Natural killer cells	Chemotaxis with no induction of Ca^{2+} mobilization (human blood)	Damaj *et al.* (2007)
Neutrophils	Expression (human blood)	Oda *et al.* (2000); Morse *et al.* (2001)
T-lymphocytes	Higher expression in resting than in activated $CD4^+$ and $CD8^+$ cells; increased release of IL-16 from $CD8^+$ cells (human, blood)	Morse *et al.* (2001); Zhu *et al.* (2001); Gantner *et al.* (2002); Ling *et al.* (2004)
	Suppression of STAT1α formation, phosphorylation and DNA binding (human non-atopic PBMCs); H_4 receptor blockade → inhibition of STAT6 DNA binding (human atopic PBMCs)	Horr *et al.* (2006); Michel *et al.* (2008)

BM, bone marrow; DC, dendritic cell; HL60.15, eosinophilic precursor cell line; IDEC, inflammatory dendritic epidermal cells; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MoDC, monocyte-derived DC; PBMC, peripheral blood mononuclear cells; STAT, signal transduction and activator of transcription; T_H, helper T cell.

chemotaxis to sites of inflammation via $G\alpha_{i/o}$ proteins and increases in intracellular Ca^{2+} concentration (Hofstra *et al.*, 2003; de Esch *et al.*, 2005; Table 1). In addition to histamine, liver-expressed chemokine LEC/CCL16 has been reported to be a non-histamine endogenous H_4 receptor agonist, demonstrating additive effects with histamine and involved in eosinophil trafficking (Nakayama *et al.*, 2004).

The expression of the H_4 receptor in several types of human immune cells and its chemotactic properties denote its role in immunomodulation (Figure 2, Table 1). Despite the interspecies differences in amino acid sequence, expression levels, ligand binding and receptor activation, the comparable tissue distribution suggests similar physiological roles for this receptor across the species (Liu *et al.*, 2001b; Oda *et al.*, 2005; Jiang *et al.*, 2008).

Eosinophil chemotaxis

Histamine was first described as a selective chemoattractant for eosinophils more than 30 years ago (Clark *et al.*, 1975). In a retrospective literature evaluation, the reported histamine effects on eosinophil chemotaxis can now be attributed to the H_4 receptor. The existence of a histamine receptor on the surface of eosinophils that was distinct from H_1, H_2 or H_3 receptors and demonstrated low-affinity binding for *R*-(α)-methylhistamine antagonized by the H_3/H_4 antagonist thioperamide was hypothesized in 1994 (Raible *et al.*, 1994). Concrete evidence that H_4 receptors control leukocyte trafficking and pro-inflammatory responses was derived from the H_4 receptor-mediated histamine-induced activation of eosinophils (Table 1), increased expression of adhesion molecules like CD11b/CD18(Mac1) and CD54(ICAM-1) and rearrangement of the actin cytoskeleton leading to eosinophil migration from the bloodstream into the sites of inflammation (O'Reilly *et al.*, 2002; Buckland *et al.*, 2003; Ling *et al.*, 2004; Barnard *et al.*, 2008).

Mast cell chemotaxis and chronic inflammation

Interestingly, human MCs constitutively express H_4 receptors that govern autocrine and paracrine histamine-induced processes (Lippert *et al.*, 2004). H_4 receptor activation mediates chemotaxis and intracellular Ca^{2+} mobilization in murine MCs, without affecting degranulation, thus providing a mechanism for the selective recruitment of these effector cells into the tissues and the amplification of the histamine-mediated reaction eventually leading to chronic allergic inflammation (Hofstra *et al.*, 2003). Supportive evidence for

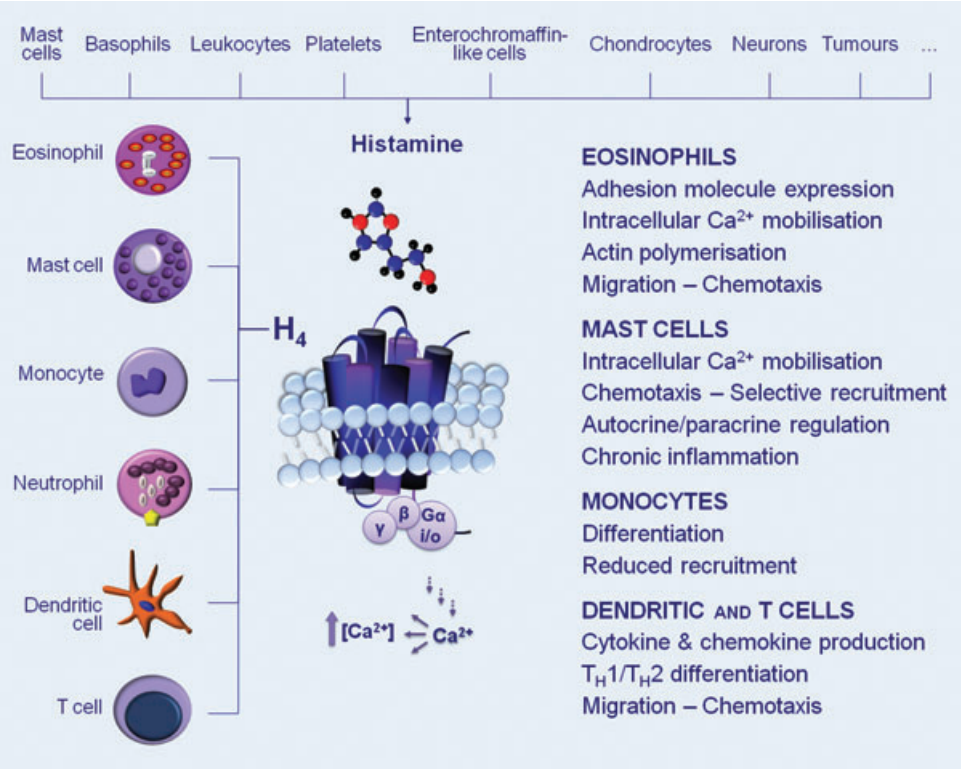

Figure 2 Indicative immunomodulatory actions of histamine that are mediated through histamine H_4 receptors (H_4) predominately expressed in immune cells. $G\alpha_{i/o}$, G-protein; T_H, helper T cell.

an autoregulatory function of the MC-expressed H_4 receptor comes from its critical role in zymosan-induced recruitment of neutrophils *in vivo*, possibly via regulation of leukotriene B_4 release from MCs (Takeshita *et al.*, 2003; Thurmond *et al.*, 2004), without however excluding the possibility of additional effects of other immune cells in the response (Liu *et al.*, 2001b; Dunford *et al.*, 2007).

Dentritic cell activation and T cell differentiation

The H_4 receptor expressed on DCs, $CD4^+$ and $CD8^+$ T cells appears to control cytokine and chemokine production (Table 1). In general, histamine can enhance T_H1 responses through H_1 receptor activation and negatively regulate both T_H1 and T_H2 responses by acting on H_2 receptors (Jutel *et al.*, 2001). However, data concerning the differential expression of histamine receptor subtypes that mediate DC activation and T_H1/T_H2 differentiation have been somewhat contradictory (Dy and Schneider, 2004). The interest was revived after the identification of the H_4 receptor, which alongside H_1 and H_2 receptors, modulates cytokine secretion during the integration of T_H1/T_H2 differentiation (Jutel *et al.*, 2001). Cytokines mediate their effects via the signal transduction and activators of transcription (STAT), with STAT6 activation causing a shift towards the T_H2 response implicated 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 H_4 receptor has been reported to suppress *ex vivo* the mitogen-induced STAT1 phosphorylation and its specific interaction with DNA in peripheral blood mononuclear cells derived from non-atopic individuals (Horr *et al.*, 2006), while the H_4 receptor antagonist JNJ7777120 inhibited STAT6 DNA binding in cells derived from atopic subjects (Michel *et al.*, 2008). However, in mouse splenocytes, the H_4 receptor exerted no effect on STAT4 (Liu *et al.*, 2006) or STAT6 (Kharmate *et al.*, 2007) phosphorylation.

Additional evidence for the immunomodulatory function of the H_4 receptor is provided by its involvement in the release of the $CD4^+$ cell chemoattractant interleukin (IL)-16 from human $CD8^+$ T-lymphocytes *in vitro* (Gantner *et al.*, 2002), the influence on mouse $CD4^+$ T cell activation possibly via signalling in DCs (Dunford *et al.*, 2006), as well as by its up-regulation during monocyte differentiation, suppression of IL-12p70 production and chemoattraction of human monocyte-derived DCs (Gutzmer *et al.*, 2005). A reciprocal crosstalk between histamine and cytokines or chemokines involving the H_4 receptor seems to be in operation. Interferon (IFN)-γ up-regulates H_4 receptor expression in human peripheral blood monocytes/$CD14^+$ (Dijkstra *et al.*, 2007) and in inflammatory DCs from atopic dermatitis skin (Dijkstra *et al.*, 2008). The H_4 receptor-mediated induction of Ca^{2+} mobilization and down-regulation of synthesis and release of the T_H2-linked chemokine CCL2 from monocytes is indicative of a negative feedback mechanism that would avoid the T_H2 environment in case of high histamine levels in allergic inflammation and contribute to the shift to T_H1 that is observed in the transition from acute to chronic allergic inflammation (Dijkstra *et al.*, 2007). Comparably, H_4 receptor stimulation down-regulates the production of the T_H1

Table 2 Evidence for the contribution of histamine H_4 receptor to inflammatory disorders

Condition	*Function of the H_4 receptor*	*References*
Airway inflammation	Decreased lung inflammation, lung eosinophil/lymphocyte infiltration and T_H2 responses in $H_4R^{-/-}$ and JNJ7777120-treated mice; decreased IL-4, IL-5, IL-13, IL-6, IL-17 levels upon *ex vivo* re-stimulation of mouse T cells → disrupted T cell functions; blockade of DC H_4 receptors *in vitro* → decreased cytokine and chemokine production → limited ability of DC to induce T_H2 responses in murine T cells	Dunford *et al.* (2006)
	Intratracheal administration of H_4 receptor agonist 4-MH before Ag challenge in a murine model of allergic asthma → reduced airway hyperreactivity and inflammation, increased IL-10 and IFN-γ and decreased IL-13 in the bronchoalveolar lavage fluid; accumulation of $FoxP3^+$ T cells	Morgan *et al.* (2007)
	In vitro stimulation of human T cells with H_4 receptor agonist 4-MH → increased T cell migration skewed towards CD25- and intracellular FoxP3-expressing $CD4^+$ cells; suppressed proliferation of autologous T cells dependent on IL-10 production	Morgan *et al.* (2007)
	Increased H_4 receptor expression in human nasal turbinate mucosa and nasal polyp tissue, tendency for correlation between H_4 receptor expression and eosinophil cationic protein	Jókúti *et al.* (2007)
	Suppression of STAT1α formation and phosphorylation by H_4 receptor agonist clobenpropit and enhancement of STAT1α levels, phosphorylation and DNA binding by JNJ7777120 in non-atopic human stimulated PBMCs	Horr *et al.* (2006)
	Inhibition of STAT6 DNA binding by JNJ7777120 in atopic human PBMCs	Michel *et al.* (2008)
	Inhibition of MC and eosinophil migration into oesophageal mucosal epithelium of sensitized guinea pigs by the H_3/H_4 receptor antagonist thioperamide	Yu *et al.* (2008)
Pruritus & dermatitis	Reduction of H_4 receptor agonist clobenpropit-induced scratching by the H_3/H_4 receptor antagonist thioperamide in female Balb C mice	Bell *et al.* (2004)
	No pruritic response with 4-MH in $H_4R^{-/-}$ mice; attenuation of MC- or other haematopoietic cell-independent scratching by JNJ7777120 in mice	Dunford *et al.* (2007)
	Strain differences between NMRI and Balb C mice in H_4 receptor-mediated scratching, not associated with H_4 receptor expression and protein levels in murine BM-derived DCs; clobenpropit-induced DC migration blocked by JNJ7777120	Bäumer *et al.* (2008)
	H_4 receptor expression in skin IDECs, up-regulation by IFN-γ in Mo-IDECs; clobenpropit and 4-MH-induced down-regulation of CCL2 and IL-12 production in Mo-IDECs blocked by JNJ7777120 in human atopic dermatitis	Dijkstra *et al.* (2008)
	Suppression of late-phase swelling and eosinophil infiltration by H_3/H_4 receptor antagonist thioperamide in Ag-non-specific dermatitis in mice	Hirasawa *et al.* (2008)
Arthritis	Variable mRNA expression in synovial cells (superficial layer membrane, villi and vascular wall cells, fibroblast- and macrophage-like cells) from rheumatoid arthritis and osteoarthritis patients	Ikawa *et al.* (2005); Grzybowska-Kowalczyk *et al.* (2007; 2008); Ohki *et al.*, 2007
	Increased cartilage histamine content without arthritis signs in JNJ7777120-treated rats with adjuvant arthritis	Zampeli *et al.* (2008)
Acute/subchronic inflammation	Reduction of early-phase paw oedema and thermal hyperalgesia by JNJ7777120 and VUF6002 in carrageenan-induced inflammation in rats	Coruzzi *et al.* (2007)
	Reduced neutrophil release from BM and MC-dependent neutrophil recruitment by the H_3/H_4 receptor antagonist thioperamide in zymosan-induced peritonitis in mice	Takeshita *et al.* (2003; 2004); Thurmond *et al.* (2004)
	Reduction in macroscopic damage, mucosal and submucosal thickness and neutrophil infiltration and inhibition of colonic myeloperoxidase and TNF-α elevation by JNJ10191584 and JNJ7777120 in trinitrobenzene sulphonic acid-induced subchronic colitis in rats	Varga *et al.* (2005)
	Increased conjunctival histamine content upon topical JNJ7777120 instillation in experimental conjunctivitis in rats	Zampeli *et al.* (2009)
Ischaemia/reperfusion injury	H_4 receptor stimulation → prevention of reperfusion injury development in the rat liver	Adachi *et al.* (2006)

4-MH, 4-methylhistamine; Ag, antigen; BM, bone marrow; DC, dendritic cell; $H_4R^{-/-}$, H_4 receptor-deficient mice; IDEC, inflammatory dendritic epidermal cells; IFN, interferon; IL, interleukin; JNJ10191584, selective H_4 receptor antagonist; JNJ7777120, selective H_4 receptor antagonist; MC, mast cell; Mo-IDEC, monocyte-derived IDEC; PBMC, peripheral blood mononuclear cells; STAT, signal transduction and activator of transcription; T_H, helper T cell; TNF-α, tumour necrosis factor-alpha; VUF6002, selective H_4 receptor antagonist.

cytokine IL-12 and that of CCL2 in human monocyte-derived inflammatory dendritic epidermal cells, the latter leading to decreased monocyte migration (Dijkstra *et al.*, 2008).

H_4 receptor-mediated effects in inflammatory disorders

Histamine has long been known to mediate inflammatory, and allergic responses acting predominately through H_1 receptors and H_1 receptor antagonists have been used to treat allergies for many years (Hill *et al.*, 1997). Accumulating evidence derived from diverse *in vivo* and *in vitro* studies using animal models of disease and human biological samples (Table 2) substantiates the fundamental role of the H_4 receptor in histamine-induced chemotaxis of MCs, eosinophils and other immune cells (Thurmond *et al.*, 2004; Ikawa *et al.*, 2005; Dunford *et al.*, 2006). In addition, the presence of H_4 receptors mostly in immune system organs and their immunomodulatory role in cytokine production (Cogé *et al.*, 2001; Gantner

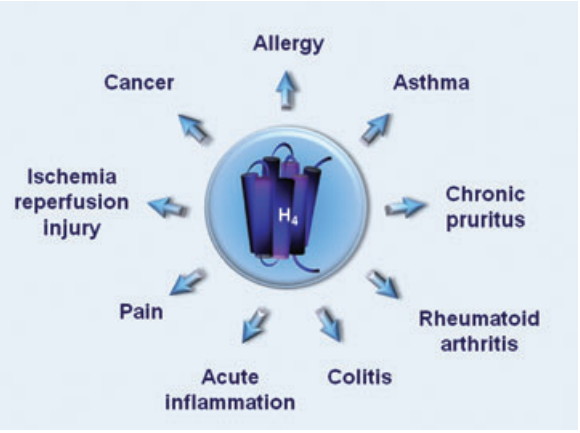

Figure 3 Involvement of the histamine H_4 receptor in a number of inflammatory disorders.

et al., 2002; Gutzmer *et al.*, 2005) argue for the pathophysiological significance of H_4 receptors in inflammatory conditions that are characterized by increases in immune cell numbers, such as asthma, allergic disorders and autoimmune diseases (Figure 3) and imply their contribution not only in the histamine-mediated initial inflammatory signal but also in the maintenance of inflammation (Thurmond *et al.*, 2004; Kakavas *et al.*, 2006; Dunford *et al.*, 2007; Zhang *et al.*, 2007; Table 2).

Consequently, the H_4 receptor is currently an attractive target for the pharmacological modulation of histamine-transferred signals in inflammatory conditions (Buckland *et al.*, 2003; Hofstra *et al.*, 2003; de Esch *et al.*, 2005; Bäumer *et al.*, 2008) and for the development of beneficial therapeutic strategies for these conditions (Kiss *et al.*, 2008; Thurmond *et al.*, 2008). Furthermore, the use of H_4 receptor-targeting agents in related studies, including JNJ7777120, the first highly selective H_4 receptor antagonist developed (Jablonowski *et al.*, 2003; Thurmond *et al.*, 2004) and the potent selective agonist 4-methylhistamine (Lim *et al.*, 2005), has provided useful information on the physiological role of histamine receptors in inflammatory conditions.

Airway inflammation and allergy

In inflammatory lung disorders, histamine acts as a mediator of both acute and chronic phases. Accumulating data support the function of histamine in cellular immunity through control of cytokine and chemokine production and migration of inflammatory cells, beyond its traditional role in mediating immediate airway hyper-responsiveness (Barnes *et al.*, 1998). Although H_1 receptor antagonists offer symptomatic relief in atopic nasal, conjunctival and skin disease, they are not optimally effective in asthma, where the contribution of each type of histamine receptor in histamine-mediated effects is currently subject to intense research. The H_4 receptor is present in low amounts in the lung, where its expression in bronchial epithelial and smooth muscle cells and microvascular endothelial cells (Gantner *et al.*, 2002) may contribute to the airway disease phenotypes in various ways.

The H_4 receptor mediates redistribution and recruitment of MCs in the mucosal epithelium in response to allergens, thus amplifying allergic symptoms and maintaining chronic inflammation (Thurmond *et al.*, 2004). Supportive evidence is derived from the H_4 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 MC precursors *in vitro* (Godot *et al.*, 2007). Moreover, the H_4 receptor seems to regulate only locally MC redistribution in the oesophageal mucosal epithelium followed by infiltration of eosinophils in ovalbumin-challenged guinea pigs (Yu *et al.*, 2008).

The reduced lung inflammation and the decreases in T_H2 responses observed in H_4 receptor-deficient ($H_4R^{-/-}$) mice and upon oral gavage administration of selective antagonists in a murine model of allergic airway inflammation documented the role of the H_4 receptor in modulating T_H2 allergic responses, by influencing $CD4^+$ T cell activation attributed to decreased cytokine and chemokine production by DCs (Dunford *et al.*, 2006). 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 H_4 receptor agonist 4-methylhistamine administered intratracheally into the lungs of asthmatic mice (Morgan *et al.*, 2007). The beneficial actions of both H_4 agonists and antagonists observed in asthmatic mice were attributed to the local versus systemic administration of the compounds, respectively, and to the resulting concentration gradient within the lung in the former case that would allow the migration of the immune response suppressive Treg cells (Morgan *et al.*, 2007).

Considering the role of the H_4 receptor in the modulation of the asthmatic response revealed by these studies and the reported inhibitory effect of H_4 receptor agonists on antigen-specific responses in human peripheral blood mononuclear cells and T cell lines, which, however, was not reversed by the H_3/H_4 receptor antagonist thioperamide (Sugata *et al.*, 2007), additional data are a prerequisite imperative of providing conclusive evidence concerning the optimal therapeutic exploitation of H_4 receptor ligands in chronic airway disease (Daugherty, 2004). Furthermore, species and strain differences should be considered carefully before data interpretation as murine DC chemotactic response needs very high histamine concentrations to be observed (Bäumer *et al.*, 2008) and different cytokine secretion patterns are observed in $H_4R^{-/-}$ mice and murine DCs (Dunford *et al.*, 2006).

Chronic pruritus

Chronic pruritus is a common clinical condition associated with cutaneous or systemic disease and although histamine, MCs and basophils are increased in patients, classical H_1 receptor antagonists are of limited use due to lack of effectiveness (O'Donoghue and Tharp, 2005). Histamine has been shown to induce scratching in Balb C mice via H_4 receptors (Bell *et al.*, 2004). Treatment of mice with JNJ7777120 attenuated the pruritic response to histamine, IgE and compound 48/80, the inhibitory effect of the H_4 receptor antagonist being greater than that observed with H_1 receptor antagonists (Dunford *et al.*, 2007). Even so, H_1 receptor-mediated actions seem to complement the H_4 receptor-mediated enhanced DC

migration through skin, and therefore H_1 combined with H_4 receptor antagonists could be a beneficial approach (Bäumer *et al.*, 2008; Roßbach *et al.*, 2009). In addition, although H_4 receptor antagonism strongly attenuated the pruritic response to the classical contact allergen 2,4-dinitrochlorobenzene and to the respiratory chemical allergen toluene-2,4-diisocyanate, which mediate T_H1- and T_H2-dominated inflammation, respectively, JNJ7777120 failed to reduce the allergic inflammatory response associated with allergic dermatitis (Roßbach *et al.*, 2009).

Although H_4 receptors are expressed in human skin MCs (Lippert *et al.*, 2004), inflammatory dendritic epidermal cells (Dijkstra *et al.*, 2008) and dermal fibroblasts (Ikawa *et al.*, 2008), the H_4 receptor-mediated pruritus was suggested to be MC-independent and possibly coupled to actions on the peripheral terminals of sensory neurons rather than to effects on haemopoietic cells (Dunford *et al.*, 2007). However, before extrapolating these results to human pathophysiology that may lead to misinterpretation of the complex regulatory MC-DC interactions, one should consider the pharmacological differences in agonist affinity between human and mouse H_4 receptors. Results from functional studies in experimental animals need cautious interpretation as species differences certainly occur. Indeed, detailed site-directed mutagenesis data reported recently demonstrated Phe^{169} in the second extracellular loop as the single amino acid responsible for the differences in agonist affinity between the human and mouse H_4 receptors (Lim *et al.*, 2008). Moreover, strain differences in the mouse response to the H_4 receptor agonist/H_3 receptor antagonist clobenpropit were recently reported, NMRI mice being more susceptible to H_4 receptor-induced itching compared with Balb C mice (Bäumer *et al.*, 2008).

Autoimmune disorders

Histamine has been recognized to play a role in autoimmune diseases, including rheumatoid arthritis (RA) that is characterized mainly by synovial tissue inflammation leading to erosion and destruction of articular cartilage with subsequent joint deformity (Woolley and Tetlow, 1997). Although a recent report argued for the anti-inflammatory properties of histamine in RA (Adlesic *et al.*, 2007), the amine has been largely regarded as a pro-inflammatory mediator in arthritic disease (Maslinska *et al.*, 2004; Grzybowska-Kowalczyk *et al.*, 2007; 2008; Ohki *et al.*, 2007). Besides the presence of H_1 and H_2 receptors, the considerable variations in H_4 receptor expression in human synovial cells could be related to RA severity and duration (Ikawa *et al.*, 2005). The localization of H_4 receptors in synovial and vascular wall cells of patients with RA (Grzybowska-Kowalczyk *et al.*, 2007) and osteoarthritis (Grzybowska-Kowalczyk *et al.*, 2008) and the identification of H_4 receptors in fibroblast- and macrophage-like cells from RA synovial tissues (Ohki *et al.*, 2007) further support the contribution of the receptor in the pathophysiology of the disease. Moreover, evidence for the systemic contribution of histamine in the arthritic phenotype was obtained by using a rat model of adjuvant arthritis, and a functional role of the H_4 receptor in the normal cartilage has been suggested in the rat, raising attractive questions regarding the H_4 receptor-mediated mechanisms in this tissue (Zampeli *et al.*, 2008).

Other inflammatory conditions

The association of the H_4 receptor with immune cell function motivated the intense investigation of its implication in virtually every condition that comprises an inflammatory component (Figure 3), mostly using either the mixed H_3/H_4 receptor antagonist thioperamide or selective H_4 receptor agonists and antagonists (Zhang *et al.*, 2007). Thus, H_4 receptor agonists prevented the development of reperfusion injury following ischaemia-induced liver damage (Adachi *et al.*, 2006). Beneficial actions of the H_4 receptor antagonists have been reported in a rat model of subchronic colitis (Varga *et al.*, 2005) and in MC-dependent mouse models of zymosan-induced pleurisy or peritonitis (Takeshita *et al.*, 2003; Thurmond *et al.*, 2004), used as an experimental model of acute inflammation involving neutrophil recruitment from the bone marrow (Takeshita *et al.*, 2004).

On the other hand, H_4 receptor antagonists exerted an inhibitory effect on airway inflammation (Dunford *et al.*, 2006) and pruritic responses (Dunford *et al.*, 2007) in MC-deficient mice but they were not effective in MC-independent mouse models of acute inflammation, such as histamine-induced paw oedema, thioglycollate-induced peritonitis (Thurmond *et al.*, 2004) and carrageenan-induced neutrophilia (Takeshita *et al.*, 2003). In a rat model of carrageenan-induced acute inflammation and pain, H_4 receptor antagonists reduced the early phase development of oedema but not the late inflammatory responses and attenuated the hyperalgesic response to thermal stimuli, possibly acting through peripheral nociceptive pathways (Coruzzi *et al.*, 2007).

In addition to the localization of H_4 receptors in synovial specimens from RA patients (Ikawa *et al.*, 2005; Grzybowska-Kowalczyk *et al.*, 2007; 2008; Ohki *et al.*, 2007), a limited number of studies have attempted to identify H_4 receptor alterations in human samples derived from inflamed tissues. For instance, the increased levels of H_4 receptors in normal nasal turbinate mucosa and in nasal polyp tissue and the tendency for correlation between the expression of H_4 receptors and eosinophil cationic protein led to the speculation that the receptor may have a role in mediating histamine effects and eosinophil accumulation and activation in nasal and paranasal sinus mucosa inflammatory diseases (Jókúti *et al.*, 2007).

These results certainly reflect the complex cellular and biochemical networks orchestrating inflammation. However, species differences in H_4 receptor-mediated responses and/or ligand efficacy need to be elucidated before decisive conclusions are drawn regarding the use of H_4 receptor ligands in the treatment of inflammatory human disease. In addition, yet unidentified receptor polymorphisms must also be taken in consideration. The first two alternatively spliced H_4 receptor isoforms, which have a dominant negative effect on the full-length H_4 receptor functionality by retaining it intracellularly and inactivating it presumably via hetero-oligomerization, have been cloned in $CD34^+$ cord blood-cell-derived eosinophils and MCs (van Rijn *et al.*, 2008).

Future perspectives

Although histamine has not been ignored by immunopharmacologists for nearly a century, the discovery of the H_4 receptor offered to the amine a new perspective beyond its traditional pharmacological properties. The complexity of leukocyte immune surveillance, trafficking and recruitment and the plethora of different effects exerted by histamine through a repertoire of four receptor subtypes make hard to predict the overall effect of H_4 receptors in inflammatory conditions at present. H_4 receptor antagonists may be effective candidates in treating diseases associated with chronic pruritus and asthma, without disregarding the potential clinical application of H_4 receptor ligands in autoimmune diseases like RA. A number of candidate drugs targeting the H_4 receptor are in preclinical assessment for a range of inflammatory disorders; some showing promise for potential entry into clinical trials and even though the available data are variable in quality, they are adequate in quantity to justify an optimistic perspective for this new drug target.

Conflict of interest

The authors state no conflict of interest.

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