REVIEW

The role of histamine H₄ 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 H₄ receptor is largely expressed in haemopoietic cells as well as its chemotactic properties designate its regulatory role in the immune system. H₄ receptors modulate eosinophil migration and selective recruitment of mast cells leading to amplification of histamine-mediated immune responses and eventually to chronic inflammation. H₄ receptor involvement in dendritic cell activation and T cell differentiation documents its immunomodulatory function. The characterization of the H₄ 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 H₄ 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 H₄ 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 H₄ 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; H₄ receptor ligands; histamine; histamine H₄ 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; H₄R^{-/-}, H₄ receptor-deficient mice; HL60.15, eosinophilic precursor cell line; IDEC, inflammatory dendritic epidermal cells; IFN, interferon; IL, interleukin; JNJ10191584, selective H₄ receptor antagonist; JNJ777120, selective H₄ 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 H₄ 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 H₁, H₂, H₃ and H₄ (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 H₁, H₂, H₃ and H₄, 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 H₄ receptor shows little homology to the classical pro-inflammatory H₁ receptor or the H₂ receptor and about 35% homology with the H₃ 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 (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 tuberomammillary 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 H₁

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 H₂ receptors (Black *et al.*, 1972), neurotransmission in the central nervous system largely via H₃ receptor signalling (Arrang *et al.*, 1983; Haas *et al.*, 2008) and modulation of immune system processes through the H₁ receptor and the recently identified H₄ 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. H₁ (commonly referred to as antihistamines) and H₂ receptor antagonists are widely used in the treatment of allergy and gastrointestinal disorders, respectively, while H₃ 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 H₄ 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 H₁ receptor and inhibitory actions through H₂ 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 H₄ 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).

H₄ receptor: the immune system histamine receptor

Histamine H₄ 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 H₄ receptor appears to have higher affinity for histamine compared with the H₁ receptor, activation leading to leukocyte

Table 1 Expression and functional characteristics of the histamine H₄ 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 <i>et al.</i> (2001)
Dendritic cells	mRNA expression; chemotaxis with Ca ²⁺ fluxes (human blood)	Zhu <i>et al.</i> (2001); Ling <i>et al.</i> (2004); Damaj <i>et al.</i> (2007)
	Migration (guinea pig and mouse BM)	Bäumer <i>et al.</i> (2008)
	Up-regulation by IFN- γ ; down-regulation of T _H 2-linked chemokine CCL2 and T _H 1 cytokine IL-12 (human IDECs)	Dijkstra <i>et al.</i> (2008)
	mRNA up-regulation during differentiation; suppression of IL-12p70 production; F-actin polymerization $\rightarrow$ migration (human MoDC)	Gutzmer <i>et al.</i> (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 <i>et al.</i> (2000); Morse <i>et al.</i> (2001); Buckland <i>et al.</i> (2003); Ling <i>et al.</i> (2004); Barnard <i>et al.</i> (2008)
	Ca ²⁺ mobilization, chemotaxis (mouse)	O'Reilly <i>et al.</i> (2002)
Fibroblasts	mRNA up-regulation by LPS and indomethacin, protein levels increased by dexamethasone (human, dermal)	Ikawa <i>et al.</i> (2008)
HL60.15 cell line	IL-5 induced differentiation $\rightarrow$ increased H ₄ receptor expression	Ling <i>et al.</i> (2004)
Mast cells	H ₄ receptor mRNA and protein expression (human skin)	Lippert <i>et al.</i> (2004)
	Intracellular Ca ²⁺ mobilization; chemotaxis without degranulation (mouse)	O'Reilly <i>et al.</i> (2002); Hofstra <i>et al.</i> (2003); Thurmond <i>et al.</i> (2004)
	Enhancement of CXCL12 chemotactic activity on mast cell precursors (human umbilical cord blood)	Godot <i>et al.</i> (2007)
	Local mast cell regulation, redistribution in ovalbumin-challenged oesophageal mucosal epithelium $\rightarrow$ infiltration of eosinophils (guinea pig)	Yu <i>et al.</i> (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 $\rightarrow$ reduced monocyte recruitment (human blood)	Oda <i>et al.</i> (2000); Morse <i>et al.</i> (2001); Zhu <i>et al.</i> (2001); Dijkstra <i>et al.</i> (2007)
Natural killer cells	Chemotaxis with no induction of Ca ²⁺ mobilization (human blood)	Damaj <i>et al.</i> (2007)
Neutrophils	Expression (human blood)	Oda <i>et al.</i> (2000); Morse <i>et al.</i> (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 <i>et al.</i> (2001); Zhu <i>et al.</i> (2001); Gantner <i>et al.</i> (2002); Ling <i>et al.</i> (2004)
	Suppression of STAT1 α formation, phosphorylation and DNA binding (human non-atopic PBMCs); H ₄ receptor blockade $\rightarrow$ inhibition of STAT6 DNA binding (human atopic PBMCs)	Horr <i>et al.</i> (2006); Michel <i>et al.</i> (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 $\alpha_{i/o}$ proteins and increases in intracellular Ca²⁺ 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 H₄ receptor agonist, demonstrating additive effects with histamine and involved in eosinophil trafficking (Nakayama *et al.*, 2004).

The expression of the H₄ 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 H₄ receptor. The existence of a histamine receptor on the surface of eosinophils that was distinct from H₁, H₂ or H₃

receptors and demonstrated low-affinity binding for R-(α)-methylhistamine antagonized by the H₃/H₄ antagonist thio-peramide was hypothesized in 1994 (Raible *et al.*, 1994). Concrete evidence that H₄ receptors control leukocyte trafficking and pro-inflammatory responses was derived from the H₄ 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 H₄ receptors that govern autocrine and paracrine histamine-induced processes (Lippert *et al.*, 2004). H₄ receptor activation mediates chemotaxis and intracellular Ca²⁺ 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 H₄ receptors (H₄) predominately expressed in immune cells. Gα_{i/o}, G-protein; T_H, helper T cell.

an autoregulatory function of the MC-expressed H₄ receptor comes from its critical role in zymosan-induced recruitment of neutrophils *in vivo*, possibly via regulation of leukotriene B₄ 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).

Dendritic cell activation and T cell differentiation

The H₄ 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 H₁ receptor activation and negatively regulate both T_H1 and T_H2 responses by acting on H₂ 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 H₄ receptor, which alongside H₁ and H₂ 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 H₄ 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 H₄ receptor antagonist JNJ777120 inhibited STAT6 DNA binding in cells derived from atopic subjects (Michel *et al.*, 2008). However, in mouse splenocytes, the H₄ receptor exerted no effect on STAT4 (Liu *et al.*, 2006) or STAT6 (Kharimate *et al.*, 2007) phosphorylation.

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* (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 H₄ receptor seems to be in operation. Interferon (IFN)-γ up-regulates H₄ 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 H₄ receptor-mediated induction of Ca²⁺ 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, H₄ receptor stimulation down-regulates the production of the T_H1

Table 2 Evidence for the contribution of histamine H₄ receptor to inflammatory disorders

Condition	Function of the H ₄ receptor	References
Airway inflammation	Decreased lung inflammation, lung eosinophil/lymphocyte infiltration and T _H 2 responses in H ₄ R ^{-/-} and JNJ7777120-treated mice; decreased IL-4, IL-5, IL-13, IL-6, IL-17 levels upon <i>ex vivo</i> re-stimulation of mouse T cells → disrupted T cell functions; blockade of DC H ₄ receptors <i>in vitro</i> → decreased cytokine and chemokine production → limited ability of DC to induce T _H 2 responses in murine T cells	Dunford <i>et al.</i> (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 <i>et al.</i> (2007)
	<i>In vitro</i> 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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (2006)
	Inhibition of STAT6 DNA binding by JNJ7777120 in atopic human PBMCs	Michel <i>et al.</i> (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 <i>et al.</i> (2008)
	Reduction of H ₄ receptor agonist clobenpropit-induced scratching by the H ₃ /H ₄ receptor antagonist thioperamide in female Balb C mice	Bell <i>et al.</i> (2004)
	No pruritic response with 4-MH in H ₄ R ^{-/-} mice; attenuation of MC- or other haematopoietic cell-independent scratching by JNJ7777120 in mice	Dunford <i>et al.</i> (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 <i>et al.</i> (2008)
Pruritus & dermatitis	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 <i>et al.</i> (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 <i>et al.</i> (2008)
	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 <i>et al.</i> (2005); Grzybowska-Kowalczyk <i>et al.</i> (2007; 2008); Ohki <i>et al.</i> , 2007
Arthritis	Increased cartilage histamine content without arthritis signs in JNJ7777120-treated rats with adjuvant arthritis	Zampeli <i>et al.</i> (2008)
	Reduction of early-phase paw oedema and thermal hyperalgesia by JNJ7777120 and VUF6002 in carrageenan-induced inflammation in rats	Coruzzi <i>et al.</i> (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 <i>et al.</i> (2003; 2004); Thurmond <i>et al.</i> (2004)
Acute/subchronic inflammation	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 <i>et al.</i> (2005)
	Increased conjunctival histamine content upon topical JNJ7777120 instillation in experimental conjunctivitis in rats	Zampeli <i>et al.</i> (2009)
Ischaemia/reperfusion injury	H ₄ receptor stimulation → prevention of reperfusion injury development in the rat liver	Adachi <i>et al.</i> (2006)

4-MH, 4-methylhistamine; Ag, antigen; BM, bone marrow; DC, dendritic cell; H₄R^{-/-}, H₄ receptor-deficient mice; IDEC, inflammatory dendritic epidermal cells; IFN, interferon; IL, interleukin; JNJ10191584, selective H₄ receptor antagonist; JNJ7777120, selective H₄ 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 H₄ 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).

H₄ receptor-mediated effects in inflammatory disorders

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 (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 H₄ 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 H₄ receptors mostly in immune system organs and their immunomodulatory role in cytokine production (Cogé *et al.*, 2001; Gantner

Figure 3 Involvement of the histamine H₄ receptor in a number of inflammatory disorders.

et al., 2002; Gutzmer *et al.*, 2005) argue for the pathophysiological significance of H₄ 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 H₄ 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 H₄ receptor-targeting agents in related studies, including JNJ7777120, the first highly selective H₄ 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 H₁ 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 H₄ 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 H₄ 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 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 MC precursors *in vitro* (Godot *et al.*, 2007). Moreover, the H₄ 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 H₄ receptor-deficient (H₄R^{-/-}) mice and upon oral gavage administration of selective antagonists in a murine model of allergic airway inflammation documented the role of the H₄ 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 H₄ receptor agonist 4-methylhistamine administered intratracheally into the lungs of asthmatic mice (Morgan *et al.*, 2007). The beneficial actions of both H₄ 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 H₄ receptor in the modulation of the asthmatic response revealed by these studies and the reported inhibitory effect of H₄ receptor agonists on antigen-specific responses in human peripheral blood mononuclear cells and T cell lines, which, however, was not reversed by the H₃/H₄ receptor antagonist thioperamide (Sugata *et al.*, 2007), additional data are a prerequisite imperative of providing conclusive evidence concerning the optimal therapeutic exploitation of H₄ 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 H₄R^{-/-} 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 H₁ 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 H₄ 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 H₄ receptor antagonist being greater than that observed with H₁ receptor antagonists (Dunford *et al.*, 2007). Even so, H₁ receptor-mediated actions seem to complement the H₄ receptor-mediated enhanced DC

migration through skin, and therefore H₁ combined with H₄ receptor antagonists could be a beneficial approach (Bäumer *et al.*, 2008; Roßbach *et al.*, 2009). In addition, although H₄ 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, JNJ777120 failed to reduce the allergic inflammatory response associated with allergic dermatitis (Roßbach *et al.*, 2009).

Although H₄ 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 H₄ 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 H₄ 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 Phe¹⁶⁹ in the second extracellular loop as the single amino acid responsible for the differences in agonist affinity between the human and mouse H₄ receptors (Lim *et al.*, 2008). Moreover, strain differences in the mouse response to the H₄ receptor agonist/H₃ receptor antagonist clobenpropit were recently reported, NMRI mice being more susceptible to H₄ 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 H₁ and H₂ receptors, the considerable variations in H₄ receptor expression in human synovial cells could be related to RA severity and duration (Ikawa *et al.*, 2005). The localization of H₄ 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 H₄ 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 H₄ receptor in the normal cartilage has been suggested in the rat, raising

attractive questions regarding the H₄ receptor-mediated mechanisms in this tissue (Zampeli *et al.*, 2008).

Other inflammatory conditions

The association of the H₄ 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 H₃/H₄ receptor antagonist thioperamide or selective H₄ receptor agonists and antagonists (Zhang *et al.*, 2007). Thus, H₄ receptor agonists prevented the development of reperfusion injury following ischaemia-induced liver damage (Adachi *et al.*, 2006). Beneficial actions of the H₄ 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, H₄ 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, H₄ 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 H₄ 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 H₄ receptor alterations in human samples derived from inflamed tissues. For instance, the increased levels of H₄ receptors in normal nasal turbinate mucosa and in nasal polyp tissue and the tendency for correlation between the expression of H₄ 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 (Jóki *et al.*, 2007).

These results certainly reflect the complex cellular and biochemical networks orchestrating inflammation. However, species differences in H₄ receptor-mediated responses and/or ligand efficacy need to be elucidated before decisive conclusions are drawn regarding the use of H₄ 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 H₄ receptor isoforms, which have a dominant negative effect on the full-length H₄ 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 H₄ 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 H₄ receptors in inflammatory conditions at present. H₄ receptor antagonists may be effective candidates in treating diseases associated with chronic pruritus and asthma, without disregarding the potential clinical application of H₄ receptor ligands in autoimmune diseases like RA. A number of candidate drugs targeting the H₄ 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.

References

- Adachi N, Liu K, Motoki A, Nishibori M, Arai T (2006). Suppression of ischemia/reperfusion liver injury by histamine H₄ receptor stimulation in rats. *Eur J Pharmacol* **544**: 181–187.
- Adlesic M, Verdrengh M, Bokarewa M, Dahlberg L, Foster SJ, Tarkowski A (2007). Histamine in rheumatoid arthritis. *Scand J Immunol* **65**: 530–537.
- Akdis CA, Simons FE (2006). Histamine receptors are hot in immunopharmacology. *Eur J Pharmacol* **533**: 69–76.
- Arrang JM, Garbarg M, Schwartz JC (1983). Autoinhibition of brain histamine release mediated by a novel class (H₃) of histamine receptor. *Nature (Lond)* **302**: 832–837.
- Barger G, Dale HH (1910). The presence in ergot and physiological activity of B-iminazolyethylamine. *J Physiol* **40**: 38–40.
- Barnard R, Barnard A, Salmon G, Liu W, Sreckovic S (2008). Histamine-induced actin polymerization in human eosinophils: an imaging approach for histamine H₄ receptor. *Cytometry A* **73**: 299–304.
- Barnes PJ, Chung KF, Page CP (1998). Inflammatory mediators of asthma: an update. *Pharmacol Rev* **50**: 515–596.
- Bäumer W, Wendorff S, Gutzmer R, Werfel T, Dijkstra D, Chazot P *et al.* (2008). Histamine H₄ receptors modulate dendritic cell migration through skin – immunomodulatory role of histamine. *Allergy* **63**: 1387–1394.
- Bell JK, McQueen DS, Rees JL (2004). Involvement of histamine H₄ and H₁ receptors in scratching induced by histamine receptor agonists in BalbC mice. *Br J Pharmacol* **142**: 374–380.
- Black JW, Duncan WAM, Durant CJ, Ganellin CR, Parsons EM (1972). Definition and antagonism of histamine H₂-receptors. *Nature (Lond)* **236**: 385–390.
- Buckland KF, Williams TJ, Conroy DM (2003). Histamine induces cytoskeletal changes in human eosinophils via the H₄ receptor. *Br J Pharmacol* **140**: 1117–1127.
- Chazot PL, Tiligada E (2008). The European Histamine Research Society (EHRS) symposium for EPHAR 2008. *Inflamm Res* **57**: S05–S06.
- Clark RAF, Gallin JI, Kaplan AP (1975). The selective eosinophil chemotactic activity of histamine. *J Exp Med* **142**: 1462–1476.
- Cogé F, Guénin SP, Rique H, Boutin JA, Galizzi JP (2001). Structure and expression of the human histamine H₄-receptor gene. *Biochem Biophys Res Commun* **284**: 301–309.
- Coruzzi G, Adami M, Guaita E, de Esch IJ, Leurs R (2007). Antiinflammatory and antinociceptive effects of the selective histamine H₄-receptor antagonists JNJ777120 and VUF6002 in a rat model of carrageenan-induced acute inflammation. *Eur J Pharmacol* **563**: 240–244.
- Dale HH, Laidlaw PP (1910). The physiological action of β-imidazolyethylamine. *J Physiol* **41**: 318–341.
- Damaj BB, Becerra CB, Esber HJ, Wen Y, Maghazachi AA (2007). Functional expression of H₄ histamine receptor in human natural killer cells, monocytes, and dendritic cells. *J Immunol* **179**: 7907–7915.
- Daugherty BL (2004). Histamine H₄ antagonism: a therapy for chronic allergy? *Br J Pharmacol* **142**: 5–7.
- Dijkstra D, Leurs R, Chazot P, Shenton FC, Stark H, Werfel T *et al.* (2007). Histamine downregulates monocyte CCL2 production through the histamine H₄ receptor. *J Allergy Clin Immunol* **120**: 300–307.
- Dijkstra D, Stark H, Chazot PL, Shenton FC, Leurs R, Werfel T *et al.* (2008). Human inflammatory dendritic epidermal cells express a functional histamine H₄ receptor. *J Invest Dermatol* **128**: 1696–1703.
- Dunford PJ, O'Donnell N, Riley JP, Williams KN, Karlsson L, Thurmond RL (2006). The histamine H₄ receptor mediates allergic airway inflammation by regulating the activation of CD4⁺ T cells. *J Immunol* **176**: 7062–7070.
- Dunford PJ, Williams KN, Desai PJ, Karlsson L, McQueen D, Thurmond RL (2007). Histamine H₄ receptor antagonists are superior to traditional antihistamines in the attenuation of experimental pruritus. *J Allergy Clin Immunol* **119**: 176–183.
- Dy M, Schneider E (2004). Histamine-cytokine connection in immunity and hematopoiesis. *Cytokine Growth Factor Rev* **15**: 393–410.
- de Esch IJP, Thurmond RL, Jongejans A, Leurs R (2005). The histamine H₄ receptor as a new therapeutic target for inflammation. *Trends Pharmacol Sci* **26**: 462–469.
- Falcone FH, Zillikens D, Gibbs BF (2006). The 21st century renaissance of the basophil? Current insights into its role in allergic responses and innate immunity. *Exp Dermatol* **15**: 855–864.
- Falus A, Hegyesi H, Lazar-Molnar E, Pos Z, Laszlo V, Darvas Z (2001). Paracrine and autocrine interactions in melanoma: histamine is a relevant player in local regulation. *Trends Immunol* **22**: 648–652.
- Gantner F, Sakai K, Tusche MW, Cruikshank WW, Center DM, Bacon KB (2002). Histamine H₄ and H₂ receptors control histamine-induced interleukin-16 release from human CD8⁺ T cells. *J Pharmacol Exp Ther* **303**: 300–307.
- Godot V, Arock M, Garcia G, Capel F, Flys C, Dy M *et al.* (2007). H₄ histamine receptor mediates optimal migration of mast cell precursors to CXCL12. *J Allergy Clin Immunol* **120**: 827–834.
- Grandi D, Shenton FC, Chazot PL, Morini G (2008). Immunolocalization of histamine H₃ receptors on endocrine cells in the rat gastrointestinal tract. *Histol Histopathol* **23**: 789–798.
- Grzybowska-Kowalczyk A, Wojtecka-Lukasik E, Maslinska D, Gujski M, Maslinski S (2007). Distribution pattern of histamine H₄ receptor in human synovial tissue from patients with rheumatoid arthritis. *Inflamm Res* **56** (Suppl. 1): S59–S60.
- Grzybowska-Kowalczyk A, Maslinska D, Wojciechowska M, Szukiewicz D, Wojtecka-Lukasik E, Paradowska A *et al.* (2008). Expression of histamine H₄ receptor in human osteoarthritic synovial tissue. *Inflamm Res* **57** (Suppl. 1): S63–S64.
- Gutzmer R, Diestel C, Mommert S, Kother B, Stark H, Wittman M *et al.* (2005). Histamine H₄ receptor stimulation suppresses IL-12p70

- production and mediates chemotaxis in human monocyte-derived dendritic cells. *J Immunol* **174**: 5224–5232.
- Haas H, Panula P (2003). The role of histamine and the tuberomammillary nucleus in the nervous system. *Nat Rev Neurosci* **4**: 121–130.
- Haas HL, Sergeeva OA, Selbach O (2008). Histamine in the nervous system. *Physiol Rev* **88**: 1183–1241.
- Hill SJ, Ganellin CR, Timmerman H, Schwartz JC, Shankley NP, Young JM *et al.* (1997). International Union of Pharmacology. XIII. Classification of histamine receptors. *Pharmacol Rev* **49**: 253–278.
- Hirasawa N, Ohsawa Y, Katoh G, Shibata K, Ishihara K, Seyama T *et al.* (2008). Modification of the picryl chloride-induced allergic dermatitis model in mouse ear lobes by 12-o-tetradecanoylphorbol 13-acetate, and analysis of the role of histamine in the modified model. *Int Arch Allergy Immunol* **148**: 279–288.
- Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP (2003). Histamine H₄ receptor mediates chemotaxis and calcium mobilization of mast cells. *J Pharmacol Exp Ther* **305**: 1212–1221.
- Horr B, Borck H, Thurmond R, Gröschel S, Diel F (2006). STAT1 phosphorylation and cleavage is regulated by the histamine H₄ receptor in human atopic and non-atopic lymphocytes. *Int Immunopharmacol* **6**: 1577–1585.
- Ikawa Y, Suzuki M, Shiono S, Ohki E, Moriya H, Negishi E *et al.* (2005). Histamine H₄ receptor expression in human synovial cells obtained from patients suffering from rheumatoid arthritis. *Biol Pharm Bull* **28**: 2016–2018.
- Ikawa Y, Shiba K, Ohki E, Mutoh N, Suzuki M, Sato H *et al.* (2008). Comparative study of histamine H₄ receptor expression in human dermal fibroblasts. *J Toxicol Sci* **33**: 503–508.
- Jablonowski JA, Grice CA, Chai W, Dvorak CA, Venable JD, Kwok AK *et al.* (2003). The first potent and selective non-imidazole human histamine H₄ receptor antagonists. *J Med Chem* **46**: 3957–3960.
- Jiang W, Lim HD, Zhang M, Desai P, Dai H, Colling PM *et al.* (2008). Cloning and pharmacological characterization of the dog histamine H₄ receptor. *Eur J Pharmacol* **592**: 26–32.
- Jókúti A, Hellinger E, Hellinger A, Darvas Z, Falus A, Thurmond RL *et al.* (2007). Histamine H₄ receptor expression is elevated in human nasal polyp tissue. *Cell Biol Int* **31**: 1367–1370.
- Jutel M, Watanabe T, Klunker S, Akdis M, Thomet OA, Malolepszy J *et al.* (2001). Histamine regulated T-cell and antibody responses by differential expression of H₁ and H₂ receptors. *Nature* **413**: 420–425.
- Kakavas S, Zampeli E, Papamichael K, Delitheos B, Tiligada E (2006). The mast cell pathway to inflammation and homeostasis: pharmacological insights. *Anti-Inflamm Anti-Allergy Agents Med Chem* **5**: 323–334.
- Kharmate G, Liu Z, Patterson E, Khan MM (2007). Histamine affects STAT6 phosphorylation via its effects on IL-4 secretion: role of H₁ receptors in the regulation of IL-4 production. *Int Immunopharmacol* **7**: 277–286.
- Kiss R, Kiss B, Könczöl A, Szalai F, Jelinek I, László V *et al.* (2008). Discovery of novel human histamine H₄ receptor ligands by large-scale structure-based virtual screening. *J Med Chem* **51**: 3145–3153.
- Krishnaswamy G, Ajitaw O, Chi DS (2006). The human mast cell: an overview. *Methods Mol Biol* **315**: 13–34.
- Leurs R, Hoffmann M, Wieland K, Timmerman H (2000). H₃ receptor gene is cloned at last. *Trends Pharmacol Sci* **21**: 11–12.
- Lim HD, van Rijn RM, Ling P, Bakker RA, Thurmond RL *et al.* (2005). Evaluation of histamine H₁-, H₂-, and H₃-receptor ligands at the human histamine H₄ receptor: identification of 4-methylhistamine as the first potent and selective H₄ receptor agonist. *J Pharmacol Exp Ther* **314**: 1310–1321.
- Lim HD, Jongejan A, Bakker RA, Haaksma E, de Esch IJ, Leurs R (2008). Phenylalanine 169 in the second extracellular loop of the human histamine H₄ receptor is responsible for the difference in agonist binding between human and mouse H₄ receptors. *J Pharmacol Exp Ther* **327**: 88–96.
- Ling P, Ngo K, Nguyen S, Thurmond RL, Edwards JP, Karlsson L *et al.* (2004). Histamine H₄ receptor mediates eosinophil chemotaxis with cell shape change and adhesion molecule upregulation. *Br J Pharmacol* **142**: 161–171.
- Lippert U, Artuc M, Grutzkau A, Babina M, Guhl S, Haase I *et al.* (2004). Human skin mast cells express H₂ and H₄, but not H₃ receptors. *J Invest Dermatol* **23**: 116–123.
- Liu C, Ma XJ, Jiang X, Wilson SJ, Hofstra CL, Blevitt J *et al.* (2001a). Cloning and pharmacological characterization of a fourth histamine receptor (H₄) expressed in bone marrow. *Mol Pharmacol* **59**: 420–426.
- Liu C, Wilson SJ, Kuel C, Lovenberg TW (2001b). Comparison of human, mouse, rat, and guinea pig histamine H₄ receptors reveals substantial pharmacological species variation. *J Pharmacol Exp Ther* **299**: 121–130.
- Liu Z, Kharmate G, Patterson E, Khan MM (2006). Role of H₁ receptors in histamine-mediated up-regulation of STAT4 phosphorylation. *Int Immunopharmacol* **6**: 485–493.
- Masini E, Di Bello MG, Raspanti S, Fomusi Ndisang J, Baronti R, Cappugi P *et al.* (1998). The role of histamine in platelet aggregation by physiological and immunological stimuli. *Inflamm Res* **47**: 211–220.
- Maslinska D, Gujski M, Laure-Kamionowska M, Szukiewicz D, Wojtecka-Lukasik E (2004). Subcellular localization of histamine in articular cartilage chondrocytes of rheumatoid arthritis patients. *Inflamm Res* **53**: S35–36.
- Michel I, Borck H, McElligott S, Krieg C, Diel F (2008). Histamine receptor H₄R-selective ligands influence the STAT6 Transcription Activation Domain (TAD) and the DNA-binding. *Inflamm Res* **57**: S47–S48.
- Morgan RK, McAllister B, Cross L, Green DS, Kornfeld H, Center DM *et al.* (2007). Histamine 4 receptor activation induces recruitment of FoxP3⁺ T cells and inhibits allergic asthma in a murine model. *J Immunol* **178**: 8081–8089.
- Morse KL, Behan J, Laz TM, West RE Jr, Greenfeder SA, Anthes JC *et al.* (2001). Cloning and characterization of a novel human histamine receptor. *J Pharmacol Exp Ther* **296**: 1058–1066.
- Nakamura T, Itadani H, Hidaka Y, Ohta M, Tanaka K (2000). Molecular cloning and characterization of a new human histamine receptor, HH4R. *Biochem Biophys Res Commun* **279**: 615–620.
- Nakayama T, Kato Y, Hieshima K, Nagakubo D, Kunori Y, Fujisawa T *et al.* (2004). Liver-expressed chemokine/CC chemokine ligand 16 attracts eosinophils by interacting with histamine H₄ receptor. *J Immunol* **173**: 2078–2083.
- Nguyen T, Shapiro DA, George SR, Setola V, Lee DK, Cheng R *et al.* (2001). Discovery of a novel member of the histamine receptor family. *Mol Pharmacol* **59**: 427–433.
- O'Donoghue M, Tharp MD (2005). Antihistamines and their role as antipruritics. *Dermatol Ther* **18**: 333–340.
- O'Reilly M, Alpert R, Jenkinson S, Gladue RP, Foo S, Trim S *et al.* (2002). Identification of a histamine H₄ receptor on human eosinophils-role in eosinophil chemotaxis. *J Recept Signal Transduct Res* **22**: 431–448.
- Oda T, Morikawa N, Saito Y, Masuho Y, Matsumoto S (2000). Molecular cloning and characterization of a novel type of histamine receptor preferentially expressed in leukocytes. *J Biol Chem* **275**: 36781–36786.
- Oda T, Matsumoto S, Matsumoto M, Takasaki J, Kamohara M, Soga T *et al.* (2005). Molecular cloning of monkey histamine H₄ receptor. *J Pharmacol Sci* **98**: 319–322.
- Ohki E, Suzuki M, Aoe T, Ikawa Y, Negishi E, Ueno K (2007). Expression of histamine H₄ receptor in synovial cells from rheumatoid arthritic patients. *Biol Pharm Bull* **30**: 2217–2220.
- Prinz C, Zanner R, Gratzl M (2003). Physiology of gastric enterochromaffin-like cells. *Annu Rev Physiol* **65**: 371–382.
- Raible DG, Lenahan T, Fayvilevich Y, Kosinski R, Schulman ES (1994). Pharmacologic characterization of a novel histamine receptor on human eosinophils. *Am J Respir Crit Care Med* **149**: 1506–1511.

- Riley JF, West GB (1952). Histamine in tissue mast cells. *J Physiol* **117**: 72–73.
- van Rijn RM, van Marle A, Chazot PL, Langemeijer E, Qin Y, Shenton FC *et al.* (2008). Cloning and characterization of dominant negative splice variants of the human histamine H₄ receptor. *Biochem J* **414**: 121–131.
- Roßbach K, Wendorff S, Sander K, Stark H, Gutzmer R, Werfel T *et al.* (2009). Histamine H₄ receptor antagonism reduces hapten-induced scratching behaviour but not inflammation. *Exp Dermatol* **18**: 57–63.
- Sugata Y, Okano M, Fujiwara T, Matsumoto R, Hattori H, Yamamoto M *et al.* (2007). Histamine H₄ receptor agonists have more activities than H₄ agonism in antigen-specific human T-cell responses. *Immunology* **121**: 266–275.
- Takeshita K, Sakai K, Bacon KB, Gantner F (2003). Critical role of histamine H₄ receptor in leukotriene B₄ production and mast cell dependent neutrophil recruitment induced by zymosan *in vivo*. *J Pharmacol Exp Ther* **307**: 1072–1078.
- Takeshita K, Bacon KB, Gantner F (2004). Critical role of L-selectin and histamine H₄ receptor in zymosan-induced neutrophil recruitment from the bone marrow: comparison with carrageenan. *J Pharmacol Exp Ther* **310**: 272–280.
- Thurmond RL, Desai PJ, Dunford PJ, Fung-Leung WP, Hofstra CL, Jiang W *et al.* (2004). A potent and selective histamine H₄ receptor antagonist with anti-inflammatory properties. *J Pharmacol Exp Ther* **309**: 404–413.
- Thurmond RL, Gelfand EW, Dunford PJ (2008). The role of histamine H₁ and H₄ receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov* **1**: 41–53.
- Varga C, Horvath K, Berko A, Thurmond RL, Dunford PJ, Whittle BJ (2005). Inhibitory effects of histamine H₄ receptor antagonists on experimental colitis in the rat. *Eur J Pharmacol* **522**: 130–138.
- Venable JD, Thurmond RL (2006). Development and chemistry of histamine H₄ receptor ligands as potential modulators of inflammatory and allergic responses. *Anti-Inflamm Anti-Allergy Agents Med Chem* **5**: 307–322.
- Woolley DE, Tetlow LC (1997). Observations on the microenvironmental nature of cartilage destruction in rheumatoid arthritis. *Ann Rheum Dis* **56**: 151–161.
- Yu S, Stahl E, Li Q, Ouyang A (2008). Antigen inhalation induces mast cells and eosinophils infiltration in the guinea pig esophageal epithelium involving histamine-mediated pathway. *Life Sci* **82**: 324–330.
- Zampeli E, Thurmond RL, Tiligada E (2008). Effect of the H₄R antagonist JNJ7777120 on the cartilage histamine content in rats with adjuvant arthritis. *Fund Clin Pharmacol* **22** (Suppl. 2): 10.
- Zampeli E, Thurmond RL, Tiligada E (2009). The histamine H₄ receptor antagonist JNJ7777120 induces increases in the histamine content of the rat conjunctiva. *Inflamm Res* **58**: 1–7.
- Zhang M, Thurmond RL, Dunford PJ (2007). The histamine H₄ receptor: a novel modulator of inflammatory and immune disorders. *Pharmacol Ther* **113**: 594–606.
- Zhu Y, Michalovich D, Wu H, Tan KB, Dytko GM, Mannan IJ *et al.* (2001). Cloning, expression, and pharmacological characterization of a novel human histamine receptor. *Mol Pharmacol* **59**: 434–441.
- Zwadlo-Klarwasser G, Braam U, Mühl-Zürbes P, Schmutzler W (1994). Macrophages and lymphocytes: alternative sources of histamine. *Agents Actions* **41**: C99–C100.