

REVIEW

Histamine, histamine receptors and their role in immune pathology

M. Jutel¹, M. Akdis² and C. A. Akdis²

¹Department of Clinical Immunology, Wrocław University of Medicine, Wrocław, Poland and ²Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland

Clinical & Experimental Allergy

Summary

The important roles of histamine in body physiology and various pathologic events have been well established, whereas new and exciting findings are still being uncovered. Histamine is not only the major mediator of the acute inflammatory and immediate hypersensitivity responses, but has also been demonstrated to affect chronic inflammation and regulate several essential events in the immune response. The diverse effects of histamine on immune regulation are due to the differential expression and regulation of four histamine receptors (HR) and their distinct intracellular signals. Differences in the affinities of these receptors are highly decisive on the biological effects of histamine and agents that target HRs. In particular, the discovery of reciprocal regulation of T cell activity by H1 and H2 receptor activation indicating histamine-cytokine cross-talk, as well as the characterization of the fourth histamine receptor (HR4) and its expression on numerous immune and inflammatory cells have prompted a re-evaluation of the actions of histamine. This accounts for a new potential for HR antagonists and agonists in targeting various immunopathologic conditions.

Correspondence:

Dr Marek Jutel, Department of Clinical Immunology, Wrocław Medical University, Wrocław, Poland.

E-mail: mjudel@ak.am.wroc.pl

Cite this as: M. Jutel, M. Akdis and C. A. Akdis, *Clinical & Experimental Allergy*, 2009 (39) 1786–1800.

Introduction

Histamine was isolated and characterized in the beginning of the 20th century and drugs targeting its receptors have been in clinical use since the 1940s [1, 2]. Although substantial evidence has accumulated on histamine metabolism, receptors, signal transduction, physiological and pathological effects, the complex interrelationship and cross-talk by histamine, its receptors and other G-protein-coupled receptors remain to be understood. Histamine can influence numerous functions of the cells involved in the regulation of immune response and haematopoiesis including macrophages, dendritic cells (DCs), T lymphocytes, B lymphocytes and endothelial cells [3–6]. These cells express histamine receptors (HR) and also secrete histamine, which can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization and effector, functions leading to chronic inflammation. In this review, we discuss four different types of receptors for histamine binding and their diversity in cellular expression and signal transduction, the role of histamine in inflammatory reactions as well as the immunoregulatory effects of histamine in physiology and various pathological conditions.

Biology, synthesis, regulation and metabolism of histamine

Histamine (2-[4-imidazole]-ethylamine) was first identified as an autacoid having potent vasoactive properties. Its smooth muscle-stimulating and vasodepressor action was demonstrated in the first experiments by Dale and Laidlaw [7], who also found that the effects of histamine mimicked those occurring during anaphylaxis. In 1927, histamine was isolated from liver and lung tissue, followed by several other tissues, demonstrating that it is a natural constituent of the body; hence, the name histamine was given after the Greek word for tissue, *histos*. Histamine is a low-molecular-weight amine synthesized from L-histidine exclusively by histidine decarboxylase. It is produced by various cells throughout the body [3, 6, 8–10].

Histamine is involved in the regulation of many physiological functions including cell proliferation and differentiation, haematopoiesis, embryonic development, regeneration and wound healing [3, 6, 8–10]. Within the central nervous system, it affects cognition and memory, the regulation of cycle of sleeping and waking, energy and endocrine homeostasis [11, 12]. In human pathology, histamine triggers acute symptoms due to its very rapid activity on vascular endothelium and bronchial and

smooth muscle cells, leading to the development of such symptoms as acute rhinitis, bronchoconstriction, cramping, diarrhoea or cutaneous weal and flare responses. Moreover, in addition to these effects on the immediate-type response, histamine also significantly modulates chronic-phase inflammatory events [3, 6, 9, 10, 13]. In this article, the findings leading to a change of perspective in histamine immunobiology are highlighted.

Gastric enterochromaffin-like cells, histaminergic neurons as well as mast cells and basophils are classical cellular sources of histamine. Several haematopoietic cell lineages have been shown to synthesize histamine, but at 100–1000-fold lower levels than mast cells and basophils. These cells display low intracellular levels of histamine, which is secreted immediately after synthesis [14–18]. However, some of these data have been demonstrated in cell lines and might have not been purified enough to draw a definitive conclusion. *De novo* histamine synthesis has also been shown in other cell types, such as platelets, monocytes/macrophages, DCs, neutrophils and lymphocytes [19–24].

Histamine is synthesized by decarboxylation of histidine by L-histidine decarboxylase (HDC), which is dependent on the cofactor pyridoxal-5'-phosphate [16]. Histamine regulation is dependent on the gene of HDC enzyme, which is expressed in the cells throughout the body. The location of the HDC gene is found on chromosome 2 in mice and chromosome 15 in human, and their expression is controlled by lineage-specific transcription factors. These factors interact with a promoter region consisting of a GC box, four GATA consensus sequences, a c-Myb-binding motif and four CACC boxes [25]. It has been demonstrated in several studies that the HDC transcription is regulated by various factors in gastric cancer cells such as gastrin, oxidative stress and PMA, through an Ras-independent, Raf-dependent mechanism, MAP kinase/ERK and a protein kinase C (PKC) pathway functioning on three overlapping cisacting elements (GASRE 1, GASRE 2 and GASRE 3) known as gastrin response elements [26]. In haematopoietic cells, the regulation of the HDC gene is unknown and it is observed that nuclear factor E2 (NF-E2) appears to be involved indirectly in this mechanism [27]. It is well known that the expression of HDC in basophils and mast cells seems to be a consequence of the state of CpG methylation in the promoter region [28]. Mast cells and basophils are the major source of granule-stored histamine, where it is closely associated with the anionic proteoglycans and chondroitin-4-sulphate. Histamine is released when these cells degranulate in response to various immunologic and non-immunologic stimuli. In addition, several myeloid and lymphoid cell types (DCs and T cells), which do not store histamine, show high HDC activity and are capable of production of high amounts of histamine [21, 24]. HDC activity is modulated by cytokines, such as IL-1, IL-3, IL-12, IL-18, GM-CSF,

macrophage-colony stimulating factor, TNF- α and calcium ionophore, *in vitro* [29, 30]. HDC activity has been demonstrated *in vivo* in conditions such as lipopolysaccharide (LPS) stimulation, infection, inflammation and graft rejection [14]. The generation of HDC-deficient mice provided histamine-free systems to study the role of endogenous histamine in a broad range of normal and disease processes. These mice show decreased numbers of mast cells and significantly reduced granule content, which suggests that histamine might affect the synthesis of mast cell granule proteins [31]. IgE binding to the Fc ϵ RI on IL-3-dependent mouse bone marrow-derived mast cells induces the expression of HDC through a signalling pathway different from that operating during antigen-stimulated Fc ϵ RI activation [32]. More than 97% of the histamine is metabolized in two major pathways before excretion [33]. Histamine N-methyltransferase metabolizes the majority of histamine to N-methylhistamine, which is further metabolized to the primary urinary metabolite M-methylimidazole acetic acid by monoamine oxidase. Diamine oxidase metabolizes 15–30% of histamine to imidazole acetic acid.

Histamine receptors

The pleiotropic effects of histamine are triggered by activating through one or several histamine membrane receptors on different cells. Four subtypes of receptors [histamine receptor (HR)1, HR2, HR3 and HR4] have been described (Table 1). In 1966, HRs were first differentiated into HR1 and HR2 [34]. In 1999, a third HR subtype was cloned and termed as HR3 [35]. Subsequently, in 2000, the fourth HR subtype was reported, which was termed as HR4 [36]. All these receptors belong to the G-protein-coupled receptor family. They are heptahelical transmembrane molecules that transduce the extracellular signal by using G-proteins and intracellular second messenger systems [36–39]. The active and inactive states of HRs exist in equilibrium. However, it has been shown in recombinant systems that HRs can trigger downstream events in the absence of receptor occupancy by an agonist, which accounts for constitutive spontaneous receptor activity [40].

HR agonists stimulate the active state in the receptor and inverse agonists stimulate the inactive one. An agonist with a preferential affinity for the active state of the receptor stabilizes the receptor in its active conformation leading to a continuous activation signal. An inverse agonist with a preferential affinity for the inactive state stabilizes the receptor in this conformation and consequently induces an inactive state, which is characterized by blocked signal transduction via the HR [34]. In reporter gene assays, constitutive HR1-mediated nuclear factor (NF)- κ B activation has been shown to be inhibited by many of the clinically used H1 antihistamines, indicating

Table 1. Histamine receptors (HR), expression, coupled G-proteins and activated intracellular signals

Histamine receptors	Expression	Activated intracellular signals	G-proteins
HR1	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, macrophages, DC, T and B cells	Ca ²⁺ , cGMP, phospholipase D, phospholipase A ₂ , NFκB	G _{q/11}
HR2	Nerve cells, airway and vascular smooth muscles, hepatocytes, chondrocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, monocytes, macrophages, DC, T and B cells	Adenylate cyclase, cAMP, c-Fos, c-Jun, PKC, p70S6K	Gα _s
HR3	Histaminergic neurons, eosinophils, DC, monocytes, low expression in peripheral tissues, macrophages – unknown	Enhanced Ca ²⁺ , MAP kinase, inhibition of cAMP	G _{i/o}
HR4	High expression on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, DC, T cells, basophils, mast cells, low expression in nerve cells, hepatocytes peripheral tissues, spleen, thymus, lung, small intestine, colon and heart, macrophages – unknown	Enhanced Ca ²⁺ , Inhibition of cAMP,	G _{i/o}

DC, dendritic cells; PKC, protein kinase C.

that these agents are inverse HR1 agonists [34]. Constitutive activity has now been shown for all four HRs [34]. In addition to four membrane receptors, histamine binds to some intracellular receptors such as cytochrome p450 and cytochrome c, and high-affinity lipocalins isolated from the saliva of ticks [41].

Specific activation or blockade of HRs showed that they differ in expression, signal transduction or function and improved the understanding of the role of histamine in physiology and disease mechanisms.

Histamine receptor 1

The human G_{q/11}-coupled HR1 is encoded by a single exon gene located on the distal short arm of chromosome 3p25b and contains 487 amino acids. The HR1 is expressed in numerous cells including airway and vascular smooth muscle cells, hepatocytes, chondrocytes, nerve cells, endothelial cells, DCs, monocytes, neutrophils, T and B cells [1, 42, 43]. Histamine binds to transmembrane domains 3 and 5. Activation of the HR1-coupled G_{q/11} stimulates the inositol phospholipid signalling pathways, resulting in the formation of inositol-1,4,5-triphosphate (IP₃) and diacylglycerol and an increase in intracellular calcium [44]. The increase in intracellular calcium accounts for nitric oxide production; the release of arachidonic acid from phospholipids increased cyclic AMP. The HR1 also activates phospholipase D and phospholipase A₂. More recently, the HR1 has also been shown to activate the transcription factor NF-κB [45] through G_{q/11} and G_{βγ} upon agonist binding. Constitutive activation of NF-κB occurs only through G_{βγ} [44]. H1-receptor polymorphisms have been described, although it is not yet clear how they influence the clinical response to H1 antihistamines [46]. Activation of H1R results in airway and vascular smooth muscle contraction. The contractile responses to H1R

stimulation initially involve mobilization of calcium (Ca²⁺) from intracellular stores such as inositol phospholipid hydrolysis [1]. HR1 stimulation induces various cellular responses in vascular endothelial cells including changes in vascular permeability as a result of cell contraction, synthesis of prostacyclin and platelet-activating factor synthesis, release of Von Willebrand factor and nitric oxide release [13, 47]. Thus, HR1 mediates many pathological processes, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, asthma and anaphylaxis. The receptors also mediate bronchoconstriction and enhanced-vascular permeability in the lung [42, 47]. Targeted disruption of the HR1 gene in mice results in the impairment of neurologic functions such as memory, learning, locomotion and nociception and in aggressive behaviour [48]. Immunologic abnormalities have also been described in HR1-deleted mice, with impairment of both T and B cell responses. [4, 5].

Histamine receptor 2

In humans, the intronless gene encoding HR2 is located on chromosome 5. The human HR2 is a protein of 359 aminoacids coupled to both adenylate cyclase and phosphoinositide second messenger systems by separate GTP-dependent mechanisms including Gα_s and also induces activation of c-Fos, c-Jun PKC and p70S6 kinase [49]. Similar to what has been demonstrated for H1R, the histamine binds to transmembrane (TM) domains 3 (aspartate) and TM 5 (threonine and aspartate). The short third intracellular loop and the long C-terminal tail are a feature of the H2R subtype [49]. Similar to H1R, H2R is expressed in different cell types. Studies in different species and several human cells demonstrated that inhibition of characteristic features of the cells primarily by cAMP formation dominates in HR2-dependent effects

of histamine. H2R is coupled both to adenylate cyclase and to phosphoinositide second messenger systems via separate GTP-dependent mechanisms. Receptor binding stimulates activation of c-Fos, c-Jun PKC and p70S6kinase [1, 8].

Inhibitory effects of H2R stimulation were observed on phospholipase A2 activity in CHO cells transfected with the human H2R [1]. Thus, these cAMP-independent effects might depend on the level of receptor expression or subtle differences between clonal cell lines. Positive chronotropic and inotropic impacts on atrial or ventricular tissues by H2R, H2R-mediated smooth muscle relaxation have been documented in vascular smooth muscle, uterus and in airway. The effects of H2Rs can inhibit a variety of functions within the immune system. H2Rs have been shown to negatively regulate the release of histamine on basophils and mast cells [50]. The inhibition of antibody synthesis, T cell proliferation, cell-mediated cytotoxicity and cytokine production represented increasing evidence of H2Rs on lymphocytes [3].

Histamine receptor 3

Human HR3 encoded by a gene, which consists of four exons on chromosome 20, has been demonstrated in 1987 and cloned [35]. More than one H3R subtype has been suggested [51]. H3R has initially been identified in the central and peripheral nervous system as pre-synaptic receptors controlling the release of histamine and other neurotransmitters (dopamine, serotonin, noradrenaline, GABA and acetylcholine). HR3 signal transduction involves $G_{i/o}$ of G-proteins leading to inhibition of cAMP and accumulation of Ca^{2+} and activation of the mitogen-activated protein kinase (MAPK) pathway. R- α -methyl-histamine and imetit are agonists; thioperamide and clobenpropit are antagonists of HR3. It was mainly involved in brain functions, and also the peripheral effect of histamine on mast cells via H3Rs, which mainly involves the nervous system, and might be connected to a local neuron–mast cell interaction [52]. It is involved in cognition, sleep–wake status, energy homeostatic regulation and inflammation. It is pre-synaptically located as an autoreceptor controlling the synthesis and release of histamine [53]. H3-autoreceptor activation stimulates the negative feedback mechanism that reduces central histaminergic activity [54]. The control of mast cells by histamine acting on HR3 involves neuropeptide-containing nerves and might be related to a local neuron–mast cell feedback loop controlling neurogenic inflammation [52]. Dysregulation of this feedback loop may lead to excessive inflammatory responses and suggests a novel therapeutic approach by using HR3 agonists.

In several haematopoietic cell lines expressing HR4, which do not express H3R, histamine binding shares pharmacological properties established for H3 receptors.

It has been proposed that H4 receptors might be involved instead [55]. Thus, it is difficult to establish that HR3 and HR4 receptors are both expressed and functional in the different cell subsets, because most polyclonal antibodies recognize the intracellular receptor domain [8].

In addition, a large number of alternatively spliced isoforms of H3R have been described [56, 57]. Naturally occurring splice variants may have practically identical pharmacological properties as the full-length receptor, but can also have altered functionality or lack any functional responses [53].

Histamine receptor 4

Human HR4 is encoded by a gene containing three exons, separated by two large introns located in chromosome 18q11.2. It has 37–43% homology to HR3 (58% in the transmembrane region). HR4 is functionally coupled to G-protein $G_{i/o}$, inhibiting forskolin-induced cAMP formation like the HR3 [39]. Its activation leads to an inhibition of adenylyl cyclase and downstream of cAMP-responsive elements (CRE) as well as activation of MAPK and phospholipase C with Ca^{2+} mobilization. HR4 shows high expression in the bone marrow and peripheral haematopoietic cells, neutrophils, eosinophils and T cells, and moderate expression in the spleen, thymus, lung, small intestine, colon and heart [39]. Both basophils and mast cells express HR4 mRNA [58].

The most clearly established activities of H4R consist in the recruitment and activation of cells involved in inflammatory responses such as eosinophils, mast cells, neutrophils, conventional T lymphocytes and DCs [59–62]. It seems to be involved in immune regulatory functions including chemotaxis and cytokine secretion [63–67]. It is assumed that H4R plays an important role in nociceptive responses, autoimmune disorders, allergic conditions, colon cancer and breast cancer [68–70].

Early results in animal models suggest that H4R antagonists may be helpful in treating conditions in which H1R antagonists are not clinically effective [71]. Selective H4R antagonists like JNJ7777120 show a potential role in the treatment of inflammation in humans [71].

Related to high homology between the two receptors, presently available HR3 agonists and antagonists are also recognized by the HR4 [43]. However, clobenpropit, an H3 receptor antagonist exerts agonistic activity on HR4. Until now, relatively little is known about the biological function of HR4. It was reported that the H1 antagonists doxepin, cinnarizine and promethazine exhibit high-affinity binding to the H4 receptor [72]. HRs form dimers and even oligomers, which allow cooperation between HRs and other G-protein-coupled receptors. The affinity of histamine binding to different HRs varies significantly, with K_i values ranging from 5–10 nM for the H3 and H4 receptors to 2–10 μ M for the H1 and H2 receptors [16, 67].

Thus, the effects of histamine on receptor stimulation can be very complex.

The identification of H4R isoforms is of utmost importance for the future understanding of their pharmacology. For example, the H4R splice variants may show a dominant negative effect on H4R(390) functionality, as they are able to retain H4R(390) intracellularly and inactivate a population of H4R(390) [73].

Histamine: non-conventional binding sites

Histamine can affect cell function by binding to non-classical binding sites that include cytochrome P450 and histamine transporters. The binding of histamine to CYP450 had been shown by Brandes, who proposed a second messenger role for intracellular histamine via this binding site. This hypothesis was mainly based on a finding that *N,N* diethyl-2-(4-(phenylmethyl)phenoxy) ethanamine (DPPE), an arylalkylamine analogue of tamoxifen, inhibits the binding of histamine to CYP450 [74]. The effect of DPPE on histamine binding is dependent on the activity of the P450 enzymes. It has been shown that CYP2E1 and CYP3A are up-regulated in HDC-deficient mice [75]. Vesicular monoamine histamine transporter 2 (VMAT2) had been cloned from rat and human brain. The gene expression of VMAT2 was found to be modulated via cytokines, either positively (TGF- α) or negatively (IL-1 and TNF- α) [76]. The bone marrow-derived mast cells from HDC-deleted mice are completely devoid of endogenous histamine but can take up the mediator from a histamine-supplemented medium and store it in secretory granules. Recently, the bidirectional organic cation transporter 3 (OCT3/Slc22a3), a molecule responsible for histamine uptake by murine basophils, was identified [77]. OCT3 participates in the control of basophil functions. Ligands of H3/H4 HRs or OCT3 inhibit histamine uptake and thus mimic the effect of exogenous histamine, which inhibits its own synthesis as well as IL-4, IL-6 and IL-13 production in basophils [77].

Regulation of immune response

Antigen-presenting cells

DCs are often located in the vicinity of various histamine sources such as connective tissue mast cells. They are potent antigen-presenting cells (APCs) and cytokine-producing cells. Therefore, histamine may effectively influence the immune response through DC. These professional APCs mature from monocytic and lymphoid precursors and acquire DC1 and DC2 phenotypes, which in turn facilitate the development of T-helper type-1 (Th1) and Th2 cells, respectively. Endogenous histamine is actively synthesized during cytokine-induced DC differentiation, which acts in an autocrine and a paracrine fashion and

modifies DC markers [21]. Histamine actively participates in the functions and activity of DC precursors as well as their immature and mature forms (Fig. 1). Immature and mature DCs express all four HR; however, comparison of their levels of expression has not yet been performed [64, 78–80]. In the differentiation process of DC1 from monocytes, HR1 and HR3 act as positive stimulants that increase antigen-presentation capacity and pro-inflammatory cytokine production and Th1-priming activity. In contrast, HR2 acts as a suppressive molecule for antigen-presentation capacity, enhances IL-10 production and induces IL-10-producing T cells or Th2 cells [81–83].

In monocytes stimulated with toll-like receptor-triggering bacterial products, histamine inhibits the production of pro-inflammatory IL-1-like activity, TNF- α , IL-12 and IL-18, but enhances IL-10 secretion, through HR2 stimulation [84, 85]. Histamine also down-regulates CD14 expression via H2 receptors on human monocytes [84]. The inhibitory effect of histamine via the H2 receptor appears through the regulation of ICAM-1 and B7.1 expression, leading to the reduction of the innate immune response stimulated by LPS [85].

Macrophages purified from human lung tissue, monocyte-derived macrophages (MDMs) and DCs express larger amounts of the H1 receptor than their precursor monocytes and the expression of the H1 receptor is up-regulated at both the mRNA and the protein levels. Differentiation of monocytes into macrophages also induces a drastic down-regulation of the H2 receptors, whereas differentiation into DCs has no significant influence on H2 receptor expression. An overexpressed H1 receptor is functionally active, and it induces increased production of IL-8 in histamine-stimulated macrophages [86].

Histamine induces intracellular Ca²⁺ flux, actin polymerization and chemotaxis in immature DCs due to stimulation of HR1 and HR3 subtypes. Maturation of DCs results in the loss of these responses. In maturing DCs, however, histamine dose dependently enhances the intracellular cAMP levels and stimulates IL-10 secretion, while inhibiting the production of IL-12 via HR2 [82]. Interestingly, although human monocyte-derived dendritic cells (MoDC) have both histamine H1 and H2 receptors and can induce CD86 expression by histamine, human epidermal Langerhans cells express neither H1 nor H2 receptors [87]. Inflammatory DCs express a functionally active H4R, which, upon stimulation, leads to down-regulation of CCL2 and IL-12. This might have implications for the treatment of atopic dermatitis [88].

T cells and antibody isotypes

Histamine has been shown to intervene in the Th1, Th2 Treg cell balance and consequently antibody formation. Differential patterns of HR expression on Th1 and Th2

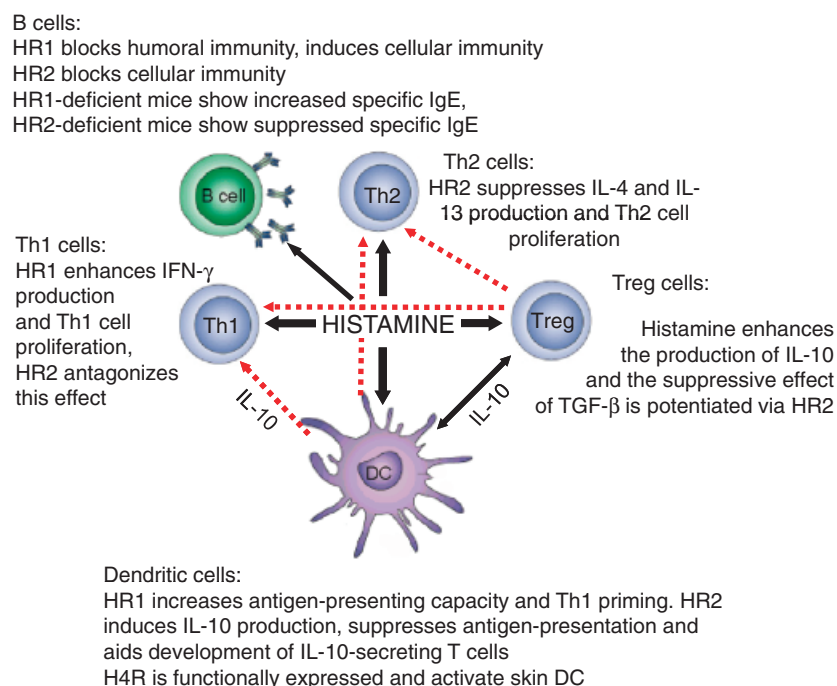


Fig. 1. In lymphatic organs and subepithelial tissues of allergic inflammation, histamine regulates monocytes, dendritic cells, T cells and B cells. Monocytes and dendritic cells express all known histamine receptors (HRs). HR1 and HR3 induce pro-inflammatory activity and increased antigen-presenting cell capacity, whereas HR2 plays a suppressive role in monocytes and monocyte-derived dendritic cells (DC). T-helper type-1 (Th1) cells show a predominant, but not exclusive, expression of HR1, whereas Th2 cells show up-regulation of HR2. Histamine induces increased proliferation and IFN- γ production in Th1 cells. Th2 cells express predominant HR2, which acts as the negative regulator of proliferation, IL-4 and IL-13 production. Histamine enhances Th1-type responses by triggering the HR1, whereas both Th1- and Th2-type responses are negatively regulated by HR2, showing an essential role for immune regulation for this receptor. These distinct affects may suggest roles of HR1 and HR2 on T cells for autoimmunity and peripheral tolerance, respectively. Histamine also modulates antibody production. Histamine directly effects B cell antibody production as a co-stimulatory receptor on B cells. HR1 predominantly expressed on Th1 cells may block humoral immune responses by enhancing Th1-type cytokine IFN- γ . In contrast, HR2 enhances humoral immune responses. Allergen-specific IgE production is differentially regulated in HR1- and HR2-deficient mice. HR1-deleted mice show increased allergen-specific IgE production, whereas HR2-deleted mice show suppressed IgE production.

cells determine reciprocal T cell responses following histamine stimulation (Fig. 1) [4]. Th1 cells show predominant, but not exclusive expression of HR1, while Th2 cells show increased expression of HR2. Histamine enhances Th1-type responses by triggering the HR1, whereas both Th1- and Th2-type responses are negatively regulated by HR2, due to activation of different biochemical intracellular signals [4]. In mice, deletion of HR1 results in the suppression of IFN- γ and dominant secretion of Th2 cytokines (IL-4 and IL-13). HR2-deleted mice show up-regulation of both Th1 and Th2 cytokines. *Bphs*, a non-major histocompatibility complex-linked gene involved in the susceptibility to many autoimmune diseases, has been identified as the HR1 gene in mice. HR1-deleted mice showed delayed disease onset and decreased disease severity when immunized to develop experimental allergic encephalomyelitis [89]. It has also been shown that histamine stimulation induced IL-10 secretion through HR2 [90]. Increased IL-10 production in both DC and T cells may account for an important regulatory mechanism in the control of inflammatory functions through histamine.

Various cytokines regulate the production of histamine and its receptor expression. IL-3 and GM-CSF are enhancers of histamine release from basophils, and SCF for mast cells [8]. In addition, IL-3 stimulation significantly increases HR1 expression on Th1, but not on Th2 cells [4].

In mice, histamine enhances anti-IgM-induced proliferation of B cells, which is abolished in HR1-deleted mice. In HR1-deleted mice, antibody production against a T cell-independent antigen-TNP-Ficoll is decreased [48], suggesting an important role of HR1 signalling in responses triggered from B cell receptors. Antibody responses to T cell-dependent antigens like ovalbumin (OVA) show a different pattern [48]. HR1-deleted mice produced high OVA-specific IgG1 and IgE in comparison with wild-type mice. In contrast, HR2-deleted mice showed decreased serum levels of OVA-specific IgE in comparison with wild-type mice and HR1-deficient mice. Although T cells of HR2-deficient mice secreted increased IL-4 and IL-13, OVA-specific IgE was suppressed in the presence of highly increased IFN- γ . Thus, HR1 and the

related Th1 response may play a dominant role in the suppression of humoral immune response.

Peripheral T cell tolerance characterized by immune deviation to regulatory/suppressor T cells represents a key event in the control of a specific immune response during allergen-specific immunotherapy [91]. Although multiple suppressor factors including contact-dependent or -independent mechanisms might be involved, IL-10 and TGF- β predominantly produced by allergen-specific T cells play an essential role [91, 92]. High-dose bee venom exposure in beekeepers by natural bee stings represents a model to understand mechanisms of T cell tolerance to allergens in healthy individuals. Continuous exposure of non-allergic beekeepers to high doses of bee venom antigens induces diminished T cell-related cutaneous late-phase swelling to bee stings in parallel with suppressed allergen-specific T cell proliferation and Th1 and Th2 cytokine secretion [93]. After multiple bee stings, venom antigen-specific Th1 and Th2 cells show a clonal switch towards IL-10-secreting type 1 T regulatory (Tr1) cells. T cell regulation continues as long as antigen exposure persists and returns to initial levels within 2–3 months after bee stings. HR2 up-regulated on specific-Th2 cells displays a dual effect by directly suppressing allergen-stimulated T cells and increasing IL-10 production. Thus, rapid clonal switch to and expansion of IL-10-producing Tr1 cells and the HR2-related effects represent essential mechanisms in immune tolerance to a high dose of allergens in non-allergic individuals [93]. Apparently, histamine interferes with the peripheral tolerance induced during SIT in several pathways. Histamine induces the production of IL-10 by DCs [82]. In addition, histamine induces IL-10 production by Th2 cells [90]. Furthermore, histamine enhances the suppressive activity of TGF- β on T cells [94]. All three of these effects are mediated via HR2, which is relatively highly expressed on Th2 cells and suppresses IL-4 and IL-13 production and T cell proliferation [4]. Apparently, these recent findings suggest that HR2 may represent an essential receptor that participates in peripheral tolerance or active suppression of inflammatory/immune responses. It has been shown recently in the murine model that H4R stimulation enriches for a regulatory FoxP3+T cell with potent suppressive activity for proliferation [95].

The long-term protection from honeybee stings by terfenadine premedication during rush immunotherapy with honeybee venom in a double-blind, placebo-controlled trial was analysed [96]. After an average of 3 years, 41 patients were re-exposed to honeybee stings. Surprisingly, none of 20 patients, who had been given HR1 antihistamine premedication, but 6 of 21 given placebo, had a systemic allergic reaction to the re-exposure by either a field sting or a sting challenge. This highly significant difference suggests that H1 antihistamine premedication during the initial dose-increase phase may have enhanced the long-term efficacy of immunotherapy.

Expression of HR1 on T lymphocytes is strongly reduced during ultra-rush immunotherapy, which may lead to a dominant expression and function of tolerance-inducing HR2. This indicates a positive role of histamine in immune regulation during SIT [97]. In a recent DBPC prospective study, the effect of treatment with L-cetirizine during ultra-rush venom immunotherapy was investigated. Decreased H1R/H2R expression ratio, indicating H2 signal dominance after 21 days, was observed in the placebo group [98]. L-cetirizine pre-treatment prevented the decrease of the HR1/HR2 expression ratio. Consequently, patients treated with L-cetirizine produced significantly more IFN- γ . IL-10 production was induced in both groups but only significantly in the L-cetirizine group.

In the same study, we were able to confirm a significant reduction of systemic allergic side-effects and the need for rescue medication by H1 antihistamine preventive medication during the dose-increase phase of immunotherapy with bee venom. On the other hand, an increased efficacy of BVIT, as suggested by a previous retrospective open analysis, could not be confirmed in this prospective, double-blind placebo-controlled trial. Several possible reasons can be addressed. Different desensitization and antihistamine pre-treatment protocols were used. The higher antihistamine dose, together with the much higher cumulative BV dose administered in the previous retrospective study, probably may have resulted in stronger interference with HR1 in the presence of the allergen.

Selective HR2 antagonists have attracted interest because of their potential immune response-modifying activity [99]. Most data suggest that cimetidine has a stimulatory effect on the immune system, possibly by blocking the receptors on subsets of T lymphocytes and inhibiting HR2-induced immune suppression. Cimetidine has also been used successfully to restore immune functions in patients with malignant disorders, hypogammaglobulinaemia and AIDS-related complexes. On the other hand, HR2 agonists such as dimaprit significantly reduce disease severity in EAE mice [100].

Histamine and chronic inflammatory responses

Over the course of the pollen season, there might even be a 10-fold increase in the numbers of nasal epithelial submucosal mast cells. Histamine released from these cells might not only induce acute allergic symptoms but may also be crucial for sustaining this response into a chronic phase as increasing evidence suggests that it influences several immune/inflammatory and effector functions [3, 6].

Histamine contributes to the progression of allergic-inflammatory responses by enhancement of the secretion of pro-inflammatory cytokines like IL-1 α , IL-1 β IL-6 as well as chemokines like RANTES or IL-8, both in several cell types and in local tissues [101–104]. Histamine induces the CC chemokines, monocyte chemotactic protein

1 and 3, RANTES and eotaxin in explant cultures of human nasal mucosa via HR1, suggesting a prolonged inflammatory cycle in allergic rhinitis (AR) between the cells that release histamine and their enhanced migration to nasal mucosa [105]. Endothelial cells express functional HR1 and HR2, and increased adhesion molecule expression such as ICAM-1, VCAM-1 and P-selectin was demonstrated by histamine infusion via HR1 [106–108]. Histamine regulates the expression of its own receptors on endothelial cells and influences the overall inflammatory reaction [109].

Histamine regulates granulocyte accumulation to tissues in distinct ways. Allergen-induced accumulation of eosinophils in the skin, nose and airways is potently inhibited by H1 antihistamines [110]. The effect of histamine on eosinophil migration may differ according to the dose. Whereas high doses inhibit eosinophil chemotaxis via HR2, low doses enhance eosinophil chemotaxis via HR1 [111]. Recently, it has been shown that the HR responsible for the selective recruitment of eosinophils is HR4 [66]. Histamine possesses all the properties of a classical leucocyte chemoattractant (i.e. agonist-induced actin polymerization, mobilization of intracellular calcium, alteration in cell shape and up-regulation of adhesion molecule expression). The eosinophils' chemoattractive ability of histamine is weak, when compared with the potent CCR3-binding chemokines, eotaxin and eotaxin-2 [59, 63, 66, 111]. However, histamine, upon activation of the HR4, induces enhanced migration of eosinophils towards eotaxin and eotaxin-2 [59, 63]. On the other hand, the potential of histamine alone to act as an eosinophil chemoattractant *in vivo* might be augmented by other factors, such as growth factors or cytokines like IL-5, the cytokine specific for the differentiation, activation and survival of eosinophils [66]. Triggering of HR4 also induces chemotaxis of mast cells [65]. Experiments in mice showed that mast cells from wild-type and HR3-deleted mice migrated in response to histamine, while mast cells from the HR4-deleted mice did not. Thus, chemotaxis of eosinophils and mast cells via histamine is triggered mainly through the HR4. The HR4-mediated chronic inflammatory effects of histamine may be aborted by administration of HR4 antagonists, and combination therapies with the HR1 antagonists are a promising approach.

Histamine inhibits neutrophil chemotaxis due to HR2 triggering, which is mimicked by impromidine (HR2 agonist), but not by betahistamine (HR1 agonist). In addition, histamine inhibits neutrophil activation, superoxide formation and degranulation via HR2 [86]. Down-regulation of NF- κ B, which acts as a potent transcription factor in initiating inflammation, may represent a possible mechanism for H1 antihistamines to inhibit inflammatory cell accumulation [44]. Low concentrations of H1 antihistamines, cetirizine and azelastine have been demonstrated to down-regulate NF- κ B expression in parallel to

inhibition of pro-inflammatory cytokines [112]. A study with HDC-deficient and mast cell-deficient mice demonstrated that histamine mainly derived from non-mast cells plays an essential role in angiogenesis and the generation of inflammatory granulation [113]. The pre-treatment of the nasal mucosa and the conjunctivae with topical H1 antihistamines has been shown to down-regulate the inflammation locally after an allergen challenge [114, 115]. Decreased macrophage IL-6 production, and in DCs decreased expression of CD86 and decreased IL-8 production were shown [81, 116, 117].

Histamine is an important modulator of barrier function in endothelial and epithelial cells. *In vitro*, it can interact with endothelial cells [118, 119] and epithelial cells [120, 121], leading to increases in paracellular permeability. The effects on endothelial cells *in vivo* lead directly to changes in vascular permeability, allowing for leucocyte infiltration and oedema formation. On human epithelial cells, it has been shown that HR1 mediates activation and increases in the release of mediators such as IL-6, IL-8 and granulocyte macrophage colony-stimulating factor (GM-CSF) [3, 8].

Histamine and antihistamines in asthma

Although the use of H1 antihistamine in persistent asthma is currently not recommended, some recent evidence might finally lead to reevaluation of this approach. Overall, the limited clinical efficacy of HR1 antagonists in asthma does not seem to warrant their use over existing steroid-sparing therapies, such as montelukast, although in some instances cotherapy may be useful. Histamine has been found in the airways of asthma patients even during asymptomatic periods [122–124]. Increased numbers of degranulated mast cells and basophils have been detected in biopsies of asthmatic airways long after an acute asthma attack [125, 126]. The level of histamine in bronchoalveolar lavage fluid has been found to correlate with the severity of asthma and airway hyperreactivity [127].

Inhaled and intravenous histamine causes bronchoconstriction as one of the first recognized properties of histamine, which is inhibited by H1 antihistamines. As a manifestation of airway hyperreactivity, asthmatic individuals are more sensitive to the bronchoconstrictor effect of histamine than normal individuals. In addition, *in vitro* studies have shown increased histamine release in basophils and mast cells obtained from asthmatic subjects compared with cells obtained from persons without asthma [122]. In lavage fluid of the patients treated with H1 antihistamines, decreased levels of pro-inflammatory cytokines, and mediators (e.g. histamine, leukotrienes, prostaglandin, cell adhesion molecules (e.g. intercellular adhesion molecules and vascular cell adhesion molecules), cells (e.g. eosinophils and neutrophils) and plasma

exudation, along with a reduced symptom score, have been found.

In addition, it has been shown that cultured mice T cells migrate in response to histamine *in vitro*, but this was ablated by blockade of H1R but not H2R. *In vivo*, allergen-specific WT but not H1R^{-/-} CD4⁺ H1R^{-/-} T cells failed to confer airway inflammation or AHR observed after transfer of WT T cells [128].

The potential efficacy of H1 antihistamines in asthma has been intensively investigated [129]. It was shown that inhalation, intravenous or oral administration of clemastine or chlorpheniramine induced significant bronchodilatation. However, second-generation H1 antihistamines induce only a very limited increase of forced expiratory volume in 1 s (5–10% over baseline) by recommended doses [130–133]. There is a variable effect on allergen challenge or exercise-induced bronchoconstriction. Only terfenadine with three times the recommended dose inhibited the early and late bronchoconstrictor response [134, 135]. Terfenadine, cetirizine and loratadine, with two to five times the usual dose, appeared to improve asthma symptoms in mild intermittent seasonal or chronic asthma, but did not block development of bronchial hyperresponsiveness in seasonal pollen asthma nor show an apparent benefit in patients with more severe asthma [130–133]. In patients with concurrent symptoms of AR and asthma, treatment with H1 antihistamine results in a significant decrease in the symptoms of both rhinitis and asthma, a decrease in the use of β_2 -agonists and some improvement of airway function [136, 137]. Montelukast sodium – a leukotriene receptor antagonist – showed an effect similar to desloratadine [137, 138]. However, an additive efficacy was observed, when loratadine was used together with montelukast [139].

The mechanisms of the beneficial effect of H1 antihistamines in asthma have been investigated in a mice model. Fexofenadine was found to suppress allergic immune/inflammatory responses in sensitized mice [140]. Treatment with fexofenadine reduced the Th2-like response that typically follows sensitization and challenge with allergen. Decreased secretion of IL-4, IL-5, prevention of allergen-specific IgE increase and reduced eosinophilia in lung tissue and BALF as well as normalization of airway response to metacholine were observed.

Importantly, in an adoptive transfer model, it was demonstrated that the target mechanism was T cell mediated. Lung T cells from sensitized mice, when transferred to naïve recipient mice, triggered airway hyperresponsiveness and allergic inflammatory features after an allergen challenge. In contrast, naïve mice that received T cells from sensitized mice treated before with fexofenadine showed no such responses to an allergen challenge [140]. The inability of T cells from H1 antihistamine-treated allergen-sensitized mice to transfer allergic sensitivity to naïve recipients resulted from an alteration in the

cytokine production profile of the transferred cells. Similar observations were made using desloratadine [141].

Consistently, the histamine-induced concentration-dependent release of IL-6 and β -glucuronidase from macrophages isolated from the human lung parenchyma was inhibited by fexofenadine but not by ranitidine, an H2 antagonist [116]. Thus, long-term treatment with H1 antihistamines can alter disease progression in patients with respiratory allergy associated with tissue damage/remodelling mediated by macrophage and Th2 cell activation. It has been shown that treatment with cetirizine over a period of 18 months delayed the onset of asthma in some young children with atopic dermatitis [142]. Although H1 antihistamines clearly show weaker anti-inflammatory effects than corticosteroids, they may, in a subtle way, modulate the immune response by modulating the balance between Th1, Th2 and Treg cells and suppressing the accumulation of inflammatory cells.

Although previous studies suggested a basal tone of smooth muscle mediated by histamine binding to HR1, currently, constitutive intrinsic activity of the HR1 without any occupation by histamine could be more relevant. Histamine also induces the proliferation of cultured airway smooth muscle cells [143]. A difference in histamine response between species has been reported, indicating a role for HR2-mediated bronchodilatation in cat, rat, rabbit, sheep and horse [144]. However, in humans, H2 antihistamines such as cimetidine and ranitidine do not cause bronchoconstriction in normal or asthmatic individuals [145, 146]. Although there is no direct evidence that it plays a role in disease pathogenesis, HR2-mediated gastric secretion is impaired in asthma [147]. Rather, a beneficial effect of H2 antihistamines given for the treatment of gastritis was observed in asthma [148]. In addition, recent studies suggest that histamine may play an important role in the modulation of the cytokine network in the lung via HR2, HR3 and HR4 that are expressed in distinct cells and cell subsets [149].

The discovery of the histamine H4 receptor (H4R) encouraged the investigation of the role of histamine in pulmonary allergic responses. H4R-deficient mice and mice treated with H4R antagonists exhibited decreased allergic lung inflammation, with decreases in lung infiltrating eosinophils and lymphocytes and decreases in Th2 responses. H4R can modulate allergic responses via its influence on T cell activation [60]. However, it has been demonstrated that human CD4⁺ T cells show up-regulated HR4 under TH2 conditions, and its stimulation leads to induction of AP-1 and IL-31 [150].

The role for HR4 in many cells associated with asthma suggests that it may be involved, but as yet, no clinical trials with HR4 antagonists have been reported. The circumstantial evidence for a role of histamine in asthma, along with the general lack of clinical efficacy of H1 ligands in the disease, may suggest involvement of the

HR4. HR4-deficient mice or those given HR4 antagonists during sensitization have reduced lung inflammation and a reduction in Th2 and inflammatory cytokines [151]. In addition, the reduction in antigen-specific antibody responses suggests a role for HR4 in the initial priming of the immune system.

The dual HR4/HR2 agonist, 4-methylhistamine, reduces airway hyperreactivity and inflammation when given by an inhaled route in a mouse model of asthma [95]. The recent findings may lead to recommendation of the use of antihistamines at high doses at an early stage of asthma to prevent progression. HR4 antagonists may block other functions of histamine that are not blocked by HR1. Thus, blocking of both HR1 and HR4 signals may prove beneficial. Apparently, due to the same signal transduction patterns, β_2 adrenergic receptors may function similar to HR2 in humans [152]. The role of histamine and other redundant G-protein-coupled receptors in the regulation of immune/inflammatory pathways in the lung remain to be intensely studied in future studies.

Histamine and HR1 in autoimmunity

The role of histamine in autoimmune reactions was often questioned in the past [153, 154]. Because of inadequate model systems and reagents, the roles and mechanisms of histamine in autoimmunity remained unclear. Recently, the gene encoding HR1 was identified as *Bphs*, which represents an autoimmune disease locus [89]. HR1 differs at three amino acid residues in autoimmune orchitis- and allergic encephalomyelitis-susceptible and -resistant mice. T cells from HR1-deficient mice produce significantly less IFN- γ , associated with significantly less severe autoimmune disease. Apparently, the IFN- γ -inducing capacity of HR1 on T cells might play a role in tissue injury mechanisms of several other diseases of allergic, infectious and autoimmune origin, as well as allograft rejection.

In a murine model, HR4 activation positively regulates *in vivo* IL-4 and IFN- γ production by invariant NKT cells [155].

Histamine in malignancies

Histamine might play a major role in the growth of normal and malignant tissue as a regulator of proliferation and angiogenesis. Specific HRs have been identified on the surface of bone marrow cells, immune competent cells, endothelial cells, fibroblasts and also malignant cells. This has led to tumour treatment by specific HR agonists and antagonists [156]. Results from such studies are currently accumulating and suggest that the HR2 antihistamines have potential beneficial effects in the treatment of certain malignant diseases, either alone or in combination with other drugs [157]. The beneficial effect of HR2 antihistamines as adjuvant single drugs to reduce

trauma-, blood transfusion- and sepsis-induced immunosuppression has indicated combined treatment regimens in major surgery, particularly in patients operated on for malignant diseases. Two different mechanisms are probably acting concordantly: direct inhibition of tumour cell proliferation by the HR2 antihistamines and activation of the local immune response characterized by IFN- γ production. These findings might help to elucidate the possibility of a rationally designed antihistamine strategy in tumour therapy.

Conclusion

Histamine and its four different HR and several splice variants display a complex system with distinct functions of receptor subtypes and their differential expression, which changes according to the stage of cell differentiation as well as microenvironmental influences. It has been commonly acknowledged that HR1 activates the immune system cells potentiating a pro-inflammatory activity for higher migration to the inflammation area as well as increased effector functions. HR2 seems to be a potent suppressor of inflammatory and effector functions.

This explanation has been complicated by the identification of H4R and OCT3 through which histamine can exert a negative feedback on their histamine and pro-inflammatory and Th2-type cytokine production in murine basophils. H4R is currently seen as a potential new drug target and is of significant interest to the pharmaceutical industry. Several contradictory results have been reported due to impurities in reagents, innate immune response, stimulating substances and usage of cell lines. Many clinical studies in humans and HR-deficient mice *in vivo* have better improved our knowledge of histamine biology.

H4R antagonists have shown promise in experimental models of asthma. Thus, H4R-specific antihistamines may be distinctively effective in treating allergic symptoms in which H1R antagonists are not effective. These developments open a window for therapeutic approaches based on combined anti-HR1/anti-HR4 blockade or development of selective dual HR1/HR4 antagonists.

Acknowledgements

The authors' laboratories are supported by the Swiss National Foundation Grant: 32-118226, 32-125249 and the Global Allergy and Asthma European Network (GA²-LEN) and Christian Kuhne-Centre for Allergy Research and Education (CK-CARE).

References

- 1 Leurs R, Smit MJ, Timmerman H. Molecular and pharmacological aspects of histamine receptors. *Pharmacol Ther* 1995; 66:413-63.

- 2 Jutel M, Blaser K, Akdis CA. Histamine receptors in immune regulation and allergen-specific immunotherapy. *Immunol Allergy Clin North Am* 2006; 26:245–59, vii.
- 3 Jutel M, Watanabe T, Akdis M, Blaser K, Akdis CA. Immune regulation by histamine. *Curr Opin Immunol* 2002; 14:735–40.
- 4 Jutel M, Watanabe T, Klunker S *et al*. Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature* 2001; 413:420–5.
- 5 Banu Y, Watanabe T. Augmentation of antigen receptor-mediated responses by histamine H1 receptor signaling. *J Exp Med* 1999; 189:673–82.
- 6 Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. *J Allergy Clin Immunol* 2003; 112:15–22.
- 7 Dale HH, Laidlaw PP. The physiological action of beta-imidazolethylamine. *J Physiol (London)* 1910; 41:318–44.
- 8 Dy M, Schneider E. Histamine-cytokine connection in immunity and hematopoiesis. *Cytokine Growth Factor Rev* 2004; 15:393–410.
- 9 Schneider E, Rolli-Derkinderen M, Arock M, Dy M. Trends in histamine research: new functions during immune responses and hematopoiesis. *Trends Immunol* 2002; 23:255–63.
- 10 MacGlashan D Jr. Histamine: a mediator of inflammation. *J Allergy Clin Immunol* 2003; 112:S53–9.
- 11 Haas H, Panula P. The role of histamine and the tuberomammillary nucleus in the nervous system. *Nat Rev Neurosci* 2003; 4:121–30.
- 12 Higuchi M, Yanai K, Okamura N *et al*. Histamine H(1) receptors in patients with Alzheimer's disease assessed by positron emission tomography. *Neuroscience* 2000; 99:721–9.
- 13 Akdis CA, Blaser K, Akdis M. Genes of tolerance. *Allergy* 2004; 59:897–913.
- 14 Dy M, Lebel B, Kamoun P, Hamburger J. Histamine production during the anti-allograft response. Demonstration of a new lymphokine enhancing histamine synthesis. *J Exp Med* 1981; 153:293–309.
- 15 Dy M, Lebel B. Skin allografts generate an enhanced production of histamine and histamine-producing cell-stimulating factor (HCSF) by spleen cells in response to T cell mitogens. *J Immunol* 1983; 130:2343–7.
- 16 Endo Y. Simultaneous induction of histidine and ornithine decarboxylases and changes in their product amines following the injection of *Escherichia coli* lipopolysaccharide into mice. *Biochem Pharmacol* 1982; 31:1643–7.
- 17 Kawaguchi-Nagata K, Okamura H, Tamura T *et al*. Induction of histidine decarboxylase activity in the spleen of mice treated with staphylococcal enterotoxin A and demonstration of its non-mast cell origin. *Biochem Biophys Res Commun* 1985; 129:187–92.
- 18 Wu X, Yoshida A, Sasano T, Iwakura Y, Endo Y. Histamine production via mast cell-independent induction of histidine decarboxylase in response to lipopolysaccharide and interleukin-1. *Int Immunopharmacol* 2004; 4:513–20.
- 19 Saxena SP, Brandes LJ, Becker AB, Simons KJ, LaBella FS, Gerrard JM. Histamine is an intracellular messenger mediating platelet aggregation. *Science* 1989; 243:1596–9.
- 20 Laszlo V, Rothe G, Hegyesi H *et al*. Increased histidine decarboxylase expression during in vitro monocyte maturation; a possible role of endogenously synthesised histamine in monocyte/macrophage differentiation. *Inflamm Res* 2001; 50:428–34.
- 21 Szeberenyi JB, Pallinger E, Zsinko M *et al*. Inhibition of effects of endogenously synthesized histamine disturbs in vitro human dendritic cell differentiation. *Immunol Lett* 2001; 76:175–82.
- 22 Radvany Z, Darvas Z, Kerekes K *et al*. H1 histamine receptor antagonist inhibits constitutive growth of Jurkat T cells and antigen-specific proliferation of ovalbumin-specific murine T cells. *Semin Cancer Biol* 2000; 10:41–5.
- 23 Shiraishi M, Hirasawa N, Oikawa S, Kobayashi Y, Ohuchi K. Analysis of histamine-producing cells at the late phase of allergic inflammation in rats. *Immunology* 2000; 99:600–6.
- 24 Kubo Y, Nakano H. Regulation of histamine in mouse CD4+ and CD8+ lymphocytes. *Inflamm Res* 1999; 48:149–53.
- 25 Nakagawa S, Okaya Y, Yatsunami K *et al*. Identification of multiple regulatory elements of human L-histidine decarboxylase gene. *J Biochem* 1997; 121:935–40.
- 26 Hocker M, Henihan RJ, Rosewicz S *et al*. Gastrin and phorbol 12-myristate 13-acetate regulate the human histidine decarboxylase promoter through Raf-dependent activation of extracellular signal-regulated kinase-related signaling pathways in gastric cancer cells. *J Biol Chem* 1997; 272:27015–24.
- 27 Ohtsu H, Kuramasu A, Suzuki S *et al*. Histidine decarboxylase expression in mouse mast cell line P815 is induced by mouse peritoneal cavity incubation. *J Biol Chem* 1996; 271:28439–44.
- 28 Kuramasu A, Saito H, Suzuki S, Watanabe T, Ohtsu H. Mast cell-/basophil-specific transcriptional regulation of human L-histidine decarboxylase gene by CpG methylation in the promoter region. *J Biol Chem* 1998; 273:31607–14.
- 29 Yoshimoto T, Tsutsui H, Tominaga K *et al*. IL-18, although antiallergic when administered with IL-12, stimulates IL-4 and histamine release by basophils. *Proc Natl Acad Sci USA* 1999; 96:13962–6.
- 30 Schneider E, Pollard H, Lepault F, Guy-Grand D, Minkowski M, Dy M. Histamine-producing cell-stimulating activity. Interleukin 3 and granulocyte-macrophage colony-stimulating factor induce de novo synthesis of histidine decarboxylase in hemopoietic progenitor cells. *J Immunol* 1987; 139:3710–7.
- 31 Ohtsu H, Tanaka S, Terui T, Hori Y, Makabe-Kobayashi Y, Pejler G. Mice lacking histidine decarboxylase exhibit abnormal mast cells. *FEBS Lett* 2001; 502:53–6.
- 32 Tanaka S, Takasu Y, Mikura S, Satoh N, Ichikawa A. Antigen-independent induction of histamine synthesis by immunoglobulin E in mouse bone marrow-derived mast cells. *J Exp Med* 2002; 196:229–35.
- 33 Abe Y, Ogino S, Irifune M *et al*. Histamine content, synthesis and degradation in human nasal mucosa. *Clin Exp Allergy* 1993; 23:132–6.
- 34 Ash AS, Schild HO. Receptors mediating some actions of histamine. 1966. *Br J Pharmacol* 1997; 120:302–14; discussion 300–301.
- 35 Lovenberg TW, Roland BL, Wilson SJ *et al*. Cloning and functional expression of the human histamine H3 receptor. *Mol Pharmacol* 1999; 55:1101–7.
- 36 Oda T, Morikawa N, Saito Y, Masuho Y, Matsumoto S. Molecular cloning and characterization of a novel type of histamine receptor preferentially expressed in leukocytes. *J Biol Chem* 2000; 275:36781–6.

- 37 Le Coniat M, Traiffort E, Ruat M, Arrang JM, Berger R. Chromosomal localization of the human histamine H1-receptor gene. *Hum Genet* 1994; **94**:186–8.
- 38 Gantz I, Schaffer M, DelValle J. Molecular cloning of a gene encoding the histamine H2 receptor. *Proc Natl Acad Sci USA* 1991; **88**:429–33.
- 39 Nakamura T, Itadani H, Hidaka Y, Ohta M, Tanaka K. Molecular cloning and characterization of a new human histamine receptor, HH4R. *Biochem Biophys Res Commun* 2000; **279**: 615–20.
- 40 Milligan G, Bond R, Lee M. Inverse agonism: pharmacological curiosity or potential therapeutic strategy? *Trends Pharmacol Sci* 1995; **16**:10–3.
- 41 Paesen GC, Adams PL, Harlos K, Nuttall PA, Stuart DI. Tick histamine-binding proteins: isolation, cloning, and three-dimensional structure. *Mol Cell* 1999; **3**:661–71.
- 42 Togias A. H1-receptors: localization and role in airway physiology and in immune functions. *J Allergy Clin Immunol* 2003; **112**:S60–8.
- 43 Smit MJ, Hoffmann M, Timmerman H, Leurs R. Molecular properties and signalling pathways of the histamine H1 receptor. *Clin Exp Allergy* 1999; **29** (Suppl. 3):19–28.
- 44 Bakker RA, Schoonus SB, Smit MJ, Timmerman H, Leurs R. Histamine H(1)-receptor activation of nuclear factor-kappa B: roles for G beta gamma- and G alpha(q/11)-subunits in constitutive and agonist-mediated signaling. *Mol Pharmacol* 2001; **60**:1133–42.
- 45 Aoki Y, Qiu D, Zhao GH, Kao PN. Leukotriene B4 mediates histamine induction of NF-kappaB and IL-8 in human bronchial epithelial cells. *Am J Physiol* 1998; **274**:L1030–9.
- 46 Hall IP. Pharmacogenetics of asthma. *Eur Respir J* 2000; **15**:449–51.
- 47 Leurs R, Church MK, Taglialatela M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002; **32**:489–98.
- 48 Yanai K, Son LZ, Endou M, Sakurai E, Watanabe T. Targeting disruption of histamine H1 receptors in mice: behavioral and neurochemical characterization. *Life Sci* 1998; **62**:1607–10.
- 49 Del Valle J, Gantz I. Novel insights into histamine H2 receptor biology. *Am J Physiol* 1997; **273**:G987–96.
- 50 Lichtenstein LM, Gillespie E. The effects of the H1 and H2 antihistamines on “allergic” histamine release and its inhibition by histamine. *J Pharmacol Exp Ther* 1975; **192**:441–50.
- 51 Drutel G, Peitsaro N, Karlstedt K *et al.* Identification of rat H3 receptor isoforms with different brain expression and signaling properties. *Mol Pharmacol* 2001; **59**:1–8.
- 52 Dimitriadou V, Rouleau A, Dam Trung Tuong M *et al.* Functional relationship between mast cells and C-sensitive nerve fibres evidenced by histamine H3-receptor modulation in rat lung and spleen. *Clin Sci (London)* 1994; **87**:151–63.
- 53 Leurs R, Bakker RA, Timmerman H, de Esch IJ. The histamine H3 receptor: from gene cloning to H3 receptor drugs. *Nat Rev Drug Discov* 2005; **4**:107–20.
- 54 Teuscher C, Subramanian M, Noubade R *et al.* Central histamine H3 receptor signaling negatively regulates susceptibility to autoimmune inflammatory disease of the CNS. *Proc Natl Acad Sci USA* 2007; **104**:10146–51.
- 55 Hough LB. Genomics meets histamine receptors: new subtypes, new receptors. *Mol Pharmacol* 2001; **59**:415–9.
- 56 Wiedemann P, Bonisch H, Oerters F, Bruss M. Structure of the human histamine H3 receptor gene (HRH3) and identification of naturally occurring variations. *J Neural Transm* 2002; **109**:443–53.
- 57 Hancock AA, Esbenshade TA, Krueger KM, Yao BB. Genetic and pharmacological aspects of histamine H3 receptor heterogeneity. *Life Sci* 2003; **73**:3043–72.
- 58 Zhu Y, Michalovich D, Wu H *et al.* Cloning, expression, and pharmacological characterization of a novel human histamine receptor. *Mol Pharmacol* 2001; **59**:434–41.
- 59 Ling P, Ngo K, Nguyen S *et al.* Histamine H4 receptor mediates eosinophil chemotaxis with cell shape change and adhesion molecule upregulation. *Br J Pharmacol* 2004; **142**:161–71.
- 60 Dunford PJ, O'Donnell N, Riley JP, Williams KN, Karlsson L, Thurmond RL. The histamine H4 receptor mediates allergic airway inflammation by regulating the activation of CD4+ T cells. *J Immunol* 2006; **176**:7062–70.
- 61 de Esch IJ, Thurmond RL, Jongejan A, Leurs R. The histamine H4 receptor as a new therapeutic target for inflammation. *Trends Pharmacol Sci* 2005; **26**:462–9.
- 62 Gutzmer R, Diestel C, Mommert S *et al.* Histamine H4 receptor stimulation suppresses IL-12p70 production and mediates chemotaxis in human monocyte-derived dendritic cells. *J Immunol* 2005; **174**:5224–32.
- 63 Buckland KF, Williams TJ, Conroy DM. Histamine induces cytoskeletal changes in human eosinophils via the H(4) receptor. *Br J Pharmacol* 2003; **140**:1117–27.
- 64 Gantner F, Sakai K, Tusche MW, Cruikshank WW, Center DM, Bacon KB. Histamine h(4) and h(2) receptors control histamine-induced interleukin-16 release from human CD8(+) T cells. *J Pharmacol Exp Ther* 2002; **303**:300–7.
- 65 Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP. Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells. *J Pharmacol Exp Ther* 2003; **305**:1212–21.
- 66 O'Reilly M, Alpert R, Jenkinson S *et al.* Identification of a histamine H4 receptor on human eosinophils – role in eosinophil chemotaxis. *J Recept Signal Transduct Res* 2002; **22**:431–48.
- 67 Thurmond RL, Desai PJ, Dunford PJ *et al.* A potent and selective histamine H4 receptor antagonist with anti-inflammatory properties. *J Pharmacol Exp Ther* 2004; **309**:404–13.
- 68 Varga C, Horvath K, Berko A, Thurmond RL, Dunford PJ, Whittle BJ. Inhibitory effects of histamine H4 receptor antagonists on experimental colitis in the rat. *Eur J Pharmacol* 2005; **522**:130–8.
- 69 Cianchi F, Cortesini C, Schiavone N *et al.* The role of cyclooxygenase-2 in mediating the effects of histamine on cell proliferation and vascular endothelial growth factor production in colorectal cancer. *Clin Cancer Res* 2005; **11**:6807–15.
- 70 Maslinska D, Laure-Kamionowska M, Maslinski KT, Deregowski K, Szweczyk G, Maslinski S. Histamine H(4) receptors on mammary epithelial cells of the human breast with different types of carcinoma. *Inflamm Res* 2006; **55** (Suppl. 1):S77–8.
- 71 Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov* 2008; **7**:41–53.
- 72 Nguyen T, Shapiro DA, George SR *et al.* Discovery of a novel member of the histamine receptor family. *Mol Pharmacol* 2001; **59**:427–33.

- 73 van Rijn RM, van Marle A, Chazot PL *et al*. Cloning and characterization of dominant negative splice variants of the human histamine H4 receptor. *Biochem J* 2008; **414**: 121–31.
- 74 Brandes LJ, Queen GM, LaBella FS. Displacement of histamine from liver cells and cell components by ligands for cytochromes P450. *J Cell Biochem* 2002; **85**:820–4.
- 75 Tamasi V, Fulop AK, Hegyi K, Monostory K, Falus A. Upregulation of CYP2e1 and CYP3a activities in histamine-deficient histidine decarboxylase gene targeted mice. *Cell Biol Int* 2003; **27**:1011–5.
- 76 Kazumori H, Ishihara S, Rumi MA, Ortega-Cava CF, Kadowaki Y, Kinoshita Y. Transforming growth factor- α directly augments histidine decarboxylase and vesicular monoamine transporter 2 production in rat enterochromaffin-like cells. *Am J Physiol Gastrointest Liver Physiol* 2004; **286**:G508–14.
- 77 Schneider E, Machavoine F, Pleau JM *et al*. Organic cation transporter 3 modulates murine basophil functions by controlling intracellular histamine levels. *J Exp Med* 2005; **202**: 387–93.
- 78 Idzko M, la Sala A, Ferrari D *et al*. Expression and function of histamine receptors in human monocyte-derived dendritic cells. *J Allergy Clin Immunol* 2002; **109**:839–46.
- 79 Gutzmer R, Langer K, Lisewski M *et al*. Expression and function of histamine receptors 1 and 2 on human monocyte-derived dendritic cells. *J Allergy Clin Immunol* 2002; **109**:524–31.
- 80 Caron G, Delneste Y, Roelandts E *et al*. Histamine polarizes human dendritic cells into Th2 cell-promoting effector dendritic cells. *J Immunol* 2001; **167**:3682–6.
- 81 Caron G, Delneste Y, Roelandts E. Histamine induces CD86 expression and chemokine production by human immature dendritic cells. *J Immunol* 2001; **166**:6000–6.
- 82 Mazzoni A, Young HA, Spitzer JH, Visintin A, Segal DM. Histamine regulates cytokine production in maturing dendritic cells, resulting in altered T cell polarization. *J Clin Invest* 2001; **108**:1865–73.
- 83 van der Pouw Kraan TC, Snijders A, Boeije LC *et al*. Histamine inhibits the production of interleukin-12 through interaction with H2 receptors. *J Clin Invest* 1998; **102**:1866–73.
- 84 Takahashi HK, Iwagaki H, Mori S, Yoshino T, Tanaka N, Nishibori M. Histamine inhibits lipopolysaccharide-induced interleukin (IL)-18 production in human monocytes. *Clin Immunol* 2004; **112**:30–4.
- 85 Morichika T, Takahashi HK, Iwagaki H *et al*. Histamine inhibits lipopolysaccharide-induced tumor necrosis factor- α production in an intercellular adhesion molecule-1- and B7.1-dependent manner. *J Pharmacol Exp Ther* 2003; **304**: 624–33.
- 86 Triggiani M, Petraroli A, Loffredo S *et al*. Differentiation of monocytes into macrophages induces the upregulation of histamine H1 receptor. *J Allergy Clin Immunol* 2007; **119**:472–81.
- 87 Ohtani T, Aiba S, Mizuashi M, Mollah ZU, Nakagawa S, Tagami H. H1 and H2 histamine receptors are absent on Langerhans cells and present on dermal dendritic cells. *J Invest Dermatol* 2003; **121**:1073–9.
- 88 Dijkstra D, Stark H, Chazot PL *et al*. Human inflammatory dendritic epidermal cells express a functional histamine H4 receptor. *J Invest Dermatol* 2008; **128**:1696–703.
- 89 Ma RZ, Gao J, Meeker ND *et al*. Identification of Bphs, an autoimmune disease locus, as histamine receptor H1. *Science* 2002; **297**:620–3.
- 90 Osná N, Elliott K, Khan MM. Regulation of interleukin-10 secretion by histamine in TH2 cells and splenocytes. *Int Immunopharmacol* 2001; **1**:85–96.
- 91 Akdis CA, Blesken T, Akdis M, Wuthrich B, Blaser K. Role of interleukin 10 in specific immunotherapy. *J Clin Invest* 1998; **102**:98–106.
- 92 Jutel M, Akdis M, Budak F *et al*. IL-10 and TGF- β cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003; **33**:1205–14.
- 93 Meiler F, Zumkehr J, Klunker S, Ruckert B, Akdis CA, Akdis M. In vivo switch to IL-10-secreting T regulatory cells in high dose allergen exposure. *J Exp Med* 2008; **205**:2887–98.
- 94 Kunzmann S, Mantel P-Y, Wohlfahrt J, Akdis M, Blaser K, Schmidt-Weber C. Histamine enhances TGF- β 1-mediated suppression of Th2 responses. *FASEB J* 2003; **17**:1089–95.
- 95 Morgan RK, McAllister B, Cross L *et al*. Histamine 4 receptor activation induces recruitment of FoxP3+ T cells and inhibits allergic asthma in a murine model. *J Immunol* 2007; **178**:8081–9.
- 96 Müller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. *J Allergy Clin Immunol* 2001; **107**:81–6.
- 97 Jutel M, Zak-Nejmark T, Wrzyszczyk M, Malolepszy J. Histamine receptor expression on peripheral blood CD4+ lymphocytes is influenced by ultrarush bee venom immunotherapy. *Allergy* 1997; **52** (Suppl. 37):88.
- 98 Muller UR, Jutel M, Reimers A *et al*. Clinical and immunologic effects of premedication with antihistamine during honey bee venom immunotherapy: a double blind placebo controlled study. *J Allergy Clin Immunol* 2008; **122**:1001–7.
- 99 Gifford R, Schmidke J. Cimetidine-induced augmentation of human lymphocyte blastogenesis: comparison with levamisole in mitogen stimulation. *Surg Forum* 1979; **30**:113–5.
- 100 Emerson MR, Orentas DM, Lynch SG, LeVine SM. Activation of histamine H2 receptors ameliorates experimental allergic encephalomyelitis. *Neuroreport* 2002; **13**:1407–10.
- 101 Vannier E, Dinarello CA. Histamine enhances interleukin (IL)-1-induced IL-1 gene expression and protein synthesis via H2 receptors in peripheral blood mononuclear cells. Comparison with IL-1 receptor antagonist. *J Clin Invest* 1993; **92**:281–7.
- 102 Meretey K, Falus A, Taga T, Kishimoto T. Histamine influences the expression of the interleukin-6 receptor on human lymphoid, monocytoïd and hepatoma cell lines. *Agents Actions* 1991; **33**:189–91.
- 103 Jeannin P, Delneste Y, Gosset P *et al*. Histamine induces interleukin-8 secretion by endothelial cells. *Blood* 1994; **84**:2229–33.
- 104 Bayram H, Devalia JL, Khair OA *et al*. Effect of loratadine on nitrogen dioxide-induced changes in electrical resistance and release of inflammatory mediators from cultured human bronchial epithelial cells. *J Allergy Clin Immunol* 1999; **104**: 93–9.
- 105 Fujikura T. New therapeutic approaches to the treatment of nasal allergy: antiinflammatory effects of H(1) receptor antagonists. *Drugs Today (Barcelona)* 2001; **37**:455–61.

- 106 Lo WW, Fan TP. Histamine stimulates inositol phosphate accumulation via the H1-receptor in cultured human endothelial cells. *Biochem Biophys Res Commun* 1987; **148**:47–53.
- 107 Kubes P, Kanwar S. Histamine induces leukocyte rolling in post-capillary venules. A P-selectin-mediated event. *J Immunol* 1994; **152**:3570–7.
- 108 Yamaki K, Thorlacius H, Xie X, Lindbom L, Hedqvist P, Raud J. Characteristics of histamine-induced leukocyte rolling in the undisturbed microcirculation of the rat mesentery. *Br J Pharmacol* 1998; **123**:390–9.
- 109 Schaefer U, Schmitz V, Schneider A, Neugebauer E. Histamine induced homologous and heterologous regulation of histamine receptor subtype mRNA expression in cultured endothelial cells. *Shock* 1999; **12**:309–15.
- 110 Fadel R, Herpin-Richard N, Rihoux JP, Henocq E. Inhibitory effect of cetirizine 2HCl on eosinophil migration in vivo. *Clin Allergy* 1987; **17**:373–9.
- 111 Clark RA, Sandler JA, Gallin JI, Kaplan AP. Histamine modulation of eosinophil migration. *J Immunol* 1977; **118**:137–45.
- 112 Yoneda K, Yamamoto T, Ueta E, Osaki T. Suppression by azelastine hydrochloride of NF-kappa B activation involved in generation of cytokines and nitric oxide. *Jpn J Pharmacol* 1997; **73**:145–53.
- 113 Ghosh AK, Hirasawa N, Ohtsu H, Watanabe T, Ohuchi K. Defective angiogenesis in the inflammatory granulation tissue in histidine decarboxylase-deficient mice but not in mast cell-deficient mice. *J Exp Med* 2002; **195**:973–82.
- 114 Simons FER. Antihistamines. In: Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, eds. *Middleton's allergy: principles & practice*. Philadelphia, Pennsylvania: Mosby Inc., 2003; 834–69.
- 115 Ciprandi G, Passalacqua G, Canonica GW. Effects of H1 antihistamines on adhesion molecules: a possible rationale for long-term treatment. *Clin Exp Allergy* 1999; **29** (Suppl. 3):49–53.
- 116 Triggiani M, Gentile M, Secondo A *et al*. Histamine induces exocytosis and IL-6 production from human lung macrophages through interaction with H1 receptors. *J Immunol* 2001; **166**:4083–91.
- 117 Paolieri F, Battifora M, Riccio AM *et al*. Terfenadine and fexofenadine reduce in vitro ICAM-1 expression on human continuous cell lines. *Ann Allergy Asthma Immunol* 1998; **81**:601–7.
- 118 Ehringer WD, Edwards MJ, Miller FN. Mechanisms of alpha-thrombin, histamine, and bradykinin induced endothelial permeability. *J Cell Physiol* 1996; **167**:562–9.
- 119 Rotrosen D, Gallin JI. Histamine type I receptor occupancy increases endothelial cytosolic calcium, reduces F-actin, and promotes albumin diffusion across cultured endothelial monolayers. *J Cell Biol* 1986; **103**:2379–87.
- 120 Zabner J, Winter M, Excoffon KJ *et al*. Histamine alters E-cadherin cell adhesion to increase human airway epithelial permeability. *J Appl Physiol* 2003; **95**:394–401.
- 121 Takeuchi K, Kishioka C, Ishinaga H, Sakakura Y, Majima Y. Histamine alters gene expression in cultured human nasal epithelial cells. *J Allergy Clin Immunol* 2001; **107**:310–4.
- 122 Casolaro V, Gale D. Functional comparisons of cells obtained from peripheral blood, lung parenchyma, and bronchoalveolar lavage in asthmatics. *Am Rev Respir Dis* 1989; **139**:1375–82.
- 123 Liu Y, Janeway CA Jr. Interferon gamma plays a critical role in induced cell death of effector T cell: a possible third mechanism of self-tolerance. *J Exp Med* 1990; **172**:1735–9.
- 124 Wenzel SE, Fowler AA, Schwartz LB. Activation of pulmonary mast cells by bronchoalveolar allergen challenge: in vivo release of histamine and tryptase in atopic subjects with and without asthma. *Am Rev Respir Dis* 1988; **137**:1002–8.
- 125 Crimi E, Chiaramondia M, Milanese M. Increase of mast cell numbers in mucosa after the late-phase asthmatic response to allergen. *Am Rev Respir Dis* 1991; **144**:1282–6.
- 126 Pesci A, Foresi A, Bertorelli G, Chetta A, Olivieri D. Histochemical characteristics and degranulation of mast cells in epithelium and lamina propria of bronchial biopsies from asthmatic and normal subjects. *Am Rev Respir Dis* 1993; **147**:684–9.
- 127 Jarjour NN, Calhoun WJ, Schwartz LB, Busse WW. Elevated bronchoalveolar lavage fluid histamine levels in allergic asthmatics are associated with increased airway obstruction. *Am Rev Respir Dis* 1991; **144**:83–7.
- 128 Bryce PJ, Mathias CB, Harrison KL, Watanabe T, Geha RS, Oettgen HC. The H1 histamine receptor regulates allergic lung responses. *J Clin Invest* 2006; **116**:1624–32.
- 129 Malick A, Grant JA. Antihistamines in the treatment of asthma. *Allergy* 1997; **52**:55–66.
- 130 Town GI, Holgate ST. Comparison of the effect of loratadine on the airway and skin responses to histamine, methacholine, and allergen in subjects with asthma. *J Allergy Clin Immunol* 1990; **86**:886–93.
- 131 MacFarlane PI, Heaf DP. Selective histamine blockade in childhood asthma; the effect of terfenadine on resting bronchial tone and exercise induced bronchoconstriction. *Respir Med* 1989; **83**:19–24.
- 132 Spector SL, Nicodemus CF, Corren J *et al*. Comparison of the bronchodilatory effects of cetirizine, albuterol, and both together versus placebo in patients with mild-to-moderate asthma. *J Allergy Clin Immunol* 1995; **96**:174–81.
- 133 Ghosh SK, De Vos C, McIlroy I, Patel KR. Effect of cetirizine on exercise induced asthma. *Thorax* 1991; **46**:242–4.
- 134 Hamid M, Rafferty P, Holgate ST. The inhibitory effect of terfenadine and flurbiprofen on early and late-phase bronchoconstriction following allergen challenge in atopic asthma. *Clin Exp Allergy* 1990; **20**:261–7.
- 135 Rafferty P, Jackson L, Smith R, Holgate ST. Terfenadine, a potent histamine H1-receptor antagonist in the treatment of grass pollen sensitive asthma. *Br J Clin Pharmacol* 1990; **30**:229–35.
- 136 Aaronson DW. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allergy Asthma Immunol* 1996; **76**:440–6.
- 137 Corren J, Harris AG, Aaronson D *et al*. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997; **100**:781–8.
- 138 Baena-Cagnani CE, Berger WE, DuBuske LM *et al*. Comparative effects of desloratadine versus montelukast on asthma symptoms and use of beta 2-agonists in patients with seasonal allergic rhinitis and asthma. *Int Arch Allergy Immunol* 2003; **130**:307–13.
- 139 Reicin A, White R, Weinstein SF *et al*. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a

- histamine receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 2000; **160**:2481–8.
- 140 Gelfand EW, Cui ZH, Takeda K, Kanehiro A, Joetham A. Fexofenadine modulates T-cell function, preventing allergen-induced airway inflammation and hyperresponsiveness. *J Allergy Clin Immunol* 2002; **110**:85–95.
 - 141 Bryce PJ, Geha R, Oettgen HC. Desloratadine inhibits allergen-induced airway inflammation and bronchial hyperresponsiveness and alters T-cell responses in murine models of asthma. *J Allergy Clin Immunol* 2003; **112**:149–58.
 - 142 Warner JO. A double-blind, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment followup. *J Allergy Clin Immunol* 2001; **108**:929–37.
 - 143 Panettieri RA, Yadavish PA, Kelly AM, Rubinstein NA, Kotlikoff MI. Histamine stimulates proliferation of airway smooth muscle and induces c-fos expression. *Am J Physiol* 1990; **259**:L365–71.
 - 144 Chand N, Eyre P. Classification and biological distribution of histamine receptor sub-types. *Agents Actions* 1975; **5**:277–95.
 - 145 Thomson NC, Kerr JW. Effect of inhaled H1 and H2 receptor antagonist in normal and asthmatic subjects. *Thorax* 1980; **35**:428–34.
 - 146 White JP, Mills J, Eiser NM. Comparison of the effects of histamine H1- and H2-receptor agonists on large and small airways in normal and asthmatic subjects. *Br J Dis Chest* 1987; **81**:155–69.
 - 147 Ascensao JL, Ahmed T, Arlin ZA. Autologous and allogeneic bone marrow transplantation. *NY State J Med* 1986; **86**:178–83.
 - 148 Field SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux?: a critical review of the literature. *Chest* 1998; **114**:275–83.
 - 149 Sirois J, Menard G, Moses AS, Bissonnette EY. Importance of histamine in the cytokine network in the lung through H2 and H3 receptors: stimulation of IL-10 production. *J Immunol* 2000; **164**:2964–70.
 - 150 Gutzmer R, Mommert S, Gschwandtner M, Zwingmann K, Stark H, Werfel T. The histamine H4 receptor is functionally expressed on T(H)2 cells. *J Allergy Clin Immunol* 2009; **123**:619–25.
 - 151 Dunford PJ, Williams KN, Desai PJ, Karlsson L, McQueen D, Thurmond RL. Histamine H4 receptor antagonists are superior to traditional antihistamines in the attenuation of experimental pruritus. *J Allergy Clin Immunol* 2007; **119**:176–83.
 - 152 Benovic J. Novel β 2-adrenergic receptor signaling pathways. *J Allergy Clin Immunol* 2002; **110**:s229–35.
 - 153 Colombo M, Rumi MG, Roffi L, Del Ninno E. Decrease in suppressor/cytotoxic T-cells with histamine receptors in patients with chronic active hepatitis. *Liver* 1984; **4**:201–7.
 - 154 Nielsen HJ, Hammer JH. Possible role of histamine in pathogenesis of autoimmune diseases: implications for immunotherapy with histamine-2 receptor antagonists. *Med Hypotheses* 1992; **39**:349–55.
 - 155 Leite-de-Moraes MC, Diem S, Michel ML *et al*. Cutting edge: histamine receptor H4 activation positively regulates in vivo IL-4 and IFN-gamma production by invariant NKT cells. *J Immunol* 2009; **182**:1233–6.
 - 156 Mavligit GM. Immunologic effects of cimetidine: potential uses. *Pharmacotherapy* 1987; **7**:120S–4S.
 - 157 Szincsak N, Hegyesi H, Hunyadi J *et al*. Cimetidine and a tamoxifen derivate reduce tumour formation in SCID mice xenotransplanted with a human melanoma cell line. *Melanoma Res* 2002; **12**:231–40.